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WILEY Haemophilia

POSTER PRESENTATIONS

P001 | Pediatric early warning system in hemophilia patients: A consideration

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Introduction: The Paediatric Early Warning System (PEWS) was implemented nationally two years ago in Ireland in 2015. It provides a framework for care and empowers staff to escalate care for children who show signs of deterioration or for whom there are concerns. The first doctor on call (senior house officer) is notified at a PEWS score of 3, and senior medical staff are alerted at a score of 6. The objective of this study was to determine the role of PEWS in managing a hemophilic patient with a bleed.

Methods: A retrospective analysis of the PEWS charts of six patients who attended Our Lady's Children's Hospital, Crumlin over the period 2015-2017 was undertaken. The study examined the PEWS score which is based on the patient's vital signs, including their respiratory rate, work of breathing, oxygen requirement and saturations, heart rate and systolic blood pressure. Each patient may "score" between 0 and 3 on each vital sign based on deviation from the normal range for their age group. The information from each PEWS chart was collated to obtain the final results. Patient X had his blood pressure excluded from this study due to a known history of hypertension.

Results: Six patients were identified, all male, age range 4 to 15 years (mean 9.67 years). Patients were admitted with a variety of bleeds including head injuries, joint bleeds, muscle bleeds and hematemesis. Three patients had severe factor 8 deficiency, two had severe factor 9 deficiency and one had Von Willibrand disease. All patients were admitted requiring treatment and observation for their bleed. The PEWS score for patients on admission to the ward were in the range 0-1 (mean 0.33). The PEWS score throughout their inpatient stay remained in the range 0-2 (mean 0.26). One patient had a subsequent bleed to another site while as an inpatient which PEWS did not detect; their PEWS score remained 0.

Discussion/Conclusion: Care would not have been escalated to medical staff due to the PEWS score remaining lower than 3. Therefore clinical knowledge and skill, and patient insight remain the best indicators of a bleed in a hemophiliac patient, consequently leading to appropriate management.

Disclosure of Interest: None declared.

P002 | Management of a child with mild hemophilia A and acute lymphoblastic leukemia

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Introduction: The co-existence of acute leukemia in a patient with hemophilia without HIV is rare. We report a 12-year-old boy with mild hemophilia A (baseline factor VIII 0.16 IU/mL) who was diagnosed with high count T-cell ALL. We discuss the challenges in clinical management of a previously untreated patient (PUP) and highlight the need for guidelines to standardize care and improve outcomes.

Methods: A systematic review of current literature reveals that information is scarce with limited case reports. This highlights the rare occurrence of these two conditions and the need for discussion around best management.

Results: This child was diagnosed with T-cell acute lymphoblastic and treatment was as per the UK ALL 2011 protocol where he had Regimen B Induction therapy. Further diagnostic tests such as bone marrow aspirate (BMA) and lumbar puncture (LP) needed adequate hemostatic support. He was given recombinant FVIII (rVIII) concentrate with the aim to raise FVIII to >80% to prevent traumatic bleeding. This was his first exposure to rVIII and Nuwiq manufactured in human cell lines was chosen. It was not possible to proceed with a central venous access device as this meant an invasive surgical procedure requiring frequent doses of rVIII to provide adequate hemostatic support and as a result the risk of developing a FVIII inhibitor due. Therefore a peripherally Inserted Central Catheter (PICC) was inserted. In the UK children with ALL are given asparaginase intramuscularly (IM), however his treatment was modified to minimize the risk of bleeding by giving asparaginase intravenously (IV), which he tolerated well. Day 29 bone marrow showed Risk minimal residual disease, therefore treatment was escalated to more intensive chemotherapy with Regimen C Augmented BFM consolidation. Management of hemostatic support for on-going LPs in Augmented BFM consolidation has been at a reduced dose of Nuwiq at approximately 15iu/kg as good increments were seen. Treatment in the consolidation stage has thus far been tolerated well and is on-going.

Discussion/Conclusion: This case demonstrated that one of the most difficult challenges and considerations was treatment of a PUP, due to the need for regular FVIII treatment to allow for safe treatment. The management of ensuring procedures required could be carried

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out safety without undue bleeding risk must be offset against the risk of inhibitor formation that could create further complexities.

Disclosure of Interest: None declared.

P003 | Evaluation of a three day course of tranexamic acid to prevent bleeding for patients with inherited bleeding disorders following dental procedures

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Introduction: People with Inherited Bleeding Disorders (IBD) were previously prescribed a course of Tranexamic Acid (TXA) mouthwash for 5-7 days, following dental procedures to reduce the risk of bleeding. Informal discussions with patients, suggested that many do not complete the prescribed course of treatment. A literature review suggested that TXA was being prescribed inappropriately for low bleeding risk procedures. The literature also revealed inconsistencies in the recommended dose, mode of administration and duration of TXA for this patient group. A new guideline was implemented to rationalize the prescribing of TXA for this patient group. The new regimen was three days of TXA tablets for mild bleeding disorders and mouthwash for moderate/severe disorders.

Methods: A service evaluation was undertaken following the implementation of the new guideline. Structured telephone interviews following 39 procedures were completed. Concerns about bleeding were documented along with whether TXA was taken as prescribed and reasons for non-concordance. Any unplanned treatment required post-operatively was recorded along with patient comments. The financial impact of the new prescribing guideline was explored.

Results: 46% of patients did not complete the prescribed course of TXA. The majority (37/39) were prescribed tablets rather than mouthwash; this was largely due to the patient population. No patients required additional unplanned hemostasis support to control hemorrhage. An estimated saving of £15,600 was made (over 18 months) by replacing a five to seven day course of TXA mouthwash with a three day course of TXA tablets.

Discussion/Conclusion: Data collected from patient interviews supports the newly implemented guideline. However, patients appear to be making decisions about taking TXA based on their own experience rather than following the prescribed regimen. Prescribers should support patients to make informed decisions about their medicines and incorporate patient experience into individualized regimens. Given the lack of bleeding complications experienced within this cohort of patients it is possible that TXA is being over prescribed and that patients are able to make their own decisions about duration of treatment. Further work on exploring how patients with inherited bleeding disorders make decisions about taking medicines is needed.

Disclosure of Interest: None declared

P004 | Prevalence of vitamin d deficiency in persons with severe hemophilia in Ireland

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Introduction: Vitamin D deficiency is common in the Irish population, primarily due to reduced cutaneous synthesis of Vitamin D from sunlight at Irish latitudes for 4 to 6 months per year. Vitamin D deficiency is associated with adverse health outcomes including osteomalacia, decreased muscle strength and function and increased falls risk. In 2017, a screening program for Bone Health in persons with Hemophilia commenced at the National Coagulation Centre. This study evaluates for the first time the prevalence of low Vitamin D levels in persons with severe Hemophilia (PWSH) resident in Ireland.

Methods: All patients in Ireland with Hemophilia are registered with the National Coagulation Centre. Adult patients (>16 years) with severe Factor VIII or Factor IX deficiency were identified from the National Haemophilia Electronic Record. Results of laboratory Bone Health screening (comprising blood sampling for corrected calcium, phosphate, magnesium, Vitamin D, Parathyroid hormone (PTH), testosterone and C-reactive protein (CRP) levels) from September 2016 to September 2017 were reviewed.

Results: In total, 108 PWSH were identified of whom 85 (79%) have undergone bone health screening within the 12 month study period. Vitamin D levels were normal in 46 patients (54%) and were low (≤50 nmol/L) in 39 patients (46%). Of the 39 patients with low Vitamin D levels, 28 had FVIII and 11 FIX deficiency, while 21 had previous infection with Hepatitis C and 2 had HIV infection. Vitamin D levels were <30 nmol/L in 19 individuals and between 30 and 50 nmol/L in 20 individuals. Calcium, phosphate and magnesium levels were normal in this patient group (medians 2.35 mmol/L, 1.13 mmol/L and 0.84 mmol/L respectively. Two patients had elevated PTH levels of 94.5 and 96 pg/mL (NR 15-65 pg/mL). Four patients had testosterone levels less than the lower limit of normal. All patients with low Vitamin D levels have commenced oral Vitamin D supplements.

Discussion/Conclusion: In common with the general Irish population, PWSH in Ireland have a relatively high prevalence of low Vitamin D levels. Low Vitamin D levels have been associated with poor muscle function, increased falls and contribute to poor bone health. Intervention to correct low Vitamin D levels with a once daily oral supplement is cost-effective and well tolerated.

Disclosure of Interest: None declared.

P005 | Chronic pain in hemophilia: Evidence based psychological approaches to better management

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Introduction: It is well documented that hemophiliac patients' with chronic pain have increasing needs for psychosocial intervention due to the issues that arise from inadequate pain management and poor coping strategies. Issues such as mood alteration, drug addiction and emotional problems further complications for patients with hemophilia. This adds an ever increasing burden to the conditions((Varni, 1981).Each person's experience and understanding of pain is personal to them. In order for pain management to be optimized it is essential we address all areas of their lives including psychosocial, behavioral and sociological aspects. Only then can we individualize the care for each patient. Further study is necessary to establish a deeper understanding of the many factors that have on an influences on the patients' perception of pain (Auerswald et al, 2016). The National Coagulation Centre at St James Hospital is involved in a new initiative aimed at improving the quality of life of patients with bleeding disorders who are living with long term pain. The plan is to implement a novel approach with the patients using an established technique called ACT (Acceptance Commitment Therapy). ACT is offered as a structured psychoeducational group intervention in the form of an 8 week program.

Methods: Acceptance Commitment therapy (ACT) will be offered to all patients with severe hemophilia n = 150. The program will commence in January 2018.

Results: The pilot aims to assess patient's quality of life before and after the ACT 8 week program.

Discussion/Conclusion: Like many chronic long term illnesses there is no immediate cure for Chronic Pain. However implementing strategies/techniques through self-management can help reduce pain, improve the quality of life and puts patients in control. ACT offers an exciting opportunity for a paradigm shift in the management of chronic pain in hemophilia

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P006 | Persistent effectiveness of prophylaxis with recombinant factor VIII concentrate in patients with hemophilia a in a real world setting over 4 years (international ahead study)

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Introduction: In contrast to controlled clinical trials, the noninterventional AHEAD study provides evidence on real-world outcomes of patients with hemophilia A (HA).

Methods: The AHEAD study is a non-interventional, prospective, cohort study aiming to describe long-term outcomes in patients with severe or moderate HA (FVIII <1%-5%) treated with octocog alfa (ADVATE). The global AHEAD study includes a German and an International study arm. This interim report includes data from the first 4 years of follow-up from 21 countries in the INT arm.

Results: Overall, 715 patients have thus far been enrolled and 706 have been analyzed. The mean age at screening was 19.0 years, 63% had severe HA (FVIII <1%), and 82% were on prophylaxis, defined as at least 2 non-consecutive infusions a week. Annualized bleeding rates (ABRs) were analyzed yearly from patients on prophylaxis. This included 353 patients in year 1, 244 in year 2, 177 in year 3, and 103 in year 4. During the first 4 years of observation, patients on prophylaxis had a median ABR of <2 bleeds per year 1.7 in year 1, 1.3 in year 2, 1.5 in year 3, and 1.0 in year 4. Very similar data were reported for the subset of patients with severe HA on prophylaxis (ABR 1.9, 1.9, 1.8, and 1.0 in years 1–4, respectively; sample size range 58–209). Overall, 42% of patients on prophylaxis had an ABR <1 in years 1, 2, and 3, and 49% in year 4. In each year, 30%-40% of patients were bleed free (31%, 32%, 36%, and 40%, respectively). Median annual joint bleeding rates (AJBRs) were ≤1 in the 4 years 0.9 in year 1, 1.0 in years 2 and 3, and 0.0 in year 4. Results were similar for patients with severe HA on prophylaxis (AJBR 1.0, 1.0, 1.1, and 0.9 in years 1–4, respectively; sample size range 45–158). In the first year, 55% of patients on prophylaxis had an AJBR <1, while 51% in the second and third year and 57% in the fourth year had AJBRs <1. In years 1–4, 42%, 42%, 43%, and 51% of patients, respectively, had zero joint bleeds.

Discussion/Conclusion: The AHEAD study provides important information on the long-term, real-world effects of prophylaxis in patients with moderate or severe HA. These preliminary data show that the effectiveness of prophylaxis is consistent over 4 years of follow-up. A substantial proportion of patients had zero bleeds (30%-40%) and zero joint bleeds (42%-51%) during this time period.

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Roche, Pfizer, Shire, SOBI, J. Oldenburg Grant/Research support from Shire, Bayer, Biotest, CSL-Behring, Novo Nordisk, Octapharma, Pfizer, Consultant for Shire, Bayer, Biogen Idec, Biotest, Chugai, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, and Swedish Orphan Biovitrum, Speaker Bureau of Shire, Bayer, Biogen Idec, Biotest, Chugai, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, and Swedish Orphan Biovitrum, E. Baldacci Consultant for Bayer, Shire, Novartis, Speaker Bureau of Pfizer, Bioviiix, R. Parra Grant/Research support from Pfizer, Bayer, Shire, Consultant for Pfizer, Sobi, Shire, K. Steinitz-Trost Employee of Shire, A. Gringeri Employee of Shire, P. Pina Employee of Shire.

P007 | How our patients view EHL products in hemophilia: Expectations expressed before switching (the hope study)

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Introduction: Advances in treatment of hemophilia have allowed patients to switch to extended half-life (EHL) products. Whilst clinical trials have demonstrated the efficacy of EHL products, little is known about why patients would choose to switch to a new therapy. Understanding their rationale for switching [SL1] from standard to EHL factor is an important aspect of hemophilia care provision.

Methods: Parents of children and adults with hemophilia switching or recently switched to EHL factors in the UK were invited to participate in semi-structured telephone interviews to discuss their expectations of the new EHL factor. Each interview was analyzed in "real time" using modified grounded theory methodology by the study group, until no new recurring themes were identified.

Results: Fifteen mothers of children with a mean age of 5.83 years (range 1-14) and eight adults mean age 36.75 years (range 16-26) were interviewed. Two adults had hemophilia B, 2 received on-demand treatment, the remainder of the adults and the children were treated prophylactically, including one mild child with a severe bleeding phenotype. Three key themes emerged: (1) having improved factor levels/pharmacokinetics with EHL products (2) enhanced convenience of EHL products (less packaging/waste and less infusions) (3) improved vein health, less need for central venous access and decreased peripheral venous access for prophylaxis

Discussion/Conclusion: Little real world use of patient experience of EHL products is available. This study reveals that increased factor levels (enhanced PK) is more important to patients and caregivers than decreased infusions; this is expected to result in better protection, less pain and improved joint health. Patient experience is an important part of shared decision making in hemophilia care, while sharing patient experience is reassuring for both other patients and clinicians.

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P008 | The burden of caring for a child with moderate or severe hemophilia – a European comparison

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Introduction: Caring for a child with hemophilia can cause a great burden to the caregivers reaching from personal sacrifice, financial impact on the family to emotional stress of the caregiver. Data on caregivers' burden in hemophilia are scarce. Recently a hemophilia-specific caregiver burden questionnaire was developed in the US (HEMOCAB™), the situation in Europe is still not known. The aim of the study was to assess caregivers' burden using the "HEMOphilia associated CAregiver Burden scale" (HEMOCAB™) in 7 European counties (Germany, Italy, Poland, Sweden, The Netherlands, Turkey and UK).

Methods: The HEMOCAB™ was distributed to caregivers for completion. Socio-demographic data were collected in addition to clinical data of their child, which was retrieved from medical records.

Results: So far, data from 88 caregivers (mean age 38.07 ± 6.7) and their children with hemophilia (mean age 8.47 ± 5.4 years; range 0.55-17.73) from 5 countries (Germany, Poland, Sweden, Turkey, UK) have been collected. Caregivers were caring for children with mainly hemophilia A (86.4%), severely affected (86.4%) and who were receiving prophylaxis (83%). Children had on average 3.58 ± 4.9 total bleeds and 9.31 ± 15.5 days lost in the past 12 months; 27.3% reported chronic pain with intensity (VAS) of 5.86 ± 2.4 (range 1-10). Most of the caregivers were female (85.2%), married (77.3%), living with a partner (83%), had a higher educational level (61.3%), and 64.7% were working, mainly full time (38.6%). 20.7% had a long-term condition themselves; 64.8% reported that hemophilia affected the family life and 34.5% said that hemophilia had an economic impact on the family. The HEMOCAB™ showed good psychometric characteristics in terms of internal consistency (Total Score $\alpha = 0.970$). Caregivers reported highest burden in the domains "Perception of your Child" (M = 43.94 ± 25.3), "Emotional Stress" (M = 41.0 ± 22.5) and "Impact on You" (M = 33.24 ± 28.4) of the HEMOCAB™.

Discussion/Conclusion: HEMOCAB™ was demonstrated to be a good instrument to assess caregivers' burden in Europe. Caregivers felt mainly impacted in the perception of their child and their emotional stress related to caring for a child with hemophilia. Counseling and/or support programs should be implemented to reduce the burden for caregivers of children with hemophilia.

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P009 | Improving the nursing care of the child with hemophilia through identifying the need to implement a hemophilia study day for staff nurses. – A continuing professional development initiative

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Introduction: It is widely documented that in order to practice safely and provide optimum care to patients, nurses are required to constantly assess and update their skills and knowledge also known as continuing professional development (CPD). Whilst working on an acute 22 bedded pediatric ward, combined of 7 diverse specialties, the authors recognized that their knowledge wasn't of adequate standard for the Irish National Centre of Excellence for Paediatric Hemophilia and therefore through CPD sought to improve this. The aim was to identify whether other staff nurses also recognized a gap in their knowledge and if so, to ascertain specific areas which required improvement and education.

Methods: A learning needs analysis was utilized to best highlight staff knowledge, deficits and feelings surrounding the care of the child with hemophilia at ward level. Initially the authors decided to create a hard copy questionnaire. Upon discussion with our advisors, (clinical nurse specialists, clinical nurse facilitator and hematology consultant) the questionnaire was reviewed and amended. It was agreed that our response rate could be increased by creating an online survey. This was then sent to the target audience via email and Whatsapp group.

Results: A response rate of 68% was achieved, allowing staff a two-week timeframe to complete the survey. On analysis of the data, it was identified that whilst staff had a basic understanding of the topic, there were significant deficits in the comprehensive knowledge of the condition and treatment. Staff acknowledged this during the survey when questioned on their strengths, weaknesses and learning needs. It is worth noting that 37% of staff who partook in the questionnaire did not answer 6 out of 10 questions. Whilst this may be a limitation to the study, it cannot be outruled that the lack of unanswered questions correlates to a lack of knowledge.

Discussion/Conclusion: It is evident that although staff have a basic understanding of the nursing management of a child with hemophilia at ward level, a resounding knowledge deficit has been identified. As a result, the authors conclude that a hemophilia study day would benefit staff nurses. The results of this study will also provide structure for those establishing the study day as specific areas for improvement have been identified.

Disclosure of Interest: None declared.

P010 | Thrombin generation assay: A nurse practical point of view

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Introduction: Blood collection is one of the most common nurse practices in the daily routine. However, from a practical point of view, daily operational and logistic real settings of a clinical unit limit its whole application. This project aims to analyze the impact of different blood extraction protocols in the TGT results.

Methods: Ten healthy controls were enrolled and 10.8 mL of peripheral blood were extracted by two different protocols (a) 21G needle using a vacuum extraction system without tourniquet and inserting the standard sodium citrate (3.2%) blood collector tube directly into the holder and (b) 25G needle using vacuum extraction system with tourniquet after arm was laying down until venous stasis and butterfly device. Platelet-poor plasma (PPP) was obtained by centrifugation of whole blood for 15 min at 1000 g, 23°C. PPP was separated and centrifuged twice again the first, 15 min at 1500 g, 23°C and the second 2 min at 13 000 g, 23°C. Platelet-free plasma (PFP) aliquots were stored at −80°C until TGT analysis. TGT was evaluated by *Calibrated Automated* Thrombogram (CAT) in PFP with PPP-Low-Reagent (tissue factor 1 pM plus phospholipid mixture from Thrombinoscope BV, Maastricht, The Netherlands).Lagtime (LT, minutes [min]),time from the beginning of TGT until 10 nM thrombin is formed; peak height (PH, nM),maximum thrombin concentration reached; time-to-peak (TTP, min),time required to reach the peak height; and endogenous thrombin potential (ETP, nMxmin), total amount of thrombin generated, were recorded. Statistical analysis was realized with GraphPad Prism v.5.03 (GraphPad Software© Rockfield, CA, USA).

Results: We appreciated several variations intra and inter subjects in different parameters of CAT. Some samples showed a macroscopic hemolysis when blood was drawn in the worst condition. No significative differences were shown using Student t-test, however reasonable variation in data was found according to coefficient of variation between both techniques.

Discussion/Conclusion: Our preliminary results show the necessity to standardize blood extraction. Significant differences between both experimental conditions were not observed because CAT technique

lacks sensitivity to detected them of because of the reduced number of controls included. So, future work increasing including more subjects is mandatory, in order to include evidence to our daily routine and with the aim to approach Nursing to laboratory procedures.

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P011 | Switching clotting factors: Nursing review

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Introduction: With the arrival of the new therapies, switching clotting factors is controversial because many times it generates doubts within patients and health providers. However, there is no consensus about which flowchart must be used.

Methods: We review the literature and our experience analyzing the change from Kogenate® to Kovaltry® in previously treated patients(PTPs).

Results: According to the literature review, the fear of developing inhibitors was the main reason provided by 71.4% of the patients to reject the change in the clotting factor (von Mackensen, 2017).

In our revision of PTPs (Rodin Study, UKCHDO and Coppola) we found similar conclusions the risk of developing inhibitors after changing the clotting factor trade was not proven or was similar to the global tendency in the whole population of people with hemophilia(PWH). From Kovaltry® approval in February 2016, all our PTPs with Kogenate® switched to Kovaltry®. Kovaltry® has benefits for patients such an increase of safety, an enhancement of the reconstitution mechanism and a slight half-life increase compared to Kogenate® In our Center, we performed the change from Kogenate® to Kovaltry® as follows a document explaining the reasons for the change was sent from the Coagulopathies and Pharmacy Unit to Patient Association, to avoid any misunderstanding or word of mouth. According to the literature review, 74.3% of patients expect to receive information from the patients association, who has a key role in the communication process between Hemophilia Treatment Center and community of PWH. When patients needed the prescription to collect the treatment, the physician always explained the reasons of change and resolved any doubts and fears. After this, patients were derived to nurses who performed tasks about health education on changes within the reconstitution process, continuing with the information process.

Discussion/Conclusion: New replacement factors involve advantages. These benefits can be viewed by young adults and parents with a strong knowledge of the disease as attractions to increase compliance with treatment, allowing for widely spaced regimens that are suited to busy lifestyles. Nurses play a key role in all steps of changing a treatment, and they have to be continuously formed and fully aware of the new products available, in order to transmit all the skills and knowledge to patients in terms of safety and care quality. Therefore it is mandatory for nurses to transmit calm and support throughout the whole change process.

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P012 | Clinical profile of hemophilia patients and assessment of their quality of life: Evidence from south India

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Introduction: Quality of life (QoL) is a recent focus of research in hemophilia. The clinical profile of hemophilia patients is rarely reported in India, especially in the state of Kerala. The objective of this study was to describe the clinical profile of hemophiliac patients and their QoL in Kerala, South India.

Methods: This was an observational cross-sectional study. Patients of all age groups with hemophilia admitted in the medicine and pediatrics ward for factor/fresh frozen plasma transfusion or having history of such type of transfusion were consecutively enrolled. A detailed clinical history was elicited from the accompanying parent/guardian. The HAEMO-QoL questionnaire was used for the assessment of QoL of the patients.

Results: Out of the total 71 hemophilia patients, 66.2% (51/77) were >18 years of age. Type A hemophilia was observed in 88.3% (68/71) patients. Majority of the patients had severe hemophilia (80.5%). The family history and joint involvement were present in 58.4% and 77.9% of the patients, respectively. Knee joint was observed to be as the target joint among 57.1% of the patients. 76.6% of the patients had joint swelling, resulting in compromised joint movement. Bleeding occurred in soft tissues and joints in 62.3% and 15.6% of the patients, respectively. The patients had poor QoL scores. Overall, hepatitis B and C infection were observed in 6.5% and 9.1% of the patients, respectively. Orthophysiotherapy was needed in 22/26 (84.6%) patients.

Discussion/Conclusion: The severe type of hemophilia Type A was more common than mild and moderate types. The study suggests that important determinants for QoL in hemophilia patients are availability of factor concentrate from the clinical perspective and social and psychological support to ensure a holistic care approach.

Disclosure of Interest: None declared.

P013 | Exploring patient perceptions of ultrasound "selfies" to engage patient confidence in recognizing and managing musculoskeletal bleeding episodes

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Introduction: Currently, diagnosis of hemarthroses is made empirically by patients who treat themselves at home based on clinical presentations. However, there are no standard diagnostic criteria available and the overlap in symptoms between joint arthropathy and hemarthroses make it challenging to differentiate between the two conditions. People with hemophilia have for many years been successfully trained to self-administer intravenous treatment at home and we explored their views on whether they could similarly be trained to self-administer ultrasound imaging at home to better manage their condition by accurately differentiating between joint bleeding and non-bleeding episodes.

Methods: Semi-structured interviews were conducted with five patients with severe hemophilia aged 22-59 years.

Results: All patients reported that they sometimes treated when they were not sure whether they had a bleed or not and were of the view that self-scanning would be helpful in these instances; "I like to see inside my joint or muscle when I have a bleed", "I treat with factor when it hurts, but I'm not always sure this is a bleed". Benefits included; increased confidence in their ability to manage their condition in terms of when to treat but also when to return to daily and leisure activities. Barriers included; unsure whether they could understand the images and not treating a bleed early enough, amount of training and whether someone would be available to help them when they needed it.

Discussion/Conclusion: Portable hand-held ultrasound systems are now available. Patients with hemophilia are of the opinion that learning to self scan at home to help differentiate between bleeding and non-bleeding episodes would be beneficial and empower them to better manage their condition and treatment. With this information, we plan to develop a learning package to determine whether self scanning can engage patient confidence in recognizing and managing musculoskeletal bleeding episodes.

Disclosure of Interest: None declared.

P014 | Outpatient physiotherapic management at bianchi bonomi hemophilia center: 20-year experience

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Introduction: The PWH needs rehabilitative intervention both in the acute phase (hemarthrosis) as well as in the sub-acute and chronic phase. We report here the rehabilitation experience gained at the Angelo Bianchi Bonomi Hemophilia Center in Milan. Nowadays, our clinical experience highlights the need to evaluate the patient in its entirety. During the routinary check-up we have introduced a muscular and skeletal complete evaluation with clinical analysis, Haemophilia Joint Health Score (HJHS), postural analysis, stability and baropodometric analysis with a specific platform. The purpose of this evaluation is to detect the primary dysfunction of the organism that alters the overall biomechanics of the skeletal muscle system, giving rise to recurrent hemarthroses. To stop this degenerative process, we use the osteopathic fascial treatment.

Methods: Every patient (children, adults and elderly) is annually checked with - Postural analysis - HJHS - Baropodometric platform with bipodal load analysis - Stability chart with CoP analysis The patient is also treated with osteopathic method with the use of fascial technique to improve and restore lost elasticity, and to treat eventually post-operative problems.

Results: This approach, as it immediately improves joint mobility, allows proper execution of the exercises that are given to the patient to be performed at home. In the perspective, it will then be possible to indicate to the patient an adequate sport activity.

Discussion/Conclusion: Overall the postural assessment provides evidence of the degree of mechanical stress on the joints. Manual treatment is the tool through which the physiotherapist can stop the vicious cycle "dysfunction-pathology", thus delaying or avoiding the need for major surgical interventions.

Disclosure of Interest: None declared.

P015 | The therapeutic-rehabilitative approach of ileopsoas hematoma in a pediatric patient with severe hemophilia B: Case report

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Introduction: Iliopsoas hematoma is a serious bleeding event in hemophilic patients, so a multidisciplinary approach is recommended to manage the acute phase and prevent the complications.

Methods: A 14-years-old patient with severe Hemophilia B with a previous history of inhibitors, reported the following symptoms severe pain in the groin and paraspinal area, functional impotence, impossibility to walk, irreducible hip and reduction of hip flexors, spontaneous antalgic posture. No precipitating factor was identified. Ultrasonography visualized an echogenic mass measuring 100 mm by 30 mm on the right side. He was on prophylactic Factor IX therapy (Nonacog alfa with 37 IU/Kg twice a week). The therapeutic program provided the administration of Nonacog alfa 60 IU/Kg/die for seven

days; then Nonacog alfa 45 U/kg/die up to 30 days. A short assessment was performed joint test (flexion hip = 70°; extension of the hip was no possible); muscle test (hip flexors = 3); it was impossible to administer HJHS and gait analysis; there was no evidence of femoral nerve involvement; NRS scale (pain 8). Overall, 18 physiotherapy sessions were performed under factor replacement cover. The rehabilitative program consisted *short term* relief of pain, global stretching of muscles involved, patient and caregivers education (bed rest to alleviate pain, use of wheelchair/crutches); *midterm* return to maximal function with full range of movement, to maximal strength as normal length of the muscle; *long term* improving of stability in stand position, reeducation of walking, prevention of recurrence. The techniques used were passive mobilization of lower limb and gentle stretching of tight muscle as pain-free mobility permits, manual therapy, global postural reeducation, proprioceptive training, PNF technique, isometric and concentric contractions.

Results: The outcome measures showed a progressive improvement of the function and the symptoms resolved after a personalized therapeutic-rehabilitative program in 8 weeks. The follow-up ultrasonography showed the progressively resolution of hematoma. After 30 days, the patient was switched back to prophylactic Factor IX therapy.

Discussion/Conclusion: Our experience demonstrate that a prompt diagnosis allows an early therapy and the physiotherapy is fundamental to recover the function, decreasing the risk of complications.

Disclosure of Interest: None declared.

P016 | Adverse effects after a single moderate-volume strong-intensity strength training session in patients with severe hemophilia: feasibility and safety study

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Introduction: The intensity (resistance relatively to maximal muscle strength) and the volume (total amount of work performed in a session) of exercise are two key variables when designing therapeutic strength training programs. In patients with hemophilia, intervention studies designed with long training sessions or moderate intensities are scarce. There is a need of evaluating whether these patients may perform more stressful exercise without detrimental consequences to maximize the benefits of training programs. Thus, the purpose of this feasibility and safety study was to evaluate whether patients reported adverse effects after a moderate-volume strong-intensity strength training session.

Methods: 13 adults with severe hemophilia A and B (age 34 ± 9 years; height 173 ± 9 cm; body mass 74 ± 18 kg; body fat percentage 20 ± 8 %) participated in this cross-sectional study. Two days before the experimental session, the participants received a video with the exercises that had to be performed. The experimental session was conducted after receiving the prophylactic treatment. During this session, after a warm-up, 4 different exercises were performed (elbow flexion, shoulder abduction, knee extension, plantar flexion) with 3 different conditions (elastic bands, free weights and own body weight). Each participant performed between 6-9 repetitions on each exercise and condition until a perceived intensity corresponding to 6 on the Borg CR-10 scale was achieved. The single training session lasted 90 min. Twenty-four hours and 48 h after the session, participants were asked about possible adverse effects (bleedings, pain). In addition, they were asked to inform any possible adverse event during the week after.

Results: Feedback was obtained from all patients. No participant reported any adverse effect 24 h or 48 h after the training session. In addition, no adverse effects were notified during the week after the training session.

Discussion/Conclusion: Patients with severe hemophilia are able to perform a moderate-volume training session at strong intensity during the day of prophylactic treatment without post-exercise adverse effects. This could serve to design more optimal therapeutic strength training programs and thus optimize adaptations.

Disclosure of Interest: None declared.

P017 | Usability and usefulness of a wearable activity tracker in patients with hemophilia

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Introduction: Physical activity (PA) guidelines recommend adults to adopt a physically active lifestyle to improve health, but PA levels often decline with age. Furthermore, in hemophilic patients, the arthropathy and fear of suffering bleeds aggravates the physical inactivity, that is one of the main risk factors for cardiovascular disease, diabetes, and cancer. Wearable activity trackers have been designed as wellness devices and they have considerable potential for use in health care. These devices can monitor daily PA while aiming for a particular step count or activity goal. The objective of this study is to analyze the usability and usefulness of an activity wristband in hemophilic patients.

Methods: Of 26 patients with severe hemophilia in prophylaxis treatment [type A/B 25/1; age 36.08 (9.54) years old; weight 77.70 (19.80) kg; height 1.74 (0.07) m and HJHS total score 27.92 (16.61)] from the Hospital La Fe, Valencia, Spain were recruited. Fitbit Charge HR activity wristband was used to monitor daily PA. After using the wristband

for 13 weeks (one week baseline plus 12 weeks follow-up), participants completed a technology acceptance questionnaire developed by Mercer et al. This 17-item questionnaire assesses the domains of external variables, perceived usefulness, perceived ease of use, attitude toward using, behavioral intention to use, and actual system use. Each item can be scored from 1 (strongly disagree) to 5 (strongly agree). Matlab (The MathWorks, Inc., USA, version R2015a) software was used to process and analyze the obtained data.

Results: Overall, patients were satisfied with the activity tracker [4.41 (0.64)] and they perceived that wristbands were easy to use [4.56 (0.64)], being 4.21 (0.47) points the total average score of the 17 items. The average daily wear time (min/day) was 894.1 (106.4) in week one, and 865.0 (161.5) in weeks 10-13. Finally, the average daily steps in the week one was 10793.4 (3341.6) and 10010.4 (3146.8) in weeks 10-13. No significant difference ($P > .05$) were found comparing wear time and steps of week one with week 10-13.

Discussion/Conclusion: According to the analyzed data, the adherence to wristbands and the number of daily steps were high throughout the study period. Patients with hemophilia perceive Fitbit as a useful and usable tool to self-monitor their daily PA and to be more active.

Disclosure of Interest: None declared.

P018 | Aiming for a reduced pediatric hemophilia activities list!

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Introduction: The pediatric Hemophilia Activities List (pedHAL) assesses self-reported limitations in activities in children and youth with hemophilia. The pedHAL contains 53 items, divided in seven domains. After introducing the pedHAL clinicians and researchers reported on non-informative items. In this explorative field test we aimed to systematically evaluate all items of the pedHAL in Dutch patients with access to early prophylaxis, with the aim to potentially shorten the pedHAL. In addition, we determined change scores over 3 and 5 years to explore the optimal frequency of measurement.

Methods: We analyzed longitudinal pedHAL data collected at the annual routine assessment at the Van Creveldkliniek, University Medical Center Utrecht, The Netherlands between October 2010 - June 2017. Patients (4-18 years) with moderate/severe hemophilia A/B and their parents completing ≥1 pedHAL were included. Descriptive analyses were performed per item of the last completed pedHAL per child/parent to determine the distribution of scoring. Change scores were calculated in parents for the sum score for 3 and 5 years follow-up.

Results: Eighty-two patients with hemophilia A/B (severe 94%, median 13.1 years [range 5.4-18.0]) were included in this study. In children 22 items were scored as "never problems" in >90% and 18 items were scored as "never problems" in 80%-90%. In parents 15 items were scored as "never problems" in >90% and 28 items were scored as "never problems" in 80-90%. The 13 most informative items (<80% "never problems") belonged to the 3 domains Sitting/kneeling/standing, Functions of the legs and Leisure activities and sports. Most items scored >15% as "not applicable" belonged to the domains of Household tasks and Leisure activities and sports. Median (IQR) change sum score after 3 and 5 years follow-up was respectively 0.0 (−2.2; 0.1) and 0.0 (−1.1; 0.4).

Discussion/Conclusion: Although the time to complete the pedHAL is 10-15 min, item reduction is expected enhance feasibility of the pedHAL for research and clinical proposes. This explorative analysis suggests that the number of items can be reduced, as several items appear non-informative. Lack of change in scores over 3 and 5 years suggests that annual pedHAL administration is not necessary. However, this study was performed in a single-center sample and therefore needs to be expanded to include patients treated with less intensive regimens before the pedHAL can be shortened.

Disclosure of Interest: None declared.

P019 | Phenotypes of movement behavior in adults with hemophilia

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Introduction: It is hypothesized that a less active lifestyle in persons with hemophilia (PWH) aggravates limitations in activities. Daily movement behavior is defined as a combination of day time sedentary behavior, physical activity (PA) and sleep; it is therefore mandatory to investigate daily movement behavior as a total. Previous studies investigate movement behavior in PWH using a single parameter for movement behavior or have analyzed several parameters separately, ignoring that daily movement behavior cannot be measured adequately in this way. Identifying subgroups of PWH with similar movement behavior gives a more complete insight in movement behavior in relation to clinical characteristics. The aim of this study was to identify phenotypes of movement behavior within PWH and compare clinical characteristics between phenotypes.

Methods: Movement behavior was measured using the Activ8 activity monitor. The Activ8 can distinguish between 6 postures and activities lying down, sitting, standing, walking, running and cycling. Clinical characteristics included age, severity, joint health (hemophilia joint health score), physical functioning (Hemophilia Activity List and the 40 meters self-paces walk test) and pain (Numerical pain Rating Score). Hierarchical cluster analysis was used to identify phenotypes. Clustering variables included 7 parameters of movement behavior; sitting, standing, walking, biking, running, frequency of

active bouts and length of active bouts. Clinical characteristics were compared between the identified clusters with the Kruskal-Wallis test.

Results: Cluster analysis identified 3 clusters; a "sedentary" cluster (57%), a "bikers and runners" cluster (22%) and a "walkers" cluster (20%). The "bikers and runners" have a better joint health and experienced less limitations in activities than the "walkers" and "sedentary" clusters. The "walkers" perceived fewer limitations in activities than the "sedentary", with comparable joint health. We did not identify differences in severity, pain, walking speed and age between the subgroups.

Discussion/Conclusion: For the first time we objectively assessed movement behavior in adults with hemophilia. Three different phenotypes of movement behavior were identified; the majority of PWH were categorized as sedentary. The results from the current study suggest that regular walking during the day and limited sitting is beneficial for PWH.

Disclosure of Interest: None declared.

P020 | Gait analysis comparison of adolescents with moderate and severe hemophilia using the zebris interactive FDM-T treadmill system

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Introduction: Twenty adolescents with moderate and severe hemophilia have had joint hemarthroses both in the ankle and knee joints. These hemarthroses have led to painful joints and deviations during gait. Evaluation of the stance and gait parameters of these adolescents combined with assessment of additional physical measurements may be able to provide the best possible treatment plan for these patients. The Interactive FDM-T Treadmill System from the Zebris Medical Company consists of a treadmill with over 5,000 force sensors integrated underneath the treading surface and a large screen on which a virtual running environment, for example, is depicted in the form of a path running through the forest. The runner sees his own footprints live on the screen and gains direct feedback on his movements. Obstacles then occur such as puddles that have to be jumped over or avoided. An evaluation system awards points according to how successfully this is achieved.

Methods: Participants: 20 adolescents with Hemophilia A and B with moderate or severe hemophilia. Range of motion and lower limb muscle testing was performed on each of the patients. Each participant first stood on the platform of the treadmill. He then practiced the use of the treadmill. The first activity was walking at a comfortable speed; the second was walking at an increased speed and the third walking at an increased speed with an increased incline.

Results: The main differences were found in foot rotation, step width, step length, and stride length with the moderate group having an improved gait between 10%-20% more than the severe group. The differences between the two groups increased with increasing speed and incline. Differences of between 20%-50% in weight distribution were found both between the moderate and severe hemophilia participants. Kinetic and kinematic differences were also found to be significant

Discussion/Conclusion: Hemarthroses affect the stance and gait patterns of even the young hemophilia patients. Due to the changes seen in the gait characteristics, a different approach should be considered in treatment and education. This should include a more intense and active exercise and stretching program and possibly more properly fitting insoles and shoes.

Disclosure of Interest: None declared.

P021 | Safety and effectiveness of fascial therapy in adult patients with hemophilic arthropathy of ankle. A cohort study

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Introduction: Hemophilic arthropathy is characterized by loss of function and chronic pain. Fascial therapy mobilizes the connective tissue, intervening in the state of the injured fascial complex and the surrounding tissues. The aim of this study is to evaluate the safety and efficacy of a physiotherapy program through fascial therapy in adult patients with hemophilic ankle arthropathy.

Methods: Twenty-three adult patients with hemophilia from 26 to 65 years of age were recruited. The intervention consisted of three sessions of 45-min fascial therapy for three consecutive weeks. A pre-treatment evaluation was carried out and after the treatment period. The study variables were joint status (assessed with *Hemophilia Joint Health Score*), joint pain (using visual analogue scale), ankle range of motion (with a universal goniometer) and bleeding frequency (administering self-registration of bleeding). The mean difference was calculated using the t-student test and using the Cohen formula we calculated the effect size of the dependent variables.

Results: None of the patients developed muscular or articular bleeding during the treatment period. After treatment, significant improvements in plantar flexion, ankle pain under load and joint condition ($P < .01$) were observed in both ankles. Similarly, we found improvement in left ankle dorsiflexion ($P = .007$).

Discussion/Conclusion: The application of physiotherapy through fascial therapy does not produce muscle or joint hemorrhages. A treatment through three sessions of fascial therapy can improve joint

pain, mobility and joint ankle condition in patients with hemophilic arthropathy.

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P022 | Safety and efficacy of manual and educational therapy in the treatment of hemophilic arthropathy of the elbow. A randomized clinical trial

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Introduction: Elbow arthropathy is characteristic in patients with hemophilia. Arthropathy is manifested by decreased range of motion, pain, loss of strength and muscular atrophy, and axial changes.

Objective/Hypothesis: Two Physiotherapy programs, through manual therapy and educational physiotherapy, improve the range of motion, pain and strength in patients with hemophilic arthropathy of the elbow.

Methods: Randomized pilot study. 27 patients with hemophilia and elbow arthropathy with a mean age of 34.48 (SD 12.99) years, were randomized to Manual Therapy group, educational group and control group. The physiotherapy programs were manual therapy through joint traction, passive muscles stretching and proprioceptive neuromuscular facilitation; and educational sessions and daily home exercises. The study lasted for twelve weeks, with two sessions a week in manual therapy group and one session every two weeks with daily home exercises in educational group. The dependent variables measured were range of motion of elbow, biceps strength, circumference of arm, and elbow pain perception.

Results: The treatment with manual therapy improved the circumference of arm, flexion elbow and elbow pain. Six months later, MT group still enjoyed improved. In the educational group there were improvements, but not significant, in the measured variables. Neither of the two physiotherapy interventions caused elbow hemarthrosis.

Discussion/Conclusion: The treatment with manual therapy improved the range of movement and circumference of arm, and lessened pain in hemophilic patients with chronic elbow arthropathy. No hemarthrosis was recorded during treatment or during the follow-up period. Randomized clinical trials are required to confirm the results of this study.

Disclosure of Interest: None declared.

P023 | Health-related quality of life in hemophilia: Evidence from India

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Introduction: Studies on health-related quality of life are based on the increasingly evident need for medical care not to be limited to preventing death, but to focus instead on the value of health. This study aimed to measure the health-related quality of life in hemophilia, using the Haemophilia Specific Quality of Life (Haem-A-QoL) questionnaire and describe the socioeconomic characteristics and health conditions of these patients.

Methods: Haemophilia-Specific Quality of Life questionnaire was administered to hemophiliac adults, treated in an on-demand regime at two government tertiary care hospitals in Kerala, India.. The patients were interviewed about demographic and socioeconomic data and their understanding of the questionnaire. Clinical data were collected from medical records. The Mann-Whitney U test was used for statistical analysis. The level of significance was set for *P*-values <.05. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 21.0).

Results: Thirty-nine patients were evaluated. The mean age was 36.8 years. 84.6% had haemophilia A; 20.5% of the patients had haemophilia classified as mild, 41% as moderate and 38.5% as severe. The records of 10.5% of the patients registered seropositivity for anti-HIV and 57.9% for anti-HCV. Target joints were detected in 69.2%. The mean total Haemophilia-Specific Quality of Life score was 35.55. "Sports and leisure" and "Physical health" were the most impaired dimensions and the dimension "Relationship and partners" was the least impaired. The Haemophilia Specific Quality of Life scores showed good discriminant validity for hemophilia severity (*P*-value = .001), HIV infection (*P*-value = .02), HCV-infection (*P*-value = .01) and the presence of target joints (*P*-value <.001).

Discussion/Conclusion: Health-related quality of life in hemophilia, measured by the Haemophilia-Specific Quality of Life questionnaire, was influenced by the presence of arthropathy and infectious diseases transmitted by blood products. Rehabilitation measures should be encouraged in order to improve the quality of life of these patients.

Disclosure of Interest: None declared.

P024 | Kinesiophobia, quality of life, fatigue, depression and anxiety level in adult hemophilic patients: A controlled study

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Introduction: Hemophiliac individuals often try to reduce their physical activity levels due to frequent bleeds. However, there may be some factors, such as fear of movement, which may affect the decrease in

physical activity level. For this reason the aim of present study is to examine the presence of fear of movement, depression, anxiety, and health-related quality of life in patients with hemophilia compared with healthy controls.

Methods: Of 9 patients with hemophilia A and 9 healthy subjects were included in the study. All hemophiliac individuals were mail and controlled with age matched adults. Tampa Scale for Kinesiophobia (TSK) was used to determine fear of movement. Beck Depression Inventory(BDI), a widely used indicator of the severity of depression, was used to assess the level of depression. Beck Anxiety Inventory (BAI) was used to assess the level of anxiety. This scale is a self-report measure of anxiety. SF-36 was used to evaluate quality of life. This questionnaire is a very popular instrument for evaluating Health-Related Quality of Life. The SF-36 measures eight scales physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).

Results: The results were statistically analyzed by Mann-Whitney U test. A comparison of TSK scores showed that hemophiliac patients had a significantly greater scores than control subjects ($P = .014$). These findings indicate kinesiophobia in hemophiliac patients. There was also a significant difference in the PF ($P = .019$), BP ($P = .031$) and GH ($P = .008$) subscales of SF-36 between two groups. Hemophiliac individuals showed a greater BAI and BDI scores compared with healthy controls.

Discussion/Conclusion: These results showed that high anxiety, depression levels, fear of movement, pain and low physical function in hemophiliac individuals. Despite the fact that hemophiliacs receive prophylactic treatment, they cannot integrate fully into life. Thus in addition to pharmacologic treatments supporting these patients in terms of physical function and biopsychosocial direction will increase their participation in life and their ability to cope with their illnesses.

Disclosure of Interest: None declared.

P025 | Remote monitorization of physical exercises for patients with hemophilia using kinect V2

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Introduction: Physical exercise is necessary in patients with hemophilia as a complement to factor administration to avoid joint bleeding and improve their quality of life. Without enough motivation, patients' adherence to the required exercises may be reduced. In the recent years, the use of video games for rehabilitation or "exergaming" has proven beneficial in this respect. The goal is to improve patient's motivation to perform physical exercise at their homes using software that leverages the body tracking capabilities of the Microsoft Kinect™ V2 sensor to evaluate exercises of the most critical joints elbows, knees, ankles and help improve multi-directional balance. As the final goal is remote interaction between patient and specialist, it is essential that feedback from the exercises can be submitted.

Methods: Specifically designed Matlab (The Mathworks Inc.) software has been used to interact with Kinect V2 using Microsoft's Software Development Kit (SDK) v 2.0 and a Windows PC. The software is able to track the patient's body and display it on top of a real-time video stream. Additionally, summary performance reports and graphs can be generated and sent to the specialist via e-mail.

Results: Ten healthy subjects and eight subjects with hemophilia were recorded conducting 25 repetitions of each exercise. Exercise detection rate for the healthy subjects was 100%, 100%, 77%, for counting elbow flexions/extensions, knee flexions/extensions (squat) and step climbs, respectively. For patients the obtained rates have been 100%, 86%, 65%, respectively. Difficulty in counting knee extensions for patients was due to subject limits on joint motion caused by the disease. Step climbs are counted making use of hip center height and knee angle, as an alternative to ankle angle variation, which is inherently noisy in Kinect V2. Regarding the balance exercise, a rapid motor learning process of the patients is observed during exercise execution when increasing difficulty.

Discussion/Conclusion: Kinect V2 represents an example of how motion capture technology can overcome the difficulties of implementing exergaming routines for home care of hemophilic patients, improving motivation and allowing a specialist to receive periodic joint mobility reports.

Disclosure of Interest: None declared.

P026 | Tolerability of knee and ankle exercises with machines and elastic resistance in patients with severe hemophilia

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Introduction: Knees and ankles are a common target in therapeutic strength training programs for people with severe hemophilia. These two joints are typically trained by using constant load machines. However, the use of machine-based exercises difficult home-based training. Alternatively, elastic bands are portable, but still need validation as a tolerable way of performing lower-body training in patients with severe hemophilia. Hence, the purpose of the study was to evaluate tolerability of lower-body exercises with elastic resistance and machines in these patients.

Methods: Twelve adults with severe hemophilia A and B (age 34 ± 9 years; height 173 ± 9 cm; body mass 74 ± 18 kg; body fat

percentage 20 ± 8 %) participated. Two days before the experimental session, the participants received a video with the exercises that had to be performed. The experimental session was conducted after receiving the prophylactic treatment. During the experimental session, after a warm-up, two exercise were performed knee extension and ankle plantar flexor at 6 on the Borg CR-10 scale and with two conditions each exercise (elastic bands and machines). Participants performed 3-6 light intensity reps to warm-up and then 3 reps were performed with each condition. Participants were asked to rate how tolerable was each individual condition, according to a scale ranging from "very tolerable" to "not tolerable".

Results: The machine-based knee flexion was considered "very tolerated" by 38.46%, "tolerable" by 46.15%, "neutral" by 7.69% and "little tolerated" by 7.69% of the patients. The elastic-based knee flexion was considered "very tolerated" by 53.85%, "tolerable" by 30% and "neutral" by 15.38% of the patients. The machine-based ankle plantar flexion was considered "very tolerated" by 38.46%, "tolerable" by 46.15%, "neutral" by 7.69% and "little tolerated" by 7.69% of the patients. The elastic-based ankle plantar flexion was considered "very tolerated" by 58.33% and "tolerable" by 41.67% of the patients.

Discussion/Conclusion: Both load-variations are generally well tolerated. However, elastic-based exercises have greater tolerability rates to perform the ankle plantar flexion exercise and also provide a greater rate of high tolerability for the knee extension exercise. Because of the individual variation, planning should be based on individual tolerance to intensity.

Disclosure of Interest: None declared.

P027 | The clinical effectiveness of intra articular injections (IAI) in patients with hemophilia (PWH)

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Introduction: Hemophilic arthropathy is a significant musculoskeletal complication in patients with hemophilia (PWH). Intra-articular injections (IAI) containing viscosupplementation (VS) and/or corticosteroids, have been considered efficacious in the management of patients with degenerative joint disease. However, the clinical effectiveness in PWH is yet to be determined. This study aims to determine the efficacy of IAI in PWH on pain, joint health and function.

Methods: Patient medical records since 2013 from a single UK Haemophilia Centre were retrospectively reviewed to identify patients who had received IAI. Retrieved data included injection type, repeat injection rate, together with pre and 1 year follow-up measures of pain (10 point visual analogue scale [VAS]), clinical joint health of injected joint (joint specific hemophilia joint health score [HJHS]), patient reported function (Haemophilia Activities List [HAL]) and annualized bleed rate (ABR).

Results: Ten patients (mean age 41.5 ± 13.75 years) with moderate to severe hemophilia, received a palpation guided intra-articular injection (12 ankles, 2 knees) of corticosteroid only (n = 7) or corticosteroid with VS (combined) (n = 7). Significant improvement ($P < .05$) in ABR (mean difference, 1.40), pain VAS (mean difference, 3.72) and joint specific HJHS (mean difference, 0.97) were observed at 1 year when compared to pre-injection scores. No difference was found in lower limb components of the HAL. Patients who received the combined IAI demonstrated significantly ($P < .05$) greater improvements in pain VAS (mean difference, 1.73) and HJHS global gait score (mean difference, 0.6) when compared to those who received only corticosteroid. No patients underwent any orthopedic surgery; however four of the corticosteroid only group required a further IAI within 1 year.

Discussion/Conclusion: This retrospective study suggests that IAI is a safe procedure in PWH and has a significantly positive impact on pain (VAS), joint health (HJHS) and ABR although this was not accompanied by an improvement in patient reported function (HAL). Furthermore, the combination of viscosupplementation and corticosteroid may have additional benefit. A randomized controlled trial of IAI for PWH is warranted to determine the clinical efficacy and cost effectiveness, together with ascertaining the patient groups that would gain maximum benefit from this type of intervention.

Disclosure of Interest: None declared.

P028 | The uses of hypnosis with people with hemophilia

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Introduction: A birth of a baby with Hemophilia is a traumatic and stressful event for his parents. As the child grows, both the child and his family need to cope with the ongoing treatment and complications of the Hemophilia as well as the anxiety regarding the child's future. One of the central objectives of therapy with people with Hemophilia (PWH), as well as their families, is to improve their ability to cope with the pain, the stress, the anxiety, the depression and the pessimism. Hypnosis was found to be one of the most efficient methods and techniques for achieving that objective. Following will be presented a summary of the types of hypnosis - formal and Ericksonien, and the different stages of hypnosis. In addition, a description and demonstrations will be presented of the special and different uses of hypnosis with children, adolescents, adults and parents in an individual as well as in a group therapy.

Methods: A variety of hypnotic techniques were used in an individual as well as in support groups' psychotherapy and group psychotherapy settings. The hypnosis used was formal and non-formal and was used with PWH aged 8 to 72.

Results: In the last 20 years we have developed and utilized hypnotic techniques in order to help PWH improve their abilities to cope with their medical condition (pain, urinary retention, gag reflex etc.) as well

as psychological situations (stress, depression, helplessness etc.) and to improve their quality of life.

Discussion/Conclusion: We found that PWH can benefit from hypnosis. They can be helped by hypnosis to improve their abilities to cope with medical as well as psychological situations and improve by that their quality of life. Hypnosis should be used more often with PWH. Medical care givers as well as PWH should be more aware of the potential of hypnosis and its benefits.

Disclosure of Interest: None declared.

P029 | Multidisciplinary comprehensive care at the Israeli hemophilia center - a unique case of hemophilic woman and her hemophilic son

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Introduction: Over 670 Hemophilia A and B patients are being treated at the Israeli National Hemophilia Center. Treatment starts from the moment of diagnosis, which occurs at a very young age, and continues throughout the rest of their lives. Our center provides comprehensive care by a multidisciplinary team of healthcare professionals,including specialists in hematology,pediatrics, orthopedic surgery,infectious dis eases,nurses,psychologist,physiotherapist social worker,study coordinators and a genetic counselor.

Methods: LV a 30 year old woman,was diagnosed at infancy following recurrent knee hemartrosis with severe Hemophilia A, due to FVIII intron 22 inversion mutation with extreme lionization. As a multidisciplinary team, we were in contact with LV's family from kindergarten age through the years. We were there beside her in good times and bad times,watching her growing up, developing into a teenager and then a young woman, later getting married and divorced, during her pregnancy and delivery, performed as Cessarian section supported by FVIII replacement , tranexamic acid and local hemostatics . We helped her in caring for the newborn, saw how he grows, develops and helped her cope not only with her serious illness but also with the same illness of her son.

Results: In the musculoskeletal aspect, LV needed constant physical therapy treatment for recurring bleeds in a knee that became a target joint. Her son received his first FVIII infusion for circumcision at the age of 8 days,started regular prophylaxis at the age of 10 months and received treatment as well for bleeds in the knee and ankle. Both receive hydrotherapy as an integral part of their treatment and for their future activities in the pool. Recently,as part of the aquisition of independence, after constant training of our team L.V. has learned to infuse her son, three times a week in the morning before he goes to kindergarten. Now' LV's son is 3 years old, he began to attend kindergarten, our multidisciplinary team were part of his assistant's education in the kindergarten. L.V. started working, attending support groups for parents and is trying to build her independent future career.

Discussion/Conclusion: While medical care has always been important, the administration of multidisciplinary team support was crucial for her development and for the success of her therapy.

Disclosure of Interest: None declared.

P030 | Health related quality of life, developmental milestones and self-esteem in young adults with congenital bleeding disorders

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Introduction: The treatment of congenital bleeding disorders (CBD) has improved in the last decades. However, the effect of growing up with CBD on developmental, emotional and social aspects is understudied. Therefore, this study assesses HRQOL, developmental milestones and self-esteem in Dutch young adults (YA) with CBD compared to (healthy) peers.

Methods: Ninety-five YA (18-30 years) (78 men; Mean 24.7 years, SD 3.5) and 17 women (Mean 25.1 years, SD 3.8) with CBD (hemophilia A/B, von Willebrand Disease or other severe CBD) completed the Pediatric Quality of Life Inventory Young Adult version, the Course of Life Questionnaire and the Rosenberg Self-Esteem Scale. Differences between patients with CBD and peers, and between hemophilia severity groups, were tested using Mann Whitney U-tests.

Results: YA men with CBD (89% hemophilia A/B, 8% vWD and 3% other CBD) report a slightly lower HRQOL on the total scale, physical functioning and school/work functioning and a lower self-esteem in comparison to healthy peers (small effect sizes). In contrast, YA men with CBD achieved more psychosexual developmental milestones than peers, but show a delay in "paid jobs during middle and/or high school". YA men with severe hemophilia (51%) report more problems on the physical functioning scale than non-severe hemophilia (49%). In YA women with CBD (6% hemophilia A/B, 59% vWD and 35% other CBD), no differences were found on any of the outcomes in comparison to peers.

Discussion/Conclusion: This study demonstrates some impairments in HRQOL and self-esteem in YA men with bleeding disorders. Monitoring HRQOL of YA and self-esteem is warranted in daily clinical practice, especially with regard to physical and professional/school functioning.

Disclosure of Interest: None declared.

P032 | Case of victimity in a patient with hemophilia

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Introduction: Victimity - the acquisition of physical, mental, social traits predisposing to the acceptance of the victim's role(frequent situations of an accidents, crime, etc.). Victim personality is the carrier of psychopathological features, which under certain external circumstances can contribute to the manifestation of victim behavior.

Methods: Reviewed the case of patient N., hemophilia A, severe course, focusing on behavioral features and diagnosis of mental disorders in the patient

Results: Born from a normal pregnancy and childbirth, developed by age (1 year-was diagnosed with "Hemophilia-A"). Despite the parents' prohibitions, he played in court games, football, knight tournaments (getting abrasions, injuries). In the puberty his character changed became more rigid, conflictful, not tolerate injustice. In 12 year. took part in Greco-Roman wrestling club, hided his illness from the coach. At this time, his father leaved family, the patient decided to be a protector of the relatives. He was engaged in football, martial arts (fights without rules) where was seriously injured (severe craniocerebral injury). Over time, he became more aggressive, conflictful, intolerant to someone else's opinion. He often alcoholized. He entered to the National Research Center for Hematology (Moscow, Russia) 11.11.2016 with "subacute subdural hematoma of the left hemisphere", after a street incident "where he was "unjustly offended". Examination of the patient consciousness, contact is difficult due to total aphasia, inadequate, aggressive, restless. Partially understands the spoken speech, selectively follows the instructions. With CT of the brain from 11/11/2016 (subdural hematoma on the convectional surface of the left hemisphere of the brain). 25/11/2016 - neurological status positive dynamics, regress of the neurological deficit. Patient in consciousness, contact, oriented satisfactorily, speech disorders are not present.

Discussion/Conclusion: We distinguished 4 types of victimity: (1) Paranoial ("restore justice", hypoparanic traits isolation, distrust, rationalism). (2) Dissociative (underestimate the dangers of the situation); (3) Dissocial (injured as a result of their active actions, conflicts with others. 4. Dependent (no resistance, counteraction to the criminal incapable of resisting). We consider previous patient behavior as a victim behavior in dissociative reactions (dissociative type of victimity) in a schizotypal personality.

Disclosure of Interest: None declared.

P033 | Improvements in health-related quality of life in adult hemophilia b patients after receiving SP-9001 gene transfer

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Introduction: Despite available hemostatic therapies, studies have demonstrated the significant psychosocial impact of hemophilia in terms of reduced health-related quality of life (HRQoL). We previously reported sustained factor IX activity (FIX:C) in hemophilia B patients following adeno-associated virus (AAV) factor IX gene transfer that eliminated or reduced bleeding events in all subjects. We sought to evaluate sustained factor IX activity (FIX:C) following gene transfer may result in improvements in HRQoL.

Methods: Ten male adult (ages 18-53 years) hemophilia B patients (baseline FIX:C ≤ 2 IU/dL) received a single 5 x 10^{11} vg/kg infusion of *SPK-9001*, an investigational AAV gene transfer product. HRQoL was assessed by the generic EQ-5D/EQ-VAS and hemophilia-specific Haem-A-QoL questionnaires pre-vector (baseline) and post-vector (weeks 4, 12, 26 and 52) infusion. Differences were calculated from baseline (B) to post-vector (PV recent follow-up assessment). Minimal clinically important differences (MCID) for evaluating subject-level HRQoL improvements and responder definitions (RDs) of the Haem-A-QoL domains and EQ-VAS were estimated based on the one-half standard deviation criterion at baseline. Proportions of HRQoL Responders were then calculated.

Results: Nine of 10 subjects have completed 52 weeks of follow-up after gene transfer (mean age 33.7 ± 13.6 years) with a mean FIX:C at PV of 34.9% (Median 30; range 12-78). All participants reported good HRQoL in the EQ-VAS with significant improvement PV (B M = 78.0 ± 4.4 vs PV M = 88.25 ± 5.9; $P < .001$). Significant mean improvements from B to PV were found as well for the Haem-A-QoL domains "Future" ($P < .005$), "Treatment" ($P < .008$), and "Total Score" ($P < .001$). At baseline, 22% "never" feared that "their condition will be worsening" and 60% "always/often" "felt dependent on factor concentrates" compared to 100% ($P < .003$) at PV and 0% ($P < .0001$), respectively. All patients (100%) were HRQoL responders according to the RDs of the Haem-A-QoL "Total Score" (3.9-point decrease) and 77.8% according to the RDs of the EQ-VAS (4.2-point increase).

Discussion/Conclusion: Improvements in Haem-A-QoL domains "Treatment" and "Future" and "Total Score" support a single infusion of SPK-9001 resulted in meaningful HRQoL improvements. These prospective data represent the first assessment of HRQoL measures in hemophilia patients following gene transfer.

Disclosure of Interest: S. Von Mackensen Consultant for Spark Therapeutics, L. George Shareholder of Spark Therapeutics, S. Sullivan

None declared, A. Giermasz None declared, J. Rasko None declared, M. Carr Shareholder of Spark Therapeutics, Employee of Spark Therapeutics, K. High Shareholder of Spark Therapeutics, Employee of Spark Therapeutics.

P034 | Psychometric validation of the child-adapted hep-test-q instrument for the assessment of subjective physical functioning in children with hemophilia

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Introduction: Thanks to prophylaxis children with hemophilia in the Western world can participate in sport and are encouraged to undertake physical activity. For the assessment of subjective physical functioning, standardized and validated instruments are necessary, being feasible for children. Aims were to adapt the adult version of the HEP-Test-Q for children (6-17 years) and to psychometrically test it in the context of different studies.

Methods: In discussion rounds with 5 children the items of the adult HEP-Test-Q were reformulated better comprehensibility for children without changing the content of the item concept. This child-adapted version was then pre-tested (including preliminary psychometric testing, feasibility testing, cognitive interview) in 34 children from the US, UK and Germany. The revised version was pilot-tested and field-tested in the context of the EIS Study (n = 67) and the SO-FIT Study (n = 127), respectively.

Results: *Pre-testing* revealed that the completion time was 8.2 ± 4.1 minutes and children liked the instrument. Cognitive interviews demonstrated that most items were easy to understand and that 9 items had to be reformulated. *Pilot-testing* demonstrated that the child-adapted version had good psychometric characteristics in terms of reliability ($\alpha = 0.936$ Total Score) and validity. Convergent validity testing showed moderate correlations with the Haemo-QoL ($r = -.491$). Known groups validity revealed significant differences between clinical subgroups for chronic pain ($P < .002$) and target joints ($P < .021$). *Field-testing* confirmed the previously found psychometric characteristics; Cronbach's alpha ranging from $\alpha = 0.801$ ("endurance") to $\alpha = 0.935$ (Total Score). The child-adapted version of the HEP-Test-Q showed moderate correlations with subjective questionnaires PedHAL ($r = .634$, $P < .0001$) and Haemo-QoL SF ($r = -.575$, $P < .0001$) and low correlation with the objective HJHS ($r = -.323$). Known groups validity testing proved that the HEP-Test-Q was able to discriminate between different clinical subgroups (OJS $P < .006$, BMI $P < .015$, target joints $P < .0001$, type of prophylaxis $P < .038$, pain $P < .0001$).

Discussion/Conclusion: The child-adapted HEP-Test-Q is a short, well accepted and practical instrument for the assessment of subjective physical functioning. Outcomes can be compared to adults since item concepts are identical to the adult version.

Disclosure of Interest: None declared.

P035 | Vein training young people with hemophilia-toward establishing guidelines

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Introduction: While factor replacement treatments allow children with hemophilia to lead near normal lives, these treatments can be difficult to administer and learning to access one's own veins is necessary. Accessing veins can be painful and result in children attempting to avoid treatment, and refusing to begin the process of learning self-venipuncture. These types of compliance problems are prevalent during adolescence and it is important to train for self-venipuncture before difficulties begin to emerge.

Methods: Draft guidelines on vein training for young people and their families were developed by core members of the hemophilia team. The aim was to create a standard pathway of care for those beginning their vein training journey. These guidelines are being used as part of the vein training program for young people with hemophilia.

Results: The guidelines recommend that vein training should be a flexible and individualized collaborative process which has 3 broad stages: Stage 1 Assessment/ Planning - assess readiness / explore possible barriers; Stage 2 Active training - begin vein training program; Stage 3 Fine tuning skills –build confidence/trouble shooting Vein training is a process rather than a static, "before and after" event. Planning for vein training should begin when the child is a pre-adolescent either before secondary school or in the early stages (aged 8-13 years). A young person, their parents and professionals should work together as a team**.** The young person should work with the same trainer. The process should be regularly reviewed and evaluated by the team with the young person and their parents.

Discussion/Conclusion: These guidelines provide a standard framework for the process of moving toward independent self-venipuncture. The experience of vein training from the child's perspective is anecdotal. Our next step is to determine the views and concerns of children and adolescents with hemophilia in relation to their experience of vein training. The objective is to use this information to further advance our guidelines and practice.

Disclosure of Interest: None declared.

P036 | Screening for inhibitors development and it's risk factors in patients with severe hemophilia a in Oman

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Introduction: A major challenging complication of factor VIII replacement therapy is the development of neutralizing antibodies, rendering therapy ineffective. There are recognized genetic and non-genetic risk factors for inhibitors development. This study aims to screen for the prevalence of inhibitor development among Omani patients with severe hemophilia A and to define its non-genetic risk factors that might help to develop prevention protocols.

Methods: A Retrospective cohort study that includes all patients with hemophilia A registered in Oman. Data were collected using hospital information system computerized data. Patient's demographic data MRN, age at diagnosis, age at first treatment, date of the first documented inhibitor development, & data on non -genetic risk factors such as, mode of treatment (on demand vs prophylaxis) type and dose of the concentrate, time interval of exposure to factor VIII till inhibitor development, previous surgeries or major bleeding events or blood transfusion; were included. Missing data were collected through phone interviews whenever possible.

Results: Out of the 156 patients registered in Oman, 78 patients had complete data. The age of inhibitor development ranged between 16 months and 21 years (109.4 + 79.9 months). The prevalence of inhibitors among our patients was 35% and mainly of low titer 87%. There was a significant correlation between the intensity of first treatment and inhibitor development ($P < .05$). Inhibitor development was not associated with type of the factor used, time interval of exposure to factor VIII, use of on-demand or prophylaxis regimen and history of major bleed or previous surgery.

Discussion/Conclusion: Inhibitors development is a major complication in patients with hemophilia A in Oman. The reported prevalence matches the international reported figures. A larger scale study that includes all the registered patients and their genetic mutation is needed.

Disclosure of Interest: None declared.

P037 | Effects of hemarthrosis on postural balance in children with hemophilia A

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Introduction: Children with hemophilia often bleed inside joints and muscles, which may impair postural adjustments. In this study, we aimed to investigate the effect of joint hemorrhages on the postural balance of our hemophilia patients

Methods: We enrolled 38 patients with severe hemophilia A who were diagnosed with hemophilia A (factor VIII deficiency) in the Pediatric Hematology Polyclinic and 39 healthy control subjects aged 5-18 years without a chronic disease (musculoskeletal system, neurological deficit). Patient was equipped with a device (Prokin 254, Pro-kin software reliability, TecnoBody S.R.L, Dalmine, 24044 Bergamo, Italy) which is a posturographic balance platform in which rehabilitation related exercises can be performed to develop these senses in which sense of stability and feeling of proprioception can be tested in each direction. The patient was told to remain motionless for 30/60 seconds (sec), gazing at a point directly opposite the eye. He was told to remain in motionless with a closed eye for 30/60 seconds after the eye was kept open. After the time elapsed, the device gave the results of the patient's front-to-back, left-to-right oscillation lengths, velocities, and the result that the device scans an area of oscillations while oscillating. The results of Hemophilia patients and healthy children from the same age and sex group were compared and the sense of balance in hemophilia patients was evaluated.

Results: In the data after static balance measurements; Forward – Backward Standard Deviation, Medium – Lateral Standard Deviation, Average Forward – Backward Speed (mm/s), Average Medium – Lateral Speed (mm/s), Area (Ellipse Area) (mm2); There was a significant difference between Hemophilia Group and Control Group ($P < .05$)

Discussion/Conclusion: The results show that patients with hemophilia have a lower postural balance than the control group. However, it is necessary to improve the balance of activities that aim to improve the joint and muscle proprioceptive system in these patients.

Disclosure of Interest: None declared.

P038 | Hemophilia B and essential thrombocythemia: A case report

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Introduction: Essential thrombocythemia (ET) is myeloproliferative neoplasm characterized by thrombocytosis; other disease features include thrombosis and bleeding. Hemophilia B (HB) is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor IX. We diagnosed this two rare entity in a patient. Diagnose was simple but treatment and follow up period wasn't.

Methods: All these values of FIX:C were measured using APTT-based one-stage clotting assay.

Results: A 49 year old, mild HB male patient admitted to our hematology polyclinic with complaints of pain in his right arm and right upper quadrant. Physical examination revealed swelling and redness on his right arm. Also we obtained splenomegaly. Hemostatic tests indicated prolonged activated partial thromboplastin time (APTT) to 107.8 sec (norm 26-36 sec), decreased factor IX activity to 6% (norm 50-150%)

and factor IX inhibitor titer was lower than 0.3 Bethesda Units/mL (BU/mL). A full blood count showed a thrombocythemia (2238 x 10^9/L platelets), without any evidence of a reactive cause. Ristocetin cofactor assay was 57% (normal range 55%-200%) . Ultrasonography of the leukomotor system revealed intramuscular hemorrhage (3 × 3 cm) and spleen size was 16 cm in the abdominal ultrasonography. Bone marrow biopsy was done and showed large clusters of megakaryocytes with considerable variation in cell size and lobulation of the nucleus. No bcr/abl chimeric transcript was demonstrated by polymerase chain reaction. JAK2-V617F mutation was positive. He was diagnosed as ET and received low dose aspirin (100 mg/day) and hydroxyurea 1500 mg daily. His platelet count fell gradually to 350 x 10^9/L on the 21st day. And intramuscular bleeding was controlled by factor replacement therapy.

Discussion/Conclusion: Hemophilia B and essential thrombocytosis are not found together in the literature. With the increased life span in hemophilia patients, arterial and venous thromboembolism are detected, but there is no evidence based treatment guidelines for these patients. Antiplatelet /anticoagulant therapy in hemophilia patients can be performed by appropriate factor replacement if necessary. When considering anticoagulant or antiplatelet therapy in patients with inherited bleeding disorders, bleeding phenotype of the patient, characteristics of the anticoagulant, intensity of anticoagulant therapy, and duration of planned therapy must be evaluated.

Disclosure of Interest: None declared.

P039 | Personalized prophylaxis in patients with hemophilia in Argentina

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Introduction: Prophylaxis with factor FVIII is considered the gold standard for managing hemophilia A patients without inhibitors to preserve normal musculoskeletal function. Pharmacokinetic (PK-tailored prophylaxis) have been proposed in order to optimize the dose and frequency of rFVIII with the benefit of improving treatment adherence given the fact that long-term medical regimens are especially challenging. FVIII half-life is one of the most significant variables for tailoring prophylaxis; standard determination requires almost ten blood sampling. The use of Bayesian models to predict PK parameters has shown promise in this context, by reducing the number of samples needed to predict and tailor the best dose for each patient.

Methods: Find out through PK-tailored prophylaxis whether the patients receiving the adequate dose for maintain them with a trough level above 1 %. Thirty four patients with severe hemophilia A in prophylaxis treated with Octocog alfa rFVIII were evaluated. They were divided according the dose regimen in three groups low doses (<20 IU/kg), standard doses (20-40 IU/kg) and high doses (>40 IU/kg). Dosage of FVIII was done by one-stage coagulometric method in Coagulometer ACL TOP 300 (Instrumentation Laboratory). myPKFiT tool was used to find out whether currently dose is suitable for keep patient with trough level above 1% all the time or not with dosage interval of 72 h.

Results: In 34 patients evaluated, the groups were setting up as follows low doses 11.7%, standard doses 76.4% and high doses 11.7%. All treated subjects were male and their mean age was 41.8 years (14-72). Mean weight 75.8 kg (47-120). Mean Half-Life 13.4 hs. Mean dose received before PK evaluation was respectively in groups High, standard and low 45 IU/kg, 26 IU/kg, 15 IU/kg. PK evaluation was performed, with a target trough level above baseline 1% and dosing interval of 72 hs. After that the recommended doses were the following, respectively in groups High, standard and low 33 IU/kg, 25 IU/kg, and 35 IU/kg.

Discussion/Conclusion: In our experience PK-tailored prophylaxis was useful to achieve a more accurate dose in order to maintain patients all the time with trough level above baseline 1%. This tool could potentially improve the resources management in a country with economical constrains like Argentina making the prophylaxis a cost effective treatment.

Disclosure of Interest: None declared.

P040 | Impact of multiprofessional care on the follow-up of patients with hemophilia in Brazil

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Introduction: The Ministry of Health established in 2012, Primary Prophylaxis Program(PPP) for patients with hemophilia A and B (HA and HB). It emphasized the importance of multidisciplinary team in follow-up of these patients. These patients are followed in our hemophilia center, a public institution, by hematologists, dentist, psychologist, nurses, pharmacist and a social worker.

Methods: 25 patients with HA and 2 with HB, with <2% of factor VIII and IX respectively are being followed. Of the 25 patients with HA, 18 started PPP and 7 were on demand because they haven't yet met criteria, and the two patients with HB have already started it. We evaluated in this study, adherence to treatment, venous access and infusion of coagulation factors, number of joint bleeds and joint impairment, school attendance and interaction with other children

Results: Regarding adherence to treatment, 26/27 patients had good adherence and follow guidelines regarding storage of coagulation factor at home. We have trained 20 families for home infusion. Seventeen of those are doing it (three mothers haven't started yet due to insecurity). As to 7 remaining patients, 6 had recently been diagnosed and haven't yet been trained. One family was not trained due to low adherence to treatment. Regarding joint health, 25/27 patients were

followed and 3/25 presented inhibitor. 17/22 patients did not present any joint bleeding last year, 4/22 presented few bleeding episodes (AJBR 1) and 1/22 had more than 3 hemarthroses. Of the 3 patients who developed inhibitors, 01 developed a target joint. Regarding oral health, we evaluated 18/27 patients; 15/18 of them have good oral hygiene and no cavities. Of the 9 remaining patients, 4 were recently diagnosed, 4 lived in the countryside and 1 presented no compliance to treatment. 26/27 patients had a good adherence to the program and followed the guidelines. As for school attendance, 19/27 patients were evaluated. Fifteen out of 19 patients haven't developed inhibitor. 14 attend school and only 1 has school problems. The remaining 4 had inhibitor, only 1 attends school and occasionally misses classes due to few bleedings

Discussion/Conclusion: The multidisciplinary approach in this pediatric group showed an increase in treatment adherence, reduction of school absences and prevention of arthropathies, even in a countries having scarce financial resources such as Brazil

Disclosure of Interest: None declared.

P041 | Bleeding risk in hemophilia patient undergoing antithrombotic therapy, results of the ehrea multicentric study

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Introduction: Life expectancy in patient with hemophilia (PWH) has greatly increased during the last decades, leading to age related diseases, amongst which cardiovascular diseases bear a singular problem in therapeutics. Antiplatelet (AP) and oral anticoagulants (OAC), used in many of such diseases, should augment the bleeding advent, yet no studies compared their long-term bleeding impact in PWH and current recommendations are based on expert's opinion.

Methods: Here we report a multicenter national study on prospective and retrospective data comparing the frequency of bleeding events in PWH under AP or OAC. Primary onset was to evaluate their impact in term of bleeding frequency during the last 12 months. Secondary onsets were frequency of severe bleeding events (defined as requiring substitutive therapy, hospitalization or leading to death), long term stent outcome, atrial fibrillation related embolisms and impact of cardiovascular classical risk factors (CRF).

Results: Amongst the 663 screened PWH aged > 50 years old, 220 were included, with 33 undergoing AP (28), OAC (3) or both (2). These 33 patients were compared to 66 PWH matched on age and disease severity without any AP or OAC. CRF were not different than those previously published (). A long-term prophylaxis during the course of AP treatment was performed for all 4 severe PWH while only in 1/3 moderate PWH. Interestingly, both others had no increased bleedings. Bleeding frequency was similar in patients with and without AP or AOC ($P = .85$). In contrast, severe bleedings were significantly more frequent in patients with AP/OAC (7 vs 3 $P = .014$), even in mild PWH (5). No significant risk factors of severe bleedings including basal factor VIII/IX levels in non-severe PWH, were found. However, age and increased bleeding frequency showed a trend to predispose to severe bleedings ($P = .2$ and $P = .07$ respectively).

Discussion/Conclusion: This study underlines that most mild PWH under AP/OAC do not suffer from increased bleeding frequency but some experienced severe bleeding. Current recommendations proposing long term prophylaxis for all mild PWH under AP might not be accurately adapted but larger studies are necessary to conclude. Furthermore, potential markers of hemorrhagic risk other than basal factor VIII/IX levels such as global hemostasis assays or bleeding scores should be evaluated.

Disclosure of Interest: None declared.

P042 | Comparative assessment of the performance of pharmacokinetic tools for prophylactic dosing of factor VIII concentrate in patients with hemophilia A

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Introduction: Population pharmacokinetic (PopPK) based dosing is an effective way to ensure that FVIII plasma activity levels remain above a desired target. Currently, two PK-based dosing tools are available that can individualize FVIII prophylactic therapy with factor VIII.

Objective: To compare the PK parameter outputs and dosing estimates of two PopPK-based dosing tools and to compare these outputs to a two stage PK analysis.

Methods: Infusion and postinfusion measurements were extracted from the WAPPS database. The same data were analyzed using WAPPS v3.0, the Advate® model (2CO_2_V0, built by externally validating and updating the Bjorkman published model), myPKFiT v2.0 (web-based Bayesian algorithm), and compartmental analysis in WinNonLin. For each case and for each approach, we reported (1)

success of fitting, (2) clearance (CL; dL/h/kg), (3) volume at steady state (VdSS; dL/kg), (4) FVIII half-life (HL; hours), and (5) time to 0.01 above baseline IU/mL (hours). We also generated dosing estimates according to a 48 hour dosing schedule and a target trough of 0.03 IU/mL. A two tailed t-test was used to assess for differences in dosing estimates.

Results: 232 patients on Advate were found in the WAPPS database, of which 42 had post-infusion samples at 4 ± 2, 24 ± 4, and 48 ± 6 hours and were dosed with 50 ± 5 IU/kg of FVIII. The best fit using a two stage approach was a two compartment model on 9 patients (CL 0.037, 0.026 – 0.043; HL 11.2, 11.1 14.4) and a one compartment model on 16 patients (CL 0.019, 0.016–0.023; HL 9.9, 9.3 – 10.5). Clearance, volume of distribution, half-life and time to 0.01 IU/mL were not different between the two systems. The estimated dose requirement was 1969 (1368 – 2310) for WAPPS and 2394 (1684-2954) for myPKFiT; $t(23) = 3.302$, $P = .003$.

Discussion/Conclusion: Differences in PopPK individual estimates between WAPPS and myPKFiT are on average small and nondirectional. The lower dose estimates from WAPPS were similar to those determined using a NONMEM implementation of the Bjorkman et al 2012 model and similar patients [1939 IU (985–3824)] (van Moort et al. ISTH 207 Congress. ASY 27.3). Prospective studies are required to assess the clinical implications of adopting different PopPK solutions.

Disclosure of Interest: None declared.

P043 | Comparison of three assays for measuring factor IX

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Introduction: The development of new factor IX (FIX) concentrates for the treatment of hemophilia B induced new challenges with regard to monitoring. Indeed, discrepancies have already been identified between one-stage assays and chromogenic assays for some extended half-life FIX concentrates. Comparison of two chromogenic assays (BIOPHEN FIX and ROX Factor IX) for factor IX activity determination with a one-stage clotting assay using SynthASil reagent.

Methods: Factor IX activity was measured in duplicate for each sample on ACL TOP 700 (Werfen, France). Plasma was spiked with different therapeutic products [nonacog alfa (BeneFIX®), pdFIX (Betafact®), eftrénonacog (Alprolix®)] in order to obtain three concentration levels (5%, 20% et 90%). Three plasmas of hemophilia B patients treated with albutrepenonacog alfa (Idelvion®), were also evaluated. For these plasma samples, concentrations had previously been established by a one-stage assay at 7%, 12% and 28%. Three External Quality Controls (EQC) were also analyzed ECAT 17.33, 16.20 and 16.21.

Results: Given the results of our tests, we were able to conclude that all three methods are correlated ($P < .05$, and average biases were between -1.79% (SynthASil vs ROX Factor IX) and −0.207% (BIOPHEN FIX vs ROX Factor IX), in accordance with the GFHT 2014 recommendations. No significant discrepancy was observed between the results obtained with EQC, and all results were close to expected values. For each product tested, e.g. plasma-derived, recombinant or extended half-life, no significant discrepancy was observed between the three methods ($P > .05$).

Discussion/Conclusion: Our study suggests that all three assays are equivalent for monitoring hemophilia B patients treated by BeneFIX®, Betafact® or Alprolix®. More data is needed for Idelvion®.

Disclosure of Interest: None declared.

P044 | Hepatic long-term factor VIII expression in hemophilic a mice after amniotic stem cells transplant

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Introduction: Mesenchymal stem cells have the capacity to express Factor VIII (FVIII). Recently, it has been demonstrated that human fetal mesenchymal stem cells are also able to produce von Willebrand factor (vWF) and present tolerance and low immunogenicity. Our objective was to evaluate the murine amniotic membrane fetal stem cells (mAMSCs) transplant from healthy subjects into immunocompetent hemophilia A (HA) mice and its effect on the hepatic expression of FVIII.

Methods: The mAMSCs were isolated from C57BL/6 GFP^+ pregnant mice. The expression of FVIII and vWF in the cultured cells was analyzed by RT-PCR, qPCR and immunofluorescence. mAMSCs GFP^+ were transplanted intraportally (n = 38) and intraperitoneally (n = 37) in HA mice. The animals were sacrificed after 1, 2, 4 and 8 weeks, and after 6 and 12 months. The expression of FVIII light chain in the transplanted livers was studied by RT-PCR, and the localization and presence of the cells and FVIII in the hepatic tissue by immunofluorescence and confocal microscopy.

Results: mAMSCs GFP^+ showed a positive expression of FVIII and vWF at mRNA and protein levels. FVIII mRNA expression in the transplanted livers was observed in the 40% of the intraportally infused mice since week 2 to 1 year post-transplant. The intraperitoneal infusion shows a 50% positive mice at 6 months, but none at 1 year. In the studied transplanted livers it was possible to find the presence of GFP^+ cells and FVIII expression around the liver sinusoids even 1 year after the intraportal infusion and 6 months after the intraperitoneal transplant.

Discussion/Conclusion: The allogeneic transplant in immunocompetent HA mice results in the survival of the $FVIII^+$ mAMSCs even

1 year after the intraportal infusion and 6 months after intraperitoneal infusion. More broadly, our results suggest that mAMSCs represent a potential source of FVIII interesting for the treatment of Hemophilia A disease. This project was sponsored by *Seneca Foundation of Murcia (15409/PI/10)* and *Carlos III Institute of Health (PI 10/0270)*.

Disclosure of Interest: None declared.

P045 | Use of turoctocog alfa for less-frequent prophylaxis in selected patients has comparable efficacy with the overall prophylaxis cohort in Guardian™2

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Introduction: The guardian™ trial program is investigating the long-term safety and efficacy of turoctocog alfa (NovoEight®), a B-domain-truncated recombinant factor VIII (FVIII) product. guardian™2 (NCT00984126) was a phase 3b non-randomized, open-label, multicentre, single-arm, safety and efficacy extension trial, including previously treated patients (PTPs) with severe hemophilia A (FVIII activity ≤1%) who completed the guardian™1 or guardian™3 trials.

Methods: Male PTPs from 52 sites in 19 countries were included in guardian™2 and placed on either prophylaxis or on-demand treatment. Prophylaxis was administered at 20–50 IU/kg once every second day or 20–60 IU/kg three times weekly, or as less-frequent prophylaxis (LFP), defined as 40–60 IU/kg twice weekly or once every third day. Prophylactic dose was chosen at the discretion of the investigator. Secondary efficacy endpoints included annualized bleeding rate (ABR) during prophylaxis and consumption.

Results: A total of 213 patients were dosed with turoctocog alfa, with 207 treated prophylactically (<12 years, n = 55; ≥12 years, n = 152). Of these, 27 (<12 years, n = 13; ≥12 years, n = 14) were treated with LFP with a mean (standard deviation) of 70.3 (20.7) exposure days. Poisson-estimated mean ABR was 2.01 bleeds/patient/year (95% CI 1.21–3.33) in the LFP group and 2.44 bleeds/patient/year (95% CI 2.06–2.89) in the overall prophylaxis group, with an overall median ABR of 0.00 bleeds/year (range 0.00–9.91) in the LFP group and 1.37 bleeds/year (range 0.00–17.82) in the overall prophylaxis group. Mean per-patient consumption of turoctocog alfa in the LFP group was 5432 IU/kg/year, with a mean dose level of 48.2 IU/kg; respective numbers for the overall prophylaxis group were 5094 IU/kg/year and 32.5 IU/kg. A total of 34 bleeds (2 severe [5.9%]) were reported in 13/27 (48.1%) patients on LFP, compared with 1782 bleeds (221 severe [12.4%]) in 170/207 (82.1%) patients on any prophylaxis regimen; joint bleeds accounted for 91.2% and 74.6% of all bleeds in each prophylaxis group, respectively.

Discussion/Conclusion: The efficacy of turoctocog alfa when used for LFP in selected patients with severe hemophilia A is comparable to that of the overall prophylactic regimen. Less-frequent injections of turoctocog alfa may have the potential to reduce the burden of treatment while maintaining prophylactic effect.

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P046 | CSL627_3001 immune tolerance induction (ITI) sub-study design for previously untreated patients (PUPS) with severe hemophilia a treated with rviii-singlechain

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Introduction: Factor VIII (FVIII) replacement therapy is used to treat or prevent bleeding in patients with severe hemophilia A. Development of inhibitors to FVIII is a serious complication; it can render FVIII therapy ineffective, requiring treatment with bypassing agents. Inhibitors increase mortality, morbidity and disease burden. Previously untreated patients (PUPs) are at highest risk to develop inhibitors, especially before 21 Exposure Days (EDs). Recent studies report 35.4% cumulative incidence within the first 50 EDs. Inhibitor eradication can be achieved with immune tolerance induction (ITI) therapy (regular high-dose FVIII infusions) in 70-85% of patients. Recombinant single chain FVIII (rVIII-SingleChain, AFSTYLA®) is a B-domain truncated construct with a covalent bond between the heavy and light chains. Study CSL627_3001 targets enrollment of 50 PUPs with 50 EDs to rVIII-SingleChain, and allows patients developing inhibitors to attempt eradication with rVIII-SingleChain ITI, based on US guidelines.

Methods: The ITI sub-study enrolls PUPs in CSL627_3001 that develop an inhibitor to FVIII (2 samples with titer ≥ 0.6 BU/mL), unless immunosuppressive therapy is planned. ITI therapy may be delayed if the inhibitor titer is >10 BU/mL, if the patient needs central venous access or in patients with low inhibitor titers and clinical response to

rVIII-SingleChain. Three regimens can be used 50 IU/kg 3x/week, 100 IU/kg/day or 200 IU/kg/day. The regimen intensity may be decreased if inhibitor titer decreases. Bleeding during ITI is treated with rVIII-SingleChain and/or bypassing agents. Patients are assessed monthly for inhibitors and every 3 months for incremental recovery. Therapy continues until there is complete response (2 consecutive monthly inhibitor samples <0.6 BU/mL), or 18 months of ITI without complete response. Patients achieving complete response return to prophylaxis in the main study.

Results: This study will generate exploratory evidence on ITI in severe hemophilia A, enrollment data will be summarized.

Discussion/Conclusion: The ITI sub-study provides PUPs in CSL627_3001 the opportunity to attempt inhibitor eradication, addressing the most important challenge facing these patients during the treatment of hemophilia A.

Disclosure of Interest: S. Lucas Employee of CSL Behring, A. Brainsky Employee of CSL Behring.

P047 | Rare bleeding disorders in Slovakia

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Introduction: The rare bleeding disorders (RBD) are congenital diseases with variable clinical manifestation. Discrepancy between the severity of factor defect and bleeding symptoms is frequently observed, precluding reliable prediction of clinical phenotype in affected individuals. This makes the management of these disorders challenging.

Methods: All congenital coagulopathies in Slovakia are registered in the National registry of bleeding disorders, established in 1974.

Results: Except of persons with hemophilia (n = 590) and von Willebrand disease (n = 665) the registry accounts 1209 individuals with RBDs, among them 770, 71, 46, 35, 3 and 3 patients with FVII, FV, FXI , FX and FXIII and α2-antiplasmin deficiency, respectively. In a group of 290 persons with congenital disorders of fibrinogen one, 90 and 199 individuals have afibrinogenemia, hypofibrinogenemia and hypodysfibrinogenemia, respectively. Evaluation of clinical phenotype in our patients with RBD has confirmed variable bleeding manifestation with a poor correlation with coagulation defect. Genotype analysis was performed so far in 40, 98, 2 and one patient with fibrinogen disorders, FVII, FX and FV deficiency, respectively. In three and two families with dysfibrinogenemia the mutation in *FGA gene* Aa Arg16His and novel mutation Aa Gly13Glu were revealed, respectively. In three and one family with hypofibrinogenemia novel mutations *FGG* Trp3Stop and *FGG* Trp253Cys were identified, respectively. Out of 90 patients with FVII deficiency genotyped, 85% have mutation on exon 8 Ala294Val, 404delC (founder effect). This mutation in homozygous state resulted in severe FVII deficiency <0.01 IU/mL and severe bleeding phenotype 31 females in fertile age (severe menorrhagia, ovulatory intra-abdominal bleeds). FX deficiency was mild in all pats and heterozygous mutations on Exon 8 Glu329Gly and novel mutation Ile269delTCA were demonstrated. Only two of 71 pats have severe FV deficiency <0.01 IU/mL with severe bleeding phenotype, in one of them homozygous novel splice-site mutation -12T/A IVS18 was revealed. In one of 8 severe FXI deficient persons gene defect type II/III Cys128Stop /Phe283Leu was identified.

Discussion/Conclusion: So far low numbers of our patients genotyped preclude to draw out a conclusion about the genotype and phenotype relationships in persons with RBDs. Further study and international registries of RBD´ will enable to evaluate genotype and clinical characteristics and better management of RBDs.

Disclosure of Interest: None declared

P048 | Inherited hypofibrinogenemia and dysfibrinogenemia in Slovakia- a study of phenotype and genotype

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Introduction: Inherited fibrinogen (FBG) disorders represent rare blood coagulation disorders.

Methods: We analyzed clinical phenotype in 91 and genotype in 26 patients with FBG disorders.

Results: In 75 subjects with dysfibrinogenemia (DysFBG) (42F/33M) and median age of 36 y (range 13-88 y) the level of FBG:coag was 0.64 g/L (0.2-1.2 g/L), FBG:Ag 2.7 g/L (2.1-3.9 g/L) and thrombin time of 45s (21-74 s). In this group 40/53%, 31/41% and 6/8% were asymptomatic, had bleeding manifestation and developed thrombosis, respectively. Menorrhagia was present in 12/42 (28.5%) fertile age women. Forty patients underwent 114 surgical operations. Out of 86 surgeries performed without FBG replacement only 6 (7%) operations were complicated with bleeding, in 4 cases fibrinogen replacement was given. One and one patient developed thrombosis in association with FBG replacement due to the bleeding after surgery and delivery, respectively. In a group of 16 persons with hypofibrinogenemia (HypoFBG) (10F/6M) with a median age of 41 y (range 11-68y) the level of FBG:coag was 1.1 g/L (0.7-1.4 g/L), FBG:Ag 1.3 g/L (0.8-1.57 g/L) and thrombin time of 22s (18-31s). Six/38%, 7/44% and 3/18% subjects were asymptomatic, experienced bleeding or thrombosis, respectively. Menorrhagia was present in 2 of 8 fertile age women and 3 females experienced early pregnancy loss with next successful pregnancy without any intervention. One female was heterozygous for FVLeiden and she experienced thrombosis and had 7 still births. Genotype analysis in 20 DysFBG individuals revealed two heterozygous mutations on the exon 2 of the FGA gene 13 individuals from 3 unrelated families had frequent mutation Aa Arg16His

and 9 subjects coming from 2 unrelated families had mutation Aa Gly13Glu. In persons with HypoFBG two novel mutations on FGG gene were identified 6 persons from 3 unrelated families had mutation on exon 1 of FGG gTrp3Stop and one female had mutation on exon 7 of FGG gTrp253Cys. Further analysis of the later mutation demonstrated this mutation to cause a defect of FBG secretion. This patient with FBG level of 0.8 g/L presented with severe postpartum bleeding.

Discussion/Conclusion: The phenotype was variable, even in persons with the same gene mutation, and varied from asymptomatic to mostly mild bleeding symptoms. We were not able to establish the genotype-phenotype correlations nor to predict bleeding phenotype based on the gene mutation.

Disclosure of Interest: None declared.

P049 | Clinical review of pivotal trials on octocog-alfa (Kovaltry®) and other recombinant FVIII in patients with hemophilia A

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Introduction: New recombinant FVIII (rFVIIIs) products were recently approved and devolved to improve the safety and to offer the potential of decreased immunogenicity and longer half-lives, for patients with hemophilia. The aim of this analysis is to critically review and evaluate the efficacy, safety and dosage of rFVIIIs.

Methods: A systematic literature review was conducted using the electronic databases to identify the recent clinical trials on FVIIIs in patients with hemophilia A, published from January 2013 to May 2017. The FVIII products and their related clinical trials retrieved were critically analyzed to identify the main aspects of each product.

Results: Last generations of FVIIIs (including efmoroctocog-α, turoctocog-α, simoctocog-α and octocog-α) provided an important new treatment option for management of patients with hemophilia A. Clinical data were more accurately described and reported in the clinical program of octocog-α (LEOPOLD), compared with other trials. A higher prevalence of patients with target joints (>80%) were enrolled in the LEOPOLD trials. Data from efmoroctocog-α pivotal A-LONG clinical study demonstrated a prevalence of target joints among included patients of 61.8%. Frequency and dose of prophylaxis were determined in all included studies the average weekly octocog-alfa dosages ranged from 84.3 IU/kg to 87.0 IU/kg in LEOPOLD trials. The mean reported dose for efmoroctocog-alfa, turoctocog-alfa and simoctocog-alfa were 85.4 IU/kg, 93.7 IU/kg and 107.4 IU/kg, respectively.

Discussion/Conclusion: The variability in the methods used to report data and the differences patients enrolled in the clinical trials of different FVIII make the comparison among different products often difficult. For example, Octocog-α reported similar efficacy of other products, however in the LEOPOLD program a more critical patient population (high annualized bleeding rate and prevalence of target joints) was enrolled than those in the other studies.

Disclosure of Interest: None declared.

P050 | Use of extended half life factor VIII products in children with severe hemophilia A on prophylaxis: A single centre experience

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Introduction: Multiple IV infusions per week are usually required for prophylaxis of children with severe Hemophilia A (sHA), because of the short half life of the standard FVIII products (SHL). The use of extended half life (EHL) FVIII could reduce the frequency of infusions.

Methods: Analysis of clinical and laboratory data after use of EHL product in children with sHA being on prophylaxis.

Patients/Methods: Inclusion criteria for switching sHA patients from SHL to EHL FVIII, were born between 6/2000-6/2006, frequency of prophy ≥3-7/week or need for intensification, no history of inhibitor development and no participation in other clinical trial. From 31 candidates, 3 adolescents (No 1, 2, 3) were finally selected (11.8, 12.0, 16.5 years old, respectively) to investigate the safety and efficacy of an EHL FVIII (efmoroctocog alfa, Elocta, Sobi).The weekly dose of EHL FVIII given was ≥ equal of that of SHL. FVIII:C levels (aPTT-SP/FVIII deficient plasma IL, ACL TOP) were measured pre and at 30', 3, 24, 48, and 72/96 h post infusion. Trough levels of >1 IU/dL were considered as acceptable.

Results: Prior to switch, two patients were on daily prophylaxis with rFVIII (No 1 3.500 IU/week for the previous 14 months, elevated to 7.000 IU/week, due to recent bleed into (L) ankle, having had operated with Ilizarov technique 20 months ago, and No 3 3.500 IU/week, planned to be elevated to 5.250/week), with FVIII:C trough levels maintained >3-8 and >1 IU/dL, respectively. Annual bleeding rate (ABR) during the last 12 months was 1/patient. Prophylaxis with EHL FVIII every other day, 1.500 IU/dose for each patient was initiated. Patient 2 was on 500 IU X3/week, with SHL FVIII (trough levels 2-3 IU/dLand ABR:zero). EHL FVIII was given 2/week), 1.000 IU/dose. For all three patients, peak FVIII:C levels ranged 47-81 IU/dL post EHL FVIII infusion, whereas mean levels at 24 and 48 h were 18 and 5 IU/dL, respectively. Patient 2 maintained 3 IU/dL as FVIII trough levels at 96 h. EHL FVIII was well tolerated. No allergic reactions were presented. No FVIII inhibitor developed during 4-months follow up, no bleeding episode occurred, as well.

Discussion/Conclusion: EHL FVIII given in limited number of adolescents with sHA on prophylaxis, with no history of inhibitors, seemed to be safe and effective; however longer follow up and careful selection of patients is required.

Disclosure of Interest: None declared.

P051 | Benefits of switch to FVIII-FC: Experience of prophylaxis in eight patients

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Introduction: Recombinant Factor VIII-Fc (rFVIII-Fc; Efmoroctocog alpha), a fusion protein with the Fc portion of IgG1, is the first extended half-life (EHL) product available in Italy. We here report data so far collected about prophylaxis with FVIII-Fc in patients with hemophilia A followed at Hemophilia Centre of Parma.

Methods: According to expert recommendations, patients candidate to switch from prophylaxis with standard half-life FVIII concentrate to rFVIII-Fc underwent a pharmacokinetic (PK) study. At baseline FVIII:C and FVIII inhibitor were assessed after a wash out of at least 72-96 hours. Blood samples for FVIII:C were collected at 0.25, 0.5, 1, 3, 6, 24, 48, 72 and 96 hours after the infusion of 40-50 IU/kg rFVIII-Fc. After the definition of prophylaxis regimen and start of rFVIII-Fc therapy patients underwent clinical and laboratory follow-up monthly for the first three months (bleeding and infusion report; FVIII:C and inhibitor assessment, satisfaction to treatment), then every 3 months.

Results: Eight patients (6 severe and 2 moderate hemophilia A; age, mean±1SD, 29.8 ± 12.78) were switched to rFVIII-Fc. The mean follow up after switch was 4.8 ± 3.7 months. At PK analysis, mean in vivo recovery and half-life were 2.42 ± 0.23 and 19.24 ± 3.81 hours, respectively. All patients were prescribed a twice weekly prophylaxis regimen, except the youngest one over the first month (every 3 days). Mean prophylactic FVIII dose was 47 ± 2.36 IU/Kg. Due to good clinical outcomes and satisfactory trough levels (>3 IU/dL, 96 h) the intervals between infusions were prolonged every 4 days within 1-4 months in 5 patients. All patients reported high satisfaction to treatment due to less frequent venipunctures and higher sense of protection without any change in their lifestyle and physical activities. The concentrate was well tolerated, no adverse events or inhibitor development being detected. On the whole, as compared to the year before switch, prophylaxis with rFVIII-Fc allowed a mean reduction of 40% of the infusion number and of 13% of FVIII consumption, estimated according to the last prescribed regimen.

Discussion/Conclusion: Our experience show that switching to prophylaxis with a EHL FVIII concentrate (rFVIII-Fc) is safe and allows to maintain good clinical outcomes, significantly reducing the infusion numbers and factor consumption and improving patients' sense of protection.

Disclosure of Interest: None declared.

P052 | Assessment of clotting activity of recombinant fix FC fusion protein in European hemophilia treatment centers

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Introduction: As extended-half-life therapies become available, such as recombinant FIX Fc fusion protein (rFIXFc), it is important to ensure the reliability of their therapeutic monitoring. The objective of this field study was to assess agreement between European hemostasis laboratories in measuring FIX activity in plasma samples containing various levels of rFIXFc.

Methods: Human FIX immunodepleted plasma was spiked with rFIXFc (Alprolix®) at three nominal levels (based on the manufacturer's labeled potency). Samples were shipped frozen to laboratories across Europe and tested for FIX activity by the labs' own aPTT based one-stage clotting assay and plasma standard. The required information was recorded independently by each laboratory and used for central data analysis.

Results: 79 sets of results were received from 59 participating hemostasis laboratories in 12 European countries during Sept 2016-Oct 2017. Overall, 9 commercial aPTT reagents were used on 5 types of analyzers, yielding a total of 16 aPTT+analyzer combinations. Reported FIX clotting activity of the 0.80, 0.20 and 0.05 IU/mL plasma samples, ranged from 0.46 to 1.36 IU/mL (mean = 0.75; CV = 24.0 %), 0.12 to 0.42 IU/mL (mean = 0.21; CV = 27.5 %) and 0.03 to 0.14 IU/mL (mean = 0.06; CV = 32.6 %), respectively. A one-way ANOVA between 9 aPTT+analyzer combinations indicated a statistical significant difference between FIX clotting activity recovered from each level of rFIXFc samples ($P < .0001$). For CK-Prest™+Stago analyzer combinations (n = 23) the mean of observed recoveries at the 0.80, 0.20 and 0.05 IU/mL plasma samples were 0.58 (12.0% CV), 0.16 (12.5% CV), 0.05 IU/mL (18.5% CV), respectively. A relative deviation in FIX activity was also noted comparing different analyzers with the same silica aPTT reagents.

Discussion/Conclusion: This field study revealed a dose-dependent variability in overall FIX measurement and between each combination of aPTT+analyzer throughout Europe. Most laboratories measured FIX clotting activity of rFIXFc plasma samples within 30% of target levels using routine assay methods and plasma standards. Results are consistent with previously published data on laboratory rFIXFc activity assay performance across other regions. Interestingly, better FIX accuracy with the CK-Prest+Stago assay system was reached than previously described.

Disclosure of Interest: A. Willemze Employee of Sobi, A. Sadeghi-Khomami Employee of Precision BioLogic Inc., L. Sörskog Shareholder of Sobi, Employee of Sobi, M. Wikén Shareholder of Sobi, Employee of Sobi, S. Lethagen Shareholder of Sobi, Employee of Sobi. This research is funded by Sobi.

P053 | The FIX C assessment of extended half-life recombinant factor IX products in clinical practice

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Introduction: The introduction of extended half-life (EHL) recombinant Factor IX (FIX) concentrates for hemophilia B has caused uncertainty within clinical laboratories. Two EHL products are in routine use in the UK; FIX albumin fusion protein (Idelvion) and FIX Fc fusion (Alprolix). Potency was assigned by one-stage clotting FIX assay (OSA), using Pathromtin (PSL) and Actin respectively. Both manufacturers advise against the use of certain APTT reagents in the laboratory monitoring of these products. Most reports in the literature assess the EHL product recovery in assays of FIX of *in vitro*-spiked plasma. The aim of this study was to assess recovery of FIX by the OSA and chromogenic assay (CSA) in patients treated with Idelvion or Alprolix.

Methods: FIX activity was measured by OSA and CSA in 18 samples from 3 patients following treatment with Idelvion and 22 samples from 5 patients treated with Alprolix. OSA was tested with Actin, Actin FS (AFS), Actin FSL (AFSL) and PSL (all Siemens) on Sysmex CS5100i analyzer and APTT SP, Synthasil and Synthafax (all Werfen) on ACL TOP. CSA were tested with kits from Rossix and Hyphen Biomed.

Results: Mean OSA for Idelvion ranged from 24 IU/dL (AFS) to 62 IU/dL (Synthafax). Mean CSA was 71 IU/dL (Rossix) and 61 IU/dL (Hyphen). The % OSA difference compared to PSL ranged from 4.2% (Actin) to 42.8% (Synthafax). For CSA the % difference was 57.2% (Rossix) and 38.8% (Hyphen). Mean OSA for Alprolix ranged from 40 IU/dL (PSL) to 56 IU/dL (Actin). Mean CSA was 51 IU/dL (Rossix) and 38 IU/dL (Hyphen). The % OSA difference compared to Actin ranged from 5.4% (AFSL) to 27.8% (PSL). For CSA the % difference was 2.5% (Rossix) and 31% (Hyphen).

Discussion/Conclusion: Less than 10% difference in Idelvion patients was observed with Actin, APTT SP and Synthasil. Underestimation by more than 30% was observed with AFS and AFSL. Overestimation by more than 35% was observed with Synthafax and both CSA. In Alprolix patients, underestimation by at least 20% was observed with AFS, PSL, APTT SP and Synthafax. AFSL, Synthasil and Rossix produced comparable recovery whilst Hyphen was approximately 30% higher than expected. Results in this ex vivo study reflect published in vitro spiking data. The accurate monitoring of EHL FIX products relies on the use of the correct assay. It is essential that laboratories and clinicians are aware of the characteristics of the specific FIX:C assay used in their centers.

Disclosure of Interest: None declared.

P054 | Genotype/phenotype correlation in Venezuelan patients with von Willebrand disease. Identification of eight novel mutations

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Introduction: Von Willebrand disease (VWD) is the most common inherited bleeding disorder. The diagnosis is often difficult due to its clinical and laboratory results heterogeneity. The aim of the present study was to explore the causative mutations that could account to the VWD in 13 Venezuelan families.

Methods: Study was carried out in 17 patients, belonging to 13 unrelated mestizo families. Plasma Phenotype VWF:Ag levels by immunoturbidity, vWF:RCo by agglutination, and FVIII:C by one stage assay, vWF:CB by ELISA using collagen type III. Mutation screening was done by PCR and direct sequencing of the coding VWF exons 2-52 including flanking intron sequences. Possible large deletions or insertions were investigated by multiplex ligation-dependent probe amplification (MLPA) analysis. Multimer analyses were performed in SDS-agarose gel.

Results: All patients showed a bleeding tendency. ISTH/SSC score median 12 (range 4-41). Based on plasma phenotype 5 families were classified as type 3 (38.5%), 7 as type 1 (53.8%) and one (7.7 %) as type 2 (2B) vs platelet-type VWD; 15/17 patients were blood type O, and consanguinity was documented only in one family. Genetic analysis revealed that 1 patient diagnosed as type 1 was type 2B (without thrombocytopenia), and a Type 3 patient was a severe type 1 confirmed by multimer analysis. Mutations were identified in 94% of the patients (5/13 were in exon 28), 23% of probands had two variants. Eight novel mutations were found. In Type 3 7713C>A (p.Cys2571*), 2092 del A (Arg698Gly fs*43), 421G>T (p.Asp141Tyr, homozygous), and a large deletion 5621-268_6798 + 4969 Del ins CCTGG (Ex 33_38 deleted) homozygous. In Type 1 3830A>T (p.Asp1277Val), 3842T>C (p.Leu1281Pro), 107G>A (Ser36Asn), and 440A>G (p.Gln147Arg). Several polymorphic variants have been found, some of them reported only in African or African-American population, highlighting the multiethnic origin of Venezuelan inhabitants.

Discussion/Conclusion: The present work highlights the relevance of genetic analysis for the appropriate diagnosis classification and management of patients with vWD. The deleterious effects of these polymorphisms together with the mutations in some patients must be further investigated.

Disclosure of Interest: None declared.

P055 | Comparison of standard half-life to extended half-life fix products: Real-world analysis or recent factor IUS dispensed and expenditure in on-demand hemophilia B patients

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Introduction: Extended half-life (EHL) factor IX (FIX) products increased half-lives by 3-6 times via protein fusion or PEGylation. EHL products are priced higher per IU than standard half-life (SHL) FIX products. We evaluated FIX expenditures and factor IUs dispensed for US hemophilia B (hem B) patients receiving on-demand SHL vs EHL protein fusion products.

Methods: A large national specialty pharmacy dispensation claims database was used to identify monthly factor IUs dispensed and expenditures for on-demand hem B patients in the US (ICD-9 286.1 or ICD-10 D67) from Apr 2015–Sept 2017. The wholesale acquisition cost specific to each month for each product was used. Average monthly IUs dispensed and expenditures were calculated by summing all available monthly data and dividing by number of months, from first to last month when factor dispensation occurred.

Results: In total, 334 patients received nonacog alfa (NA), 51 (15%) with severe hem B; 27 received eftrenonacog alfa (EA), 6 (22%) with severe hem B; and 14 received albutrepenonacog alfa (AA), 6 (43%) with severe hem B. Median values were used due to skewness of the data. In all patients, median (interquartile range [IQR]) monthly expenditures were higher with EA ($43014 [$52,517]) and AA ($25 389 [$23,163]) than with NA ($9347 [$20 557]); $P < .002$. In all patients, median (IQR) monthly average IUs dispensed were higher with EA (14 826 [18 196]) vs NA (6918 [15 178]); $P < .006$. Units dispensed in the AA group (5974 [5450]) were lower but not statistically significantly lower vs NA. This pattern held among severe hem B patients, albeit with smaller patient numbers. In severe hem B patients, median [IQR] monthly expenditures were significantly higher ($P = .01$) with EA ($37 461 [$47 887]) vs NA ($10 539 [$21 639]) but not vs AA ($18 158 [$67 834]). No statistically significant differences occurred in median monthly IUs dispensed EA, 12 800 [17 000]; AA, 4272 [15 961]; and NA, 7693 [16 171].

Discussion/Conclusion: In all on-demand hem B patients, more factor IUs were dispensed in the EA vs NA group, with a similar pattern in severe hem B patients. In all on-demand hem B patients, average median monthly expenditures were significantly higher with EA and AA vs NA, but in severe on-demand hem B patients, the average median monthly expenditures were higher with EA vs NA but not AA.

Disclosure of Interest: B. Tortella Employee of Pfizer Inc, A. Chhabra Employee of Pfizer Inc, J. Alvir Employee of Pfizer Inc, P. Fogarty Employee of Pfizer Inc, M. McDonald Employee of Pfizer Inc, A. Pleil Employee of Pfizer Inc, D. Spurden Employee of Pfizer Inc.

P056 | A correlation between the genotype and clinical course in hemophilia B patients

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Introduction: Hemophilia B (HB) which is associated with the mutations in the F9 gene is an X-linked bleeding disorder. Carrier females with reduced FIX activity may also suffer from bleeding including menorrhagia. Mutations are identified in 97% of the cases. The aim of the present study is to analyze genotype and phenotype association in the 20 Hemophilia B patients from single centre in Istanbul.

Methods: 20 patients, selected among the 76 HB patients in our center, were screened for a F9 gene mutation by direct DNA sequencing. All the patients were severely affected (FIX level < 1%), except 2 patients (FIX level >%1). 16 of the patients were in prophylaxis. Their demographic data, including annual bleeding rate (ABR), arthropathic joint number, treatment modality, were recorded.

Results: Median age of the patients was 21 (range15-41). All severe patients were in prophylaxis except 2 patients. Number of arthropathic problems ranged between 4 to zero in the study population. Maximum and minimum number of annual bleeding rate was 5 and 0. 50% of the patients had mutations within the catalytic SP domain. Patients with SP mutation and had severe phenotype with at least 1 ABR and 1 arthropathic problem. 15% of the patients had within the pro-peptide sequence had average 3.3 arthropathic problems with ABR 3. 10% of the patients had mutations affecting EGF2 and GLA domains with milder phenotypes. 15% of the patients had large deletions. Their average number of ABR was 3.3 and arthropathy number was 2.35. 20% of the patients had mutations in either promoter or activation peptide domain. They did not have arthropathic problems and average of 0.26 ABR. Patients with mutations affecting SP domain and started prophylaxis late had the most severe phenotype while the ones who started prophylaxis early had milder phenotype. However, patients with large deletions had arthropathic problems despite early prophylaxis.

Discussion/Conclusion: This study demonstrated that the mutations affected functional domains affect the phenotype. However, prophylaxis ameliorates the phenotypic effect of the mutation if it is started earlier, except large deletions. Therefore, it is important to determine the genotype of the HB patients for a better clinical management of the patients.

Disclosure of Interest: None declared.

P057 | Can you predict the clinical efficacy of bypassing agents in patients with hemophilia and current inhibitor? Discussion about a case report in cardiovascular surgery

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Introduction: A 52 years old severe hemophilia A patient of 85 kg with inhibitor at 500UB. He had an immune tolerance induction that failed in the early 80's. He was treated on demand by NOVOSEVEN® between 1996 and 2003. The inhibitor title decreased around 30UB. Because of increased bleeding events, he was switched to prophylaxis by FEIBA® 6000UI x 3/week with a clinical success but inhibitor increased. In September 2015, a coronary heart disease was diagnosed. He was treated with aspirin, bisoprolol, perindopril and atorvastatin. It was decided to practice a bypass surgery with a single bypass grafting using an on-pump beating heart technique. Few years ago, a PRP TGA was performed to determine the most efficient bypassing agent. Based on those results it was decided to use FEIBA®.

Methods: The protocol Discussed by the French National Reference Center for Hemophilia Before the surgery Within an hour before the surgery 6000UI of FEIBA®. No use of tranexamic acid except in case of abnormal bleedings. After the surgery FEIBA® 4000UI every 6H during 24H.

Results: What happened during the surgery and the first 24H? 08:00 6000UI of FEIBA® 09:00 Beginning of the surgery 10:20 First transfusion of Packed Red Cells (PRC) 10:40 4 Fresh Frozen Plasma (FFP) 11:10 1 PRC 11:30 Tranexamic acid 1 g IV 12:00 1 PRC 12:45 Recurrent heavy bleedings second infusion of 6000UI of FEIBA® 14:00 Bleeding through the sternotomy scar 1 PRC and 1 standard platelet concentrate 14:30 1 PRC and 2 FFPs 15:45 the patient was taken back to the operating theater NOVOSEVEN® 8 mg was given 16:15 2 PRCs and 1 FFP 17:00 2 FFPs 17:15 The bleeding is under control Total bleedings 1.7L. NOVOSEVEN® 8 mg was maintained every 2H (18:30, 20:30) then every 3H (23:30, 2:30, 5:30) and finally every 4H during 24H.

Discussion/Conclusion: Despite TGA results giving FEIBA® as the best product to improve hemostasis, in this situation it was obviously not enough. This case report supports the fact that in out of control bleedings in such patients, the association FEIBA®+NOVOSEVEN® might be a solution. It would have been interesting to get plasma samples during surgery to perform TGA and get more data on this point.

Disclosure of Interest: None declared.

P058 | Modhemos (moderate hemophilia survey): A multicentric opinion survey of physicians on the treatment of bleeding episodes in patients with moderate hemophilia A or B in France

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Introduction: Specific clinical practices are relatively unknown for patients with moderate (factor VIII or IX level 1-5 IU/dL) hemophilia.

Methods: To assess opinions and preferences regarding diagnosis, treatment and follow-up in moderate hemophilia, a questionnaire was sent to physicians of French Haemophilia Treatment Centres. Among others questions, two archetypal clinical scenarios were proposed.

Results: 43/82 (52%) physicians from 26 centers answered the questionnaire. Answers dealing with substitutive treatment related items are presented here. For a knee hemarthrosis in an 8-year-old boy, the suggested initial dose was 30-40 IU/kg of factor VIII (FVIII) and 40-60 IU/kg of factor IX (FIX) for most of the physicians. A consolidation treatment was considered by 45% of the doctors (for 1-2 weeks in 2/3 of answers). In case of a psoas hematoma, hospitalization was perceived as mandatory for 98% of the physicians. The suggested doses were 40-50 UI/kg for FVIII and 60-80 IU/kg for FIX concentrates, repeated 1-3 times a day. A consolidation treatment was considered by 39% of the physicians for 1-12 weeks. The main reasons to start a prophylactic treatment were number of hemarthroses (97%), target joint (81%), hemophilic arthropathy (74%) and number of severe bleeding episodes (71%). Additional reasons for prophylaxis were sport and a combined anticoagulant/antiplatelet treatment for 76% and 64% of the physicians, respectively. In children, prophylaxis was proposed by 37% of the physicians after the first hemarthrosis, 100% in case of target joint and 38% after a psoas hematoma. A prophylaxis longer than 1 year was considered by 13% of clinicians after a first hemarthrosis, but by 63% in the case of target joint. A psoas hematoma was considered as an indication for short-term prophylaxis (less than 6 months). For patients with moderate hemophilia, most of the physicians (74%) thought that hemophilic arthropathy was underestimated, 67% that prophylaxis was not sufficiently proposed, and 48% that the risk of inhibitor could be a potential barrier to start prophylaxis.

Discussion/Conclusion: These opinions should be confronted to actual data of treatment for patients with moderate hemophilia. This survey was supported by Octapharma.

Disclosure of Interest: B. Guillet Consultant for Octapharma, M. Trossaert Consultant for Octapharma, R. d'Oiron Consultant for Octapharma, S. Dantin Employee of Octapharma, F. Volot Consultant for Octapharma.

P059 | Adult- onset severe congenital bleeding disorder

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Introduction: Most severe inherited bleeding disorders are presented in infancy and childhood period. However a few of them may be presented during adult ages.

Aim: To asses and describe the first presentation of adult –onset of severe form of inherited bleeding disorders.

Methods: A total of 480 patients of inherited bleeding disorders with definite diagnosis were registered in south west Iran. A questionnaire consist of demographic questions, clinical manifestation, laboratory data and the age of first presentation fill in for every patients.

Results: Of the 480 cases 10 patients (2%) firstly presented in adult period (mean age 22 year).The variability of 10 patients were as follows 2 were factor VII deficiency, two were factor XI deficiency ,two→factor XII deficiency (asymptomatic),one→factor XIII deficiency, one →fibrinogen deficiency, one →vit K dependent factor deficiency, one→VWD Type 3. The cases were detected as follow factor VII deficiency→ bleeding after cesarean section, factor XI deficiency→ bleeding after tooth extraction, factor XIII deficiency → bleeding after gum and nose bleeding, fibrinogen deficiency →after recurrent abortion, vit K dependent factor deficiency→ after GI bleeding, VWD Type3→after leg compartment syndrome, and factor XII deficiency was found after prolonged PTT.

Discussion/Conclusion: Differences in clinical manifestation in severe congenital factor deficiency support the discrepancy between phenotype and genotype. This uncoupling is more common in factor deficiencies such as factor XI, VII, XIII and V but is unusual in fibrinogen, vit k dependent and VWD Type3. Initial clinical manifestation of adult –onset severe inherited factor deficiencies is not common but is important due to most of them was found during minor and major surgery. The result of this manuscript is valuable for health staff to consider the coagulation factor deficiencies during unexpected bleedings.

Key Words: Adult onset, congenital, severe, factor deficiency

Disclosure of Interest: None declared.

P060 | Impact of pre-existing immunity to AAV5 on pharmacodynamics of BMN 270, an AAV5-based gene therapy for the treatment of hemophilia A

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Introduction: Neutralizing antibodies resulting from prior exposure to wild type adeno-associated virus (AAV) may limit the efficacy of AAV based gene therapies. BMN 270 is an investigational AAV5 based gene therapy encoding for a B-domain deleted human FVIII protein (hFVIII-SQ) for the treatment of Hemophilia A. In BMN 270-201, prospective patients were excluded on the basis of pre-existing anti-AAV5 total antibodies (TAb) or a positive titer in a cell based transduction inhibition (TI) assay. To understand the relationship between AAV5 immunity and the pharmacodynamics of gene delivery, we examined liver transduction and hFVIII expression in cynomolgus monkeys with varying anti-AAV5 TAb levels and TI titers following an infusion of BMN 270.

Methods: Cynomolgus monkeys were screened using anti-AAV5 TAb and TI assays and assigned to one of four groups. A TI-/TAb- control group (n = 3), a TI+/TAb- group with low (2-5) TI titers (n = 4), a TI+/TAb- group with higher (5-10) TI titers, and a TI+/TAb+ group (TI > 5). All animals were dosed with 6E13 vg/kg BMN 270 and examined over 8 weeks for plasma expression of hFVIII protein. Quantitation of hFVIII-SQ DNA in the liver was evaluated to assess transduction efficiency and associations with plasma protein expression.

Results: Following infusion of BMN 270, maximal expression of hFVIII was observed between Weeks 3-5 but was notably lower in the group that screened TAb+. In this group, 3 of 5 animals had detectable hFVIII-SQ expression with a 72% reduction relative to TI-/TAb- controls. Vector genome copies were also lower in livers from TI+/TAb+ animals and correlated with protein expression levels. In contrast, there was no detectable decrease in hFVIII levels in monkeys in either of the two TI+/TAb- groups suggesting that neutralizing anti-AAV5 antibodies, as opposed to non-antibody-based inhibitors, are responsible for diminished transduction and expression of hFVIII in vivo.

Discussion/Conclusion: These results suggest that similar TI+/TAb- Hemophilia A patients will respond to BMN 270 and that the biological threshold for clinically relevant anti-AAV5 antibody levels may be different from the statistically-derived assay cut point. These data also show that individual antibody responses may vary with respect to *in vivo* neutralizing capacity and support further studies in Hemophilia A patients with low levels of pre-existing AAV5 antibodies.

Disclosure of Interest: B. Long Employee of BioMarin Pharmaceutical Inc, K. Sandza Employee of BioMarin Pharmaceutical Inc, J. Holcomb Employee of BioMarin Pharmaceutical Inc, J. Pherarolis Employee of BioMarin Pharmaceutical Inc, L. Crockett Employee of BioMarin Pharmaceutical Inc, L. Falese Employee of Former employee of BioMarin Pharmaceutical Inc, G. Hayes Employee of BioMarin

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P061 | Interim analysis of immunogenicity to the vector capsid and transgene-expressed human FVIII IN a phase-1/2 clinical study of BMN-270, an AAV5 mediated gene therapy for hemophilia A

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Introduction: This report examines immunogenicity of BMN 270; an adeno-associated virus type-5 (AAV5)-mediated human FVIII (hFVIII) gene therapy in development for the treatment of Hemophilia A.

Methods: In clinical study BMN 270-201, patients with severe Hemophilia A were screened for both pre-existing antibodies directed against the AAV5 vector and inhibitors of transduction using a cell-based *in vitro* transduction inhibition (TI) assay. Patients testing positive in either assay or who had a history of FVIII inhibitors were excluded from the trial. Post-infusion plasma was analyzed for total antibody (TAb) responses specific for the AAV5 capsid and against FVIII using bridging ECLA immunoassays. Development of FVIII inhibitors was monitored using the Nijmegen-modified Bethesda assay. Peripheral blood mononuclear cells were analyzed by IFN-g and TNF-a ELISPOT assays for detection of capsid-specific and hFVIII-SQ (B-domain deleted hFVIII protein encoded in BMN 270) specific cellular immune responses.

Results: All patients developed anti-AAV5 TAb by Week 8 post BMN 270 infusion, the first immunogenicity time-point assessed. One patient screened and confirmed positive at a single time point in the anti-FVIII TAb assay but was negative at all subsequent time points. No patients tested positive for FVIII inhibitors. IFN-g responses against peptides spanning AAV5 capsid or hFVIII-SQ were negative in patients with or without asymptomatic elevation of alanine aminotransferase (ALT). Intermittent TNF-a responses were detected in several patients in response to hFVIII-SQ peptide. These responses were self-limiting and were not temporally associated with increases in ALT or a decline in FVIII activity, and did not correlate with IFN-g results. Similar TNF-a responses to hFVIII-SQ peptides were also observed in a subset of healthy donors.

Discussion/Conclusion: As expected, the production of anti-AAV5 antibodies were observed following BMN 270 administration. No consistent association could be made with increases in ALT and cellular immune responses. These data indicate that although antibodies to the AAV5 capsid develop in all patients, concomitant cellular immunity is not readily detectable, and has not been associated with liver function abnormalities nor changes in transgene expression levels.

Disclosure of Interest: B. Long Employee of BioMarin, B. Kim Employee of BioMarin, W. Y. Wong Employee of BioMarin, K. Yang Employee of BioMarin, C. Vettermann Employee of BioMarin, N. Pryer Employee of BioMarin, R. Hardet None declared, K. Kuranda None declared, P. Veron None declared, F. Mingozzi None declared, G. Pierce Consultant for BioMarin, Roche, B. Schweighardt Employee of BioMarin.

P062 | Extended dosing intervals with RIX-FP prophylaxis reduces factor ix consumption compared with previous prophylaxis regimens in clinical studies of hemophilia B patients

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Introduction: Prophylaxis with conventional Factor IX (FIX) requires dosing two to three times a week to maintain adequate FIX activity levels to prevent bleeding. rIX-FP, a fusion protein genetically linking recombinant human FIX with recombinant human albumin, has an improved pharmacokinetic profile enabling extended dosing intervals of 7-, 10- and 14-days in prophylaxis. The aim of this analysis was to determine the impact of extended dosing intervals on FIX consumption in hemophilia B patients in Phase 3 clinical studies.

Methods: In the Phase 3 study in adults (12–65 years) with hemophilia B (FIX ≤2%), 23 patients received on-demand treatment with rIX-FP for 6 months before switching to 7-day prophylaxis and 40 patients received 7-day prophylaxis for 6 months and then continued with 7-day prophylaxis or switched to 10- or 14-day prophylaxis. In the Phase 3 pediatric study, 27 patients (<12 years) received 7-day prophylaxis with rIX-FP. FIX consumption in patients' previous regimens was compared with rIX-FP consumption during the studies.

Results: In adults, 7- and 10-day rIX-FP prophylaxis reduced mean monthly FIX consumption by 37% compared with previous FIX (7-day rIX-FP 202.7 IU/kg; 10-day rIX-FP 201.5 IU/kg; previous FIX 320.7 IU/kg). The 14-day regimen reduced mean monthly consumption to 157.4 IU/kg, 51% less than with previous FIX. The mean ± SD weekly FIX dose prior to study entry was 69.9 ± 39.9 IU/kg,

which was reduced to 47.1 ± 10.9, 70.6 ± 9.6 and 71.9 ± 7.9 IU/kg for 7-, 10- and 14-day prophylaxis, respectively, with rIX-FP. In pediatric patients, 7-day prophylaxis with rIX-FP resulted in a decreased infusion frequency in 83% (20/24) of patients and the mean weekly dose was markedly reduced compared with previous FIX (47.2 vs. 107.1 IU/kg). The median annualized spontaneous bleeding rate was 0.00 with all rIX-FP prophylaxis regimens in both adult and pediatric patients.

Discussion/Conclusion: The extended dosing intervals made possible with rIX-FP prophylaxis substantially reduced total FIX consumption for patients in clinical studies compared to their previous regimens. The extended dosing intervals offered with rIX-FP prophylaxis may also reduce the burden of treatment for hemophilia B patients.

Disclosure of Interest: B. Pan-Petesch None declared, E. Santagostino Consultant for Bayer, Shire, CSL Behring, Novo Nordisk, Sobi, Bioverativ, Pfizer, Roche, Grifols, Octapharma and Kedrion, Speaker Bureau of Bayer, Shire, CSL Behring, Novo Nordisk, Sobi, Bioverativ, Pfizer, Roche, Grifols, Octapharma and Kedrion, C. Leissinger Grant/Research support from Baxter, CSL Behring and Roche , Consultant for Baxter, Bayer, Biogen Idec, CSL Behring, Kedrion, Novo Nordisk, Pfizer, Shire and Roche, A. Shapiro Consultant for Baxalta/Shire, Novo Nordisk, Biogen, Genentech, ProMetric Life Sciences, Kedrion Biopharma, Sangamo Biosciences Inc., Bio Products Laboratory, Biogen Idec, CSL Behring, Daiichi Sankyo, OPKO, Octopharma , J. Oldenburg Grant/Research support from Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma and Pfizer, Consultant for Baxter, Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum, Speaker Bureau of Baxter, Bayer, Biogen Idec, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Swedish Orphan Biovitrum, W. Seifert Employee of CSL Behring, M. Escobar Consultant for Shire, Bayer HealthCare, Novo Nordisk, Pfizer, Genentech and CSL Behring.

P063 | Circumcision in patients with hemophilia and the other bleeding disorders in southern part of Turkey

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Introduction: Circumcision is the oldest and most frequent surgical procedure in the world and in Turkey as is seen in the other Islamic countries because of religious and tradition. In this retrospective study, we report the experience of circumcision at Cukurova region of Turkey in two centers. We reviewed total 93 patients with hemophilia and B and four von Willebrand disease between 1994 and 2017

Methods: We retrospectively reviewed medical records of 86 hemophilia patients without inhibitors, seven hemophilia patients with inhibitors and four patients with Von Willebrand disease age ranging from two months to 33 years who had been circumcised. Before the year 2000, factor concentrates were given before and after circumcision for 6-7 days. After 2000, we used fibrin glue together with factor concentrates for only 3 days. By-passing agents were used for circumcision in hemophilia patients with inhibitors.

Results: Twelve of 86 patients without inhibitors were referred to our center with bleeding after the circumcision before diagnosis hemophilia. Nine of these 12 patients had severe life threatening bleeding and 3 of them had moderate bleeding. All patients with hemophilia and Von Willebrand disease were circumcised in two centers under general anesthesia except for 3 patients who were given local anesthesia. Sixty-seven of 74 hemophilia patients (90%) without inhibitors had 9 mild and 6 moderate bleeding complications. Five of seven hemophilia patients with inhibitors had two moderate and three mild bleeding complications. Three of four patients with Von Willebrand disease had mild bleeding complications.

Discussion/Conclusion: In this study, we aim to report the experience of circumcision at Cukurova University and Acibadem Hospital in total 97 patients with hemophilia and von Willebrand disease between 1990 and 2017. Our experience showed that circumcision for patients with hemophilia should be carefully performed by surgeons together with pediatric hematologist under appropriate conditions in hemophilia centers which has comprehensive hemophilia care centers. And we observed that bleeding rate was higher in patients with Von Willebrand disease after circumcision.

Disclosure of Interest: None declared.

P064 | The treatment perspective of generation Y hemophiliacs and their relatives

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Introduction: Generation Y; includes individuals born between the years 1980-1999. It is considered that Generation Y are more fond of their freedom and comply less with current rules. Although prophylaxis in hemophilia treatment is still accepted as the gold standard, compliance with prophylaxis varies among different age groups and from region to region. The purpose of our study is to evaluate the compliance of generation-Y hemophiliacs (Y-PwH) and their relatives with prophylaxis, the difficulties they experienced and the proposed solutions.

Methods: The 120 people included in the study were living in 5 different cities and were selected to reflect the heterogeneous distribution of Turkey. In totally 16 focus groups (8 were Y-PwH and 8 were

their relatives) selected. In this study, Pearson correlation analysis (r), Ki square analysis (χ^2) and Mann Whitney U test was used.

Results: Based on cities, the mean rate of prophylaxis by Y-PwH (45.3%) was significantly lower than that estimated for them by the relatives (71.4%) ($P < .05$). There was a significant relationship between the cities lived in and the compliance of the prophylaxis by Y-PwH ($P = .000 < .05$). Significant differences were found between Y-PwH and hemophilia relatives ($P < .05$) in prophylaxis usage between the cities. While 70.3% of Y-PwH stated that the most important difficulty in prophylaxis was the 'Intravenous usage', only 26.8% of the relatives expressed it ($P < .05$). The difficulty to reach the factor was reported as a problem by 20.3% of Y-PwH and by 19.7% of relatives. In suggestions of the study to improve the Y-PwH compliance are 1- Establishment of hemophilia treatment centers, increasing the access to treatment and introducing the use of long-acting factors 2- Public awareness and to lighten of the official rules 3- Familiar behavior of health personnel 4- Increase the scientific studies.

Discussion/Conclusion: In hemophilia treatment, not only prophylaxis is still the gold standard but also there are significant differences in compliance with the treatment according to age groups. Besides, it was suggested that apart from being a Y-PwH, the living region is important in compliance and there are still unmet needs for hemophiliacs.

Disclosure of Interest: None declared.

P065 | Massive umbilical cord bleeding and factor XIII deficiency

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Introduction: Congenital factor XIII deficiency is a severe bleeding disorder that is inherited autosomal recessive trait. Factor XIII (FXIII) deficiency is a rare congenital bleeding disorder and the incidence of disease is 1/2000000 every live birth. Inherited factor XIII (FXIII) deficiency can present with umbilical bleeding during the neonatal period, delayed soft tissue healing, mucosal bleeding and life-threatening intracranial hemorrhage. We report here a case what Factor XIII deficiency in a child that presented a massive umbilical cord bleeding as the first manifestation of the Factor XIII deficiency.

Methods: A 7-day-old neonate was admitted to our clinic for umbilical cord bleeding. Our patient was born from a primigravid woman (19 years old from Syria) during the 39th gestational week. Her parents are first-degree cousins (paternal aunt and uncle's child). Her father has been get diagnosis previously about factor XIII deficiency and was receiving treatment for factor XIII deficiency. The newborn was previously healthy and she received 1 mg vitamin K (intramuscular) at birth. She was just taking breast milk. The blood tests showed that hemoglobin was 15 g/dL , platelet count was 320 x 10^9/L. International Normalized Ratio (INR), fibrinogen, prothrombin time (PT) and partial thromboplastin time (PTT) were normal. Coagulation tests were again normal. Pressed dressing was made to the patient's umbilical cord. Elaborate coagulation tests showed factor XIII-deficiency. There was a significant decrease in hemoglobin (9.2 g/dL) due to massive hemorrhage. The infant received a blood transfusion and a second dose of vitamin K (1 mg). Coagulation tests showed that level of factor XIII is 3% (normal range 80%-150%). She received prophylactic treatment monthly with fresh frozen plasma or cryoprecipitate. She was discharged after four days. Family studies and molecular analysis were performed, it's expected result.

Results: Patient diagnosis and treatment have prevented further hemorrhaging successfully. Her development has been normal to this day.

Discussion/Conclusion: A newborn presenting with persistent and massive umbilical cord bleeding should be screened for factor XIII deficiency when routine coagulation tests are normal. The case highlights the importance of seeking family history about bleeding disorders in the neonatal period, particularly if the parents are consanguineous.

Disclosure of Interest: None declared.

P066 | The management of iliopsoas hemorrhage in hemophilia patients: Single center experience

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Introduction: Iliopsoas hematoma is a well-recognized complication of hemophilia, and is considered as potentially life threatening and significantly associated with morbidity. Often there is no history of trauma and the onset is abrupt, with severe lower abdominal or groin pain.

Methods: 264 patients with hemophilia (210 HA, 54 HB; 15.7 ± 7.3 years) followed between 1998 and 2017 in our center were involved in this retrospective study. Iliopsoas hematomas were confirmed by USG in all patients. Additionally, CT was performed only in 4 patients. Iliopsoas hemorrhage re-appearing more than 3 months from the initial episode was defined as repeat bleeding.

Results: 25 iliopsoas bleeding episodes were identified in 16 hemophiliacs (13 HA, 3 HB) during the screening period. Five episodes were observed in HB patients. Eight episodes (32%) were classified as repeat bleedings. Five of the repeat bleedings occurred on the same side with the first episode while the remaining 3 occurred on the other side. Six patients had a high titer inhibitor against FVIII and accounted for 9 bleeding episodes. Nine patients had 1 episode, five had 2 episodes and two had 3 episodes. Only one episode was occurred in a HA

patient who was receiving prophylaxis. Patients presented primarily with thigh, hip and/or groin pain, abdominal tenderness, frequently had hip flexion contracture and paresthesia in the distribution of the femoral nerve. The mean duration of therapy with clotting factor concentrate or by-passing agents was 8.3 ± 2.8 days. Mean duration of hospitalization was 5.6 ± 2.8 days. All patients started to receive a physical therapy program 6.4 ± 2.8 days after the initiation of hemostatic therapy which lasted 17.0 ± 5.0 days. USG findings disappeared in all patients within 3 months. Only in one patient with mild HA, heterotopic bone formation developed as a long-term complication.

Discussion/Conclusion: Pain around the hip joint, femoral neuropathy and hip flexion contracture in a patient with hemophilia should alert the physician to the possibility of an iliopsoas hematoma. USG is the fastest and reliable diagnostic tool in these patients. Early and effective factor replacement therapy is essential in the prevention of the complications. Finally, prophylactic therapy may also play an important role in reducing the bleeding frequency.

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P067 | Newborn bleeding frequency in hemophilia

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Introduction: Intracranial hemorrhage (ICH) is one of the most severe bleeding events that may occur in patients with hemophilia A (HA), hemophilia B (HB) and Von Willebrand disease (VWD) at any age, even though it is particularly common in the newborn (3.5%-4.0%) , being associated with high rates of mortality and disabling neurological sequelae. There are relatively few data on the epidemiology of ICH in hemophilia. There is no study investigating the frequency of newborn bleeding in hemophilias in Turkey. Our study aim is to investigate the bleedings and risk factors in hemophilias in newborn period.

Methods: The study was a questionnaire-based retrospective case series collection. All the patients with hemophilia A, hemophilia B and Von Willebrand disease treated by our hematology center were invited to participate. A standardized data sheet was prepared to collect the following information baseline patient characteristics (date of birth, sex, diagnosis, severity), mode of delivery, birth weight, newborn bleeding episodes. Descriptive statistics were reported in terms of percentage, mean or median as appropriate.

Results: A total of 132 patients (102, 12 HB and 18 VWD) with hemophilia from our center participated the study. The birth dates of patients varied between 2017 and 1985. 80% of HA were severe, 10% moderate, 12% mildly severe. 65% of patients are born with normal vaginal delivery. Seventeen bleeds were occurred in newborn period. Two children had intracranial parenchymal bleeds and three children had cephal hematoma. Six patient had umbilical bleeds and other six patient had ecchymosis in body or extremities.

Discussion/Conclusion: This study represents the first study addressing a wide range of risk factors for major neonatal bleeding, including head bleeds, in infants with hemophilia from Turkey. The incidence of newborn bleeding complies with the literature. In the future there is a need for more participatory multicenter work.

Disclosure of Interest: None declared.

P068 | Patients with bleeding of unknown cause and joint hypermobility: Clinical assessment and genetic screening

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Introduction: Symptomatic joint hypermobility has been associated with bleeding tendency, suggesting that collagen disorders could be the cause in some cases of bleeding. The aim of this study was to examine the clinical characteristics of patients with bleeding tendency of unknown cause and joint hypermobility and to perform a genetic study based on Next-Generation Sequencing (NGS).

Methods: This was a single-centre, prospective, observational study approved by the hospital ethics committee. Patients included were visited at (1) Haemophilia Centre (HC) for bleeding symptoms of unknown cause (normal or abnormal hemostatic tests not explaining the bleeding phenotype) and having joint laxity and (2) Musculoskeletal Rehabilitation Unit (RHB) for joint laxity and reporting bleeding symptoms. Bleeding severity was assessed by the hematologist using the ISTH Bleeding assessment tool (ISTH-BAT) and joint hyperlaxity by the physiatrist by the Beighton score (abnormal scores were ≥6 and ≥5 respectively). Molecular analysis was performed using TruSight One Sequencing Panel Kit (Illumina). Quality and population frequency filters were applied and the search was limited to 78 genes related with Heritable Disorders of Connective Tissue (HDCT).

Results: Forty three patients were included between June 2016 and January 2017 (25 from the HC and 18 from RHB). All were females; median age was 38.6 years (range 17-62 years). Median ISTH-BAT score was 8 (range 3-17) and Beighton score 7 out to 9 (range 3- 9). ISTH-BAT score was abnormal in 33 (77%) of patients and Beighton score in 35 (80%). In 25 patients, both scores were abnormal. A total of 175 potential mutations were identified in HDCT related genes for all except one patient. In 20 (46.5%) of the cases, a direct correlation between the identified mutation and the clinical phenotype could be established. In 10 patients, mutations in *COL5A1*, *COL5A2*, *COL1A1*

and *COL1A2* genes were identified and validated by Sanger sequencing. In these patients, median ISTH-BAT and Beighton scores were 10 and 8 respectively and seven of them were recruited from the HC.

Discussion/Conclusion: Clinical assessment for symptomatic joint hypermobility should be considered in patients with significant bleeding history of unknown cause. NGS could be a useful tool for the study of the responsible genes and the classification of patients.

Disclosure of Interest: None declared.

P069 | High compliance to prophylaxis regimens in adult and paediatric hemophilia B patients receiving RIX-FP in clinical studies

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Introduction: Adherence to a prophylaxis schedule is essential for bleed prevention in patients with hemophilia. rIX-FP (IDELVION®) is a fusion protein genetically linking recombinant human coagulation Factor IX (FIX) with recombinant human albumin. rIX-FP prophylaxis regimens resulted in median annualized spontaneous bleeding rates of 0 in two Phase 3 clinical studies (PROLONG-9FP). Here, we evaluate patient compliance to prophylaxis regimens with 7-, 10- or 14-day dosing in adults and 7-day dosing in pediatric patients with hemophilia B (FIX ≤2%) in these studies.

Methods: In the Phase 3 study in adults (≥12 years), 23 patients received on-demand treatment for 6 months followed by 7-day prophylaxis (on-demand arm) and 40 patients received 7-day prophylaxis for 6 months followed by 10- or 14-day prophylaxis (prophylaxis arm), if they met the criteria for switching to a longer dosing interval. In the pediatric Phase 3 study, 27 patients (<12 years) received 7-day prophylaxis. Patients recorded dose, dosing frequency and their rIX-FP consumption in an e-diary, which was verified by the number of used vials returned at each study visit. Compliance to prophylaxis regimens was assessed in adult and pediatric patients and to the prescribed dose in adults only.

Results: Patients were considered to be compliant to prophylaxis if they received ≥80% of the expected number of infusions for their assigned prophylaxis schedule; 94.9% of adult patients and 97.9% of pediatric patients were compliant. In adults, mean compliance rates were similar across dosing regimens; 94.7% (prophylaxis arm) and 95.1% (on-demand arm) for 7-day, and 90.7% and 97.2% for 10- and 14-day, respectively. In pediatric patients, mean compliance rates were similar between age groups; 97.3% (1-5 years) and 98.3% (6–11 years). Patients were considered dose compliant if they received within 10% of the prescribed dose ≥80% of the time; 85.7% of adult patients were dose compliant.

Discussion/Conclusion: In clinical studies, both adult and pediatric patients had high rates of compliance to rIX-FP prophylaxis regimens. This analysis demonstrates that the very low bleeding rates observed in clinical studies with rIX-FP were achieved by patients complying to rIX-FP prophylaxis with a variety of dosing intervals.

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P070 | Development of appropriate and culturally adapted educational tools on hemophilia for the patients from Ivory Coast and their families

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Introduction: The Haemophilia Treatment Center of the Cliniques universitaires Saint-Luc in Brussels is the partner of the hemophilia center of Yopougon in Abidjan, Ivory Coast, since 2014 in the frame of the twinning program of the World Federation of Haemophilia. One of the goals of the twinning is to provide education to the patients with hemophilia (PWH), the hemophilia carriers and their family. A good understanding of hemophilia, it's clinical features, treatment options and mode of transmission is indeed critical to get a better awareness

of the disease, prevent the complications, raise the number of diagnosed cases and improve the quality of care.

Methods: Numerous educational tools (booklets, movies, slide kits…) about hemophilia have been developed over the last decades and are available in several languages. However, their content, the topics addressed (eg pre-implantatory diagnosis), the specificities of the language used (words/idiomatic expressions) and the iconography (eg pictures of caucasian patients without any signs of arthropathy) used in the available materials are rarely appropriate and therefore are less efficient to provide a pertinent and useful source of information to the PWH, the carriers and their family.

Results: We developed several educational tools (booklets, an educational game and a slide kit presentation) in collaboration with the ivorian medical and paramedical teams and the local patient association. The content and the topics addressed have been adapted with a specific focus on to the local issues encountered in hemophilia care (eg prevention of bleeds due to circumcision). A special attention was also paid to linguistic and cultural aspects to improve the level of understanding and raise the impact of the information. We tried to use as much as possible pictures and smart draws to overcome potential literacy difficulties. In order to be the best in line with the ethnicity of the target population of the tool, the illustrations were essentially based on photographies taken on site during clinics and cartoons representing african subjects.

Discussion/Conclusion: The short and long-term impact of these original tools is currently being evaluated in a prospective study.

Disclosure of Interest: None declared.

P071 | Prevalence of overweight in young patients with severe hemophilia and its economic burden in Germany

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Introduction: Prevalence of overweight among children in Germany is between 10%-20%. Data on overweight in patients with hemophilia in Germany are lacking.

Aim: Investigate the prevalence of overweight in Germany among young patients with severe hemophilia A and its influence on bleeding tendency, factor VIII (FVIII) consumption/year and the possible reduction of economic burden by individualized substitution regimes and weight loss programs.

Methods: Cross sectional data on height, bodyweight, bleeds/year, factor consumption/year in young patients with severe hemophilia A (FVIII <1%, age 0-30 years) were collected in seven German Haemophilia Centres. Age dependent BMI was calculated according to Kromeyer-Hauschild. FVIII consumption and annual bleeding rate were calculated from patients' records.

Results: We identified 322 patients with a median age of 14y (mean 13, 6 year, range 0-30 year). Prevalence of overweight and obesity was 16.8% and 8.7%, respectively. In patients with a negative history for FVIII inhibitors (n = 254) the median FVIII dosage was 96.9 IE/kg/week in normal weight and 72.9 IU/kg/week in overweight and obese patient. This shows, that many patients are rather dosed on an individualized dosing regimen than purely by bodyweight. However, in a model calculating FVIII dosing using the theoretical normal body weight costs could be reduced up to 43 186€/patient/year (2 504 776.79€/year). The general difference in bleeding rates between obese and normal weight patients was not statistically significant (P = .057). There was a trend to different dosing regimens and bleeding rates between centers, but preliminary calculations show no statistical differences.

Discussion/Conclusion: Nearly 26% of patients with severe hemophilia A from seven hemophilia centers suffer from overweight or obesity, more than in the general population in Germany. We suppose that the risk factors for the development of obesity are similar in both groups but reduced physical activity possibly triggered by overprotective parents might increase prevalence in our cohort. Individualized therapy, based on the theoretical normal weight or better after pharmacokinetic measurements might reduce therapy costs. Additionally, weight loss should positively affect comorbidities associated with overweight and obesity.

Disclosure of Interest: None declared.

P072 | The "German Paediatric Hemophilia Research Database" (GEPHARD) - a project of the "standing commission paediatrics of the society for thrombosis and hemostasis research" to improve the quality of hemophilia care for children

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Introduction: In Germany approximately 40-60 newborns are diagnosed with hemophilia per year. Hemophilia leads to recurrent bleeds resulting in increased morbidity and mortality with a focus on

hemophilic arthropathy. Prophylaxis with clotting factor concentrates is the standard of care for bleeding prevention. The best timing or regimen to start prophylaxis to avoid joint disease development of neutralizing antibodies to clotting factors are still being discussed. Except for the German hemophilia database documenting a limited set of data, no data are available on incidence, treatment, clinical course and outcome of newly diagnosed hemophilia patients in Germany.

Methods: Thus, the Standing Committee Paediatrics of the Society for Thrombosis and Haemostasis Research (GTH) has establishing the multicentre, prospective, observational registry GEPHARD. The registry documents variables related to diagnosis and therapy in hemophilic children (<18 years) with factor VIII or IX levels of <25%. GEPHARD uses similar case report forms to PedNet to allow a broad collaboration. The registry concentrates on outcome in hemophilia, including inhibitor development, offers quality assurance and serves as a base for future studies.

Results: A study group and steering committee have been established under the official auspices of the GTH. Within the first 10 months of documentation, 46 boys have been registered including 41 and 5 with hemophilia A and B, respectively. Among these, 26 have a severe, 6 a moderate and 14 a mild phenotype.

Discussion/Conclusion: The newly established German Paediatric Haemophilia Research Database - GEPHARD is open to all German HTCs and offers a broad platform to investigate any kind of treatment related research questions in newly diagnosed hemophilic children. Treatment centers participate in GEPHARD and have documented 46 children (4.6/month) so far. The longitudinal documentation is currently being started to answer treatment related questions in GEPHARD and in collaboration with existing databases.

Disclosure of Interest: None declared.

P073 | Study design for reitirate - a prospective study of rescue ITI with recombinant factor VIII Fc (rFVIIIFc) in patients who have failed previous ITI attempts

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Introduction: Inhibitor development is a serious complication to FVIII replacement therapy affecting about 30% of patients with hemophilia A (HA). High titer inhibitors preclude treatment and prevention of bleeds with FVIII products, limiting patients to bypassing agents. Eradication of the inhibitor is essential to restore patients' responsiveness to FVIII. This requires a burdensome and very costly immune tolerance induction (ITI) treatment requiring large amounts of FVIII often up to twice daily over a long period of time. Early preclinical and clinical data indicate that rFVIIIFc may allow a relatively short time to negative inhibitor titer when used for ITI treatment, possibly due to immunomodulatory effects attributed to the Fc domain of the molecule (Krishnamoorthy Cell Immunol 2016, Malec Haemophilia 2016). In order to obtain more robust clinical data a standardized protocol was developed. The study design is presented here.

Methods: ReITIrate (NCT03103542), a prospective, interventional, multicentre, open label study, aims to enroll 20 severe HA inhibitor patients, all ages, who failed previous ITI attempts. Primary purpose: To describe the outcome of ITI performed with rFVIIIFc within a timeframe of 60 weeks. Primary endpoint: ITI success. Secondary endpoints assessed during ITI treatment include time to ITI success, occurrence of relapse, number of bleeds, rFVIIIFc consumption, days of missed school or work, hospitalizations and adherence. ITI treatment: rFVIIIFc 200 IU/kg/day (once daily or divided into two daily doses) for a maximum of 60 weeks. After tolerance has been achieved, a tapering period of 16 weeks and a 32 weeks follow-up with rFVIIIFc given prophylactically follows. Success criteria: Neg. inhibitor titer (<0.6 Bethesda Unit), incremental recovery >66% of expected, and terminal t½ ≥7 hours.

Results: The study is enrolling. Study results will be presented after completion of the study.

Discussion/Conclusion: This will be the first prospective study of ITI with an extended half-life FVIII product in patients with previous ITI failure. Previously published case reports, which suggest that early tolerance can be achieved with rFVIIIFc, are few and used varying treatment protocols. Therefore there is a need for describing the outcome of ITI when using a standardized ITI protocol, especially in patients with a poor prognosis of ITI success.

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P074 | The first case in literature with psoas and iliopsoas hemorrhage of Factor XIII deficiency

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Introduction: Factor XIII deficiency is a rare, an autosomal recessive disorder. Umbilical bleeding during the neonatal period, mild ecchymosis, mucosal bleedings, spontaneous or post trauma life-threatening intracranial bleeding, menorrhagia, intra-abdominal bleeding are reported in the literatüre. There is no reported hemorrhage

with iliopsoas hemorrhage in literatüre. We report here a case, Factor XIII deficiency with psoas and iliopsoas hemorrhage.

Methods: A 8 year ages girl from Syria was admitted to our clinic for psoas and iliopsoas muscle hemorrhage. She has been living in Turkey for a year. She is diagnosed Factor XIII deficiency in another center in Turkey by the symptoms include ecchymoses, but she did not follow her regular controls. Factor XIII % 0.2 U/dL. After riding a bike falling, she had a swelling in the left thigh region. She had a severe tenderness on palpation of the left flank. Her pain radiated to the hip joint and the inguinal region She could not stand on her legs. The patient exhibited an anti-pain posture, held her left leg fixed at the hip joint. Laboratory findings were wbc: 7580 μL, HgB: 8.7 g/dL, hct:%27 plt:376000 μL, PT: 14 second, Aptt: 24 second, INR: 1.13 fibrinogen: 436 mg/dL. Radiology findings: abdominal ultrasonography showed 6-7 cm hematoma in the left psoas, iliopsoas muscle. magnetic resonance imaging (MRI) showed 7 cm hematoma in the left psoas, iliopsoas muscle. She received treatment with fresh frozen plasma 2 per 10-20 U/kg/day or cryoprecipitate. Factor XIII concentrates are not found in Turkey. Bleeding was stabilized. hgb levels were follow-up closely. she took pain killers. 7th day of her following -up therapy, she had a more severe pain in her left thigh and hgb: 5 g/dl. It was detected in abdominal tomography, hematoma was increased, measured 10 cm diameter. Fresh frozen plasma treatment were given 3 per 20 U/kg/day. 15th day of treatment intracranial bleeding was developed. She had a sudden, severe headache and focal tonic-clonic seizure. Cerebral tomography was showed intracranial bleedings as 2.5-5 cm diameter in right parietal and occipital area, cortical and subcortical areas.

Results: She was intubated, and treated in intensive care unit. She was exitus.

Discussion/Conclusion: The case highlights the importance is the first case report of severe bleedings of psoas, iliopsoas muscle bleeding in literature and also accompanied by severe intracranial bleeding.

Disclosure of Interest: None declared.

P075 | The WFH world bleeding disorders registry

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Introduction: The advancement of hemophilia care is limited by factors inherent to research in rare diseases, including small sample sizes, geographical dispersion of patients and clinically heterogeneous patient populations. Registries, with international collaboration between centres and countries, are an effective way to pool data to achieve the required sample size to conduct clinical research on rare disorders, such as hemophilia. By combining data from countries around the world, the WFH World Bleeding Disorders Registry (WBDR) will provide a large amount of real-world data on the patient clinical experience, which can be used to address important clinical questions and support advocacy initiatives. As a global organization with access to a network of 134 national member organizations, more than 1000 hemophilia treatment centres (HTCs) and numerous patients in countries with varying levels of access to care, the WFH is uniquely positioned to develop such a registry. Following the success of a pilot study, implementation of the full scale WBDR is underway.

Methods: The WBDR is a prospective, global registry of patients diagnosed with hemophilia A and B. The goals are to enroll at least 200 HTCs from more than 50 countries, and at least 10 000 people with hemophilia, during the first 5 years, aiming for representation of patients from around the world and from all levels of access to care. Minimal criteria for participation of HTCs include access to reliable internet, human resources for data entry and commitment to long-term enrollment and follow-up of patients. The WBDR database is being developed through a collaboration between the WFH, Karolinska Institute and Health Solutions.

Results: Invitations to join the WBDR were sent to 134 HTCs during the first phase of enrollment (October-December 2017). The 134 invited HTCs represent 86 countries, 6 regions and all Gross National Income (GNI) categories: 24 (28%) high income countries (GNI A), 29 (34%) from upper middle income countries (GNI B), 23 (27%) from lower middle income countries (GNI C) and 10 (12%) from low income countries (GNI D). Patient enrollment will begin in January 2018.

Discussion/Conclusion: Implementation of the WBDR has begun, with representation of all regions and economic levels of development. This global network of HTCs and patients will provide a large amount of real world data, on which evidence to improve the quality of care worldwide will be generated.

Disclosure of Interest: None declared.

P076 | A comparative analysis of subvisible particles in commercially available recombinant factor VIII products

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Introduction: Regulatory agencies place increased emphasis on the potential immunogenicity of protein aggregates in the micron range in therapeutic products. With advances in analytical technologies, these particles can now be assessed further, enabling testing of possible correlations between aggregation status, molecular structure and subvisible particle content. We aimed to assess subvisible particles in six commercially available recombinant factor VIII (rFVIII) products and to

compare particle characteristics to the level of high-molecular-weight protein (HMWP) species and size heterogeneity.

Methods: Three B-domain deleted (BDD) or truncated (turoctocog alfa [NovoEight®, Novo Nordisk], products A and B) and three full-length (products C, D and E) rFVIII products were analyzed. Samples were reconstituted and prepared for needle injection according to manufacturer instructions. The amount and morphology of subvisible particles >2 µm were assessed by micro-flow imaging (MFI). Ultraviolet (UV), size-exclusion, high-performance liquid chromatography (SE-HPLC) and static light scattering (SLS) SE-HPLC evaluated HMWP content and size heterogeneity.

Results: MFI analysis showed large variation in subvisible particle concentration among the rFVIII products. Turoctocog alfa and product A had a comparable number of particles (1000-1600 and 1800-2400 particles/100 IU, respectively). Products C, D and E had a slightly higher level of particles (1800-10 000, 5300-9100 and 3100-8400 particles/100 IU, respectively), while product B had the highest level of particles (5900-38 300 particles/100 IU). There was wide variation in particle shape and size for each product. UV- and SLS-SE-HPLC data showed that product B had the greatest amount of HMWP species, and full-length rFVIII products had a higher degree of size heterogeneity versus BDD/truncated rFVIII products.

Discussion/Conclusion: Overall, there was no association between molecular structure (full-length B-domain, BDD or truncated) and subvisible particle content. Differences in production and product handling may be the primary sources of the observed dissimilarities. In this study, turoctocog alfa (B-domain truncated) had one of the lowest levels of subvisible particles and HMWP content, and high protein size homogeneity.

Disclosure of Interest: D. Baunsgaard Employee of: Novo Nordisk A/S, A. Henriksen Employee of: Novo Nordisk A/S, A. D. Nielsen Employee of: Novo Nordisk A/S, H. W. Bagger Employee of: Novo Nordisk A/S, M. Ezban Employee of: Novo Nordisk A/S.

P077 | A case of congenital fibrinogen deficiency complicated with acute lymphoblastic leukemia

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Introduction: Afibrinogenemia is a rare hereditary coagulation disorder characterized by a bleeding tendency, which is highly variable including life-threatening and spontaneous/trauma-related bleeds. Congenital fibrinogen deficiency complicated with hematological malignancy can be life threatening.

Methods: We present a 4 years old girl with congenital fibrinogen deficiency complicated with acute lymphoblastic leukemia. This case highlights the treatment of leukemia with congenital afibrinogenemia during chemotherapy protocol and emphasizes the difficulties of treatment.

Results: A 4-year-old girl patient with a history of congenital afibrinogenemia, diagnosed at 1 day of age with intracranial hemorrhage and history of an old brother had referred to emergency department with hyperleukocytosis. Her laboratory tests showed: hemoglobin 6.9 g/dL, a platelets count of 137 000 mm^{-3}, a white blood cells count of 94 530 mm^{-3}. Peripheral smear evaluation and flow cytometric analyses showed acute lymphoblastic leukemia. At the treatment, for all this time we have been checking patient's factor 1 levels, hemogram test, aPTT/PT/INR tests not just in symptomatic times of bleeding and before invasive procedures, we also have been checking the tests periodically 2 times each week. Finally, the patient was discharged with remission after taking of the BFM ALLIC protocol without bleeding and thromboembolic event.

Discussion/Conclusion: To the best of our acknowledge, there are published cases of acute childhood leukemia in a patient with hemophilia, von Willebrand syndrome however this is the first reported case of new diagnosed acute lymphoblastic leukemia in patient with congenital afibrinogenemia. The clinicians should be vigilant to manage the issues with the bleeding complications related to afibrinogenemia, and acute leukemia together.

Disclosure of Interest: None declared.

P078 | Nonacog beta pegol (N9-GP) for prophylaxis in children with hemophilia B: up to 3.5-year data from the paradigm™5 clinical trial

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Introduction: N9-GP is a recombinant, extended half-life glycoPEGylated factor IX (FIX). The phase 3 paradigm™5 trial is assessing safety and efficacy in children with hemophilia B (FIX ≤ 2%). Data presented from a planned extension phase interim analysis (cut-off: April 1, 2016).

Methods: Main trial treated 25 children (N9-GP 40 IU/kg once weekly for 52 weeks) in 2 age groups (younger: 0-6 years; older: 7-12 years). 22 patients (groups split equally) entered the extension phase.

Results: No patients developed inhibitors over a total in-trial exposure time of 71.03 years (mean [range] exposure: 2.84 years/pt [0.21-3.76 years]; total in-trial exposure days: 3811 [152.4/pt]). Overall, 80 bleeds were reported in 20 patients; 37 occurred in 15 patients during the main phase (mean treatment period: 0.97 years/pt); 43 bleeds occurred in 12 patients during the extension phase (2.13 years/pt). Overall estimated mean annualized bleeding rate (est. ABR) was 1.52 (main phase) and 0.92 (extension phase). Spontaneous bleeds: 25 in 8 patients (est. ABR: 0.35), traumatic

bleeds: 51 in 18 patients (est. ABR: 0.72) and joint bleeds: 35 in 15 patients (est. ABR: 0.49). Overall, 88.8% of bleeds showed successful hemostatic response to treatment and 80.0% of bleeds resolved after 1 dose. In total, 459 treatment-emergent adverse events (AEs) occurred in 24 (96%) patients; most common were cough (14 [56%] patients), contusion (10 [40%]) and pyrexia (10 [40%]). Only 8 AEs in 1 younger and 3 older children were considered possibly/probably related to study medication (2 occurrences of infusion/injection site pain and 1 each of abdominal pain, diarrhea, nausea, eosinophilia, headache, and wheezing). Four serious AEs (device-related infection, upper respiratory tract infection, food poisoning and hemoptysis) occurred in 3 (12%) patients; none were study medication-related. No AEs led to study withdrawal. No systematic changes over time were seen for hematologic, hepatic, or renal parameters. There were no indications of neurologic AEs, or developmental concerns.

Discussion/Conclusion: Up to 3.5-year data from the extension trial confirm longer-term safety and efficacy of N9-GP for bleed prevention and treatment in children with hemophilia B. Fewer bleeds occurred in the extension versus main phase. N9-GP was well tolerated and no unexpected safety concerns identified.

Disclosure of Interest: E. Santagostino Consultant for: Shire, Bayer, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche, and Sobi, Speaker Bureau of: Shire, Bayer, Sobi, Biogen, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer and Roche, S. Kearney Grant/Research support from: Bayer, Bioverativ, Daiichi Sankyo, Grifols, and Novo Nordisk, Speaker Bureau of: Bayer, Bioverativ and Novo Nordisk, M. Carcao Grant/Research support from: Baxter, Bayer, Biogen, CSL-Behring, Novo Nordisk, Octapharma and Pfizer, Speaker Bureau of: Baxter, Bayer, Biogen, Biotest, CSL Behring, Novo Nordisk, Octapharma and Pfizer, F. Abdul Karim: None declared, M. Taki Grant/Research support from: Baxalta, Bioverativ, Chugai, CSL Behring, Novo Nordisk, and Octapharma, Consultant for: Chugai, Bioverativ, Speaker Bureau of: Baxalta, Bayer, Bioverativ, Novo Nordisk, and Pfizer, M.-Y. Lu: None declared, M.-L. Garly Employee of: Novo Nordisk A/S, M. Zak Employee of: Novo Nordisk A/S.

P079 | BAY 94-9027 is efficacious in maintaining hemostasis during major surgery in adults and adolescents with severe hemophilia A: protect VIII results

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Introduction: BAY 94-9027 is a prolonged-half-life PEGylated recombinant factor VIII (FVIII) product. Efficacy in maintaining hemostasis during major surgery was evaluated in a subset of patients with severe hemophilia A in the phase 2/3 PROTECT VIII study.

Methods: Patients aged 12-65 years in PROTECT VIII and the ongoing extension were included in the analysis. BAY 94-9027 dosing during the perioperative period was based on preoperative pharmacokinetic measurements and adjusted at the physician's discretion. Types of procedures and duration of surgeries, BAY 94-9027 consumption on the day of surgery, intraoperative blood loss, surgeon assessment of hemostasis during surgery, and need for blood transfusion were evaluated.

Results: 17 patients (median [range] age, 37 [13-61] years) underwent 20 major surgeries, including 15 orthopedic surgeries (9 joint replacements [hip, n = 1; knee, n = 6; ankle, n = 2], 2 open synovectomies, 3 arthroscopies, and 1 thigh hematoma evacuation), 3 complex dental extractions, 1 penile prosthesis, and 1 inguinal hernia repair at data cutoff (January 2015). Median (range) surgical duration was 102 (17–217) minutes, and median (range) dose used on day of surgery was 72.4 (43–136) IU/kg. Median (range) number of FVIII infusions on the day of surgery was 2 (1-3), with 40% of procedures requiring only 1 infusion (preoperative) on that day. Following a median (range) presurgical dose of 52.1 (41-64) IU/kg, the median (range) FVIII level (chromogenic assay; central laboratory) immediately before the second infusion was 71.6 (44-140) IU/dL; median (range) time between the presurgical and second infusions was 12.3 (3.6-50.0) hours. Hemostasis during surgery was good (13/20; 65%) or excellent (7/20; 35%) for all procedures. Intraoperative blood loss was within expected ranges for all surgeries (median [range], 50 [0-1000] mL), and blood transfusions were required in 4 patients undergoing knee surgeries.

Discussion/Conclusion: BAY 94-9027 is efficacious in maintaining hemostasis during major surgeries in adolescents and adults with severe hemophilia A. Excellent or good hemostasis with blood loss as expected was achieved in all surgical procedures, which included major orthopedic surgeries (75% of all procedures), with 40% of patients requiring only a single infusion of BAY 94-9027 on the day of surgery.

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P080 | The health care for patients with rare hereditary bleeding disorders

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Introduction: Rare hereditary bleeding disorders (RBDs) include deficiencies of coagulation factors (F) I, II, V, V+VIII, VII, X, XI, XIII.

Treatment of these patients is a complex task that requires the strategy for hemostatic therapy and interaction with other professionals.

Aim: To analyze the health care for patients with RBDs at the National Research Center for Hematology.

Methods: We observe 95 patients. The distribution of coagulation factors deficiencies in this group is FI-12%; FII-1%; FV-2%; FV+VIII-4%; FVII-54%; FX-4%; FXI-16%; FXIII-4%. There are two options to manage patients with RDBs. Outpatient care in the Department of coagulation disorders includes diagnosis, consultation, observation, hemostatic therapy (on demand/prophylactic regimen). Inpatient care is carried out in the Surgical and Orthopedic/Traumatology Departments. Gynecologic, urological and dental assistance is also possible.

Results: Within the last year 17 patients were observed. There were 12 patients addressed for the first time. By results of laboratory examination the hereditary FVII deficiency is revealed at 8 patients, F I - at 2, FXI - at 1, FXIII - at 1 patients. One patient with afibrinogenemia approaches each 1-2 months for hemostatic therapy with cryoprecipitate (on demand). To one patient with hereditary FV+VIII deficiency extraction of teeth have been executed. To one patient with hereditary FXI deficiency hemostatic therapy of FFP after plastic surgery on a mammary gland was carried out. One patient with hereditary F XIII deficiency had hemostatic therapy with cryoprecipitate after CNS hemorrhage in prophylactic regimen. Two patients with hereditary FVII deficiency were hospitalized in the Orthopedic/Traumatology department for surgical treatment (left hip joint arthroplasty and osteosynthesis of tibia, respectively). There was one pregnant patient with hereditary FVII deficiency.

Discussion/Conclusion: Patients with RBDs need lifelong observation by hematologist for control of hemorrhagic syndrome. These patients demand the special regimen of hemostatic therapy and cooperative work with other specialists in cases of operation (including extraction of teeth), pregnancy or delivery.

Disclosure of Interest: None declared.

P081 | Factor VIII assays variability in post infusion samples from persons with hemophilia A

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Introduction: Replacement therapy should be monitored in the laboratory. The one-stage clotting assay (OSA) and the chromogenic substrate assay (CSA) are the main assays used to measure Factor VIII (FVIII:C) in post-infusion samples taken from patients with severe Hemophilia A. Discrepancies between methods have been documented depending on the medication used.

Aim: Analyze the discrepancies of FVIII:C values present in post-infusion samples of Recombinants and Plasma-derived products and considering the ratio CSA/OSA.

Methods: 250 Samples of patients with severe Hemophilia A were analyzed, who had been infused with recombinant (N: 188) and Plasma-derived (N: 67) products of FVIII:C. Recombinant products (Rec) were: Advate (Ad, N: 117), Kogenate (Ko, 36) and Xyntha (Xy, N: 30). Plasma-derived products (Pd) were: Hemofil-M (He, N: 15) and Koate-DVI (Kd, N: 52). FVIII:C testing was performed using OSA (APTT-SP, Instrumentation Laboratory (IL) reagents) and CSA (Electrachrome, IL). The Instrument was ACL TOP 300 IL.

Results:

	(Average ± SD)		
Plasma-derived	**Products**	**infusion**	**samples**
Hemofil-M (N: 15):	CSA: 56.3 ± 45.3, OSA: 58.9 ± 57.1	(*P*: .5238)	CSA/OSA: 0.98
Koate-DVI (N: 52):	CSA: 56.9 ± 27.5, OSA: 59.4 ± 26.7	(*P*: .1472)	CSA/OSA: 0.94
Recombinant			
Advate (N: 117):	CSA: 58.1 ± 29.0, OSA: 56.2 ± 29.9	(*P*: .0616)	CSA/OSA: 1.08
Kogenate (N: 36):	CSA: 69.3 ± 29.5, OSA: 59.0 ± 27.4	(*P*: <.0001)	CSA/OSA: 1.20
Xyntha (N: 35):	CSA: 88.5 ± 28.2, OSA: 71.4 ± 27.9	(*P*: <.0001)	CSA/OSA: 1.41

Discussion/Conclusion: The values of Pd post-infusion samples showed differences between OSA and CSA (≤10%), CSA/OSA ratio was close to 1.00; Ad post-infusion samples showed the same. However the rest of Rec samples showed differences of 20% or even more, and CSA was higher than OSA, especially in Xy samples (B-domain-deleted). Regarding the Xy the international recommendation is to perform the curve using a specific standard in order to eliminate these discrepancies.

Disclosure of Interest: None declared.

P082 | Subdural hematoma following ventriculo-peritoneal shunt insertion in an infant with factor VII deficiency and hydrocephalus

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Introduction: Congenital factor VII (FVII) deficiency is a rare autosomal recessive bleeding disorder with clinical phenotypes ranging from asymptomatic condition to severe life-threatening bleedings like central nervous system (CNS) bleeding. Prolonged prothrombin time with normal partial thromboplastin time indicates FVII

deficiency. FVII:c levels alone cannot drive the management of the disease, as they are not able to accurately predict the bleeding risk tendency. Subdural hematoma (SDH) could develop in the presence of potential hemorrhagic diathesis due to the deficiency of clotting factors or after the Ventriculo-peritoneal shunt (VPS) insertion procedures.

Methods: We report a 3-month-old, female, full-term newborn who was admitted with the diagnosis of hydrocephalus. Hematological tests revealed prolonged prothrombin time and a factor VII level of % 0.3 percent. Brain computed tomography (CT) demonstrated ventriculomegaly and hydrocephalus secondary to the Dandy Walker Syndrome. To treat the hydrocephalus, a VPS was inserted after rFVIIa was administrated intravenously. We continued rFVIIa therapy with 35 μg/kg every 6 hours for 3 days, and then prolongation of the dose interval to once a week. There was no perioperative complication.

Results: One month after VP shunt insertion, her condition deteriorated and she became comatose. Immediate computed tomography scan revealed the subdural hematoma. A craniotomy for the removal of subdural hematoma was performed by giving 35 μg/kg of rFVIIa every 6 hours for 4 days. This treatment schedule resulted in normalization of PT, control of the central nervous system (CNS) bleeding. She also received prophylactic rFVIIa at a dose of 35 μg/kg every day with gradual prolongation of the dose interval to twice per week, after CNS bleeding. She died from ileus and infection 3 months after her first presentation to our clinic.

Discussion/Conclusion: The association of subdural hematomas after VPS insertion is a very rare complication and has, to our knowledge, never previously been reported in a factor VII deficient patient in the literature. In this paper, the clinical features and management of factor VII deficiency in such a patient are discussed.

Disclosure of Interest: None declared.

P083 | Patient perspectives on current and future treatments for hemophilia

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Introduction: Treatment options for hemophilia have advanced rapidly in the past decades and new products such as gene therapy and extended half-life coagulation factor products are currently under development. Aim: To gain insight into experiences of persons with hemophilia (PWH) with their current treatment and their perspectives on future treatment options. A better understanding of their perspectives, including burden of current treatment and adherence, will help to tailor and personalize information about new treatments.

Methods: A qualitative study was performed in PWH recruited through the Dutch Haemophilia patients' association and the hemophilia clinic at the Academic Medical Center in Amsterdam, the Netherlands. Semi-structured interviews were held with 14 persons (including 2 mothers of children aged 7 and 10) with moderate-severe (n = 3) or severe (n = 11) hemophilia A or B. Ages in the adults ranged from 21 to 74 years old. We aimed to include PWH with varying involvement in the hemophilia community and therefore possibly different levels of familiarity with new products. Interviews were transcribed verbatim. A thematic content analysis was used with the help of MAXQDA (version 12).

Results: All PWH were satisfied with the convenience of home treatment of current products. In some cases, they describe to be not fully adherent to their prescribed prophylaxis schedule and enjoy having the freedom to adjust their schedule to their activities. For them, this works well and therefore they feel they do not need a change in product. They also believed that new products would especially benefit others for whom injecting was more difficult or for those who struggle more with hemophilia. On the other hand, most of them also indicated that they were willing to switch to new products, if and when they become widely available. Lower costs, good efficacy to prevent bleeds and information provision about side effects of new products were mentioned to be important factors in their decision to switch.

Discussion/Conclusion: Among the aims of new treatments is to make them more convenient and less burdensome for patients. In this study, however, PWH did not experience their treatment as a burden. If they decided to switch, cost and safety of new products would be the main factors influencing this decision.

Disclosure of Interest: None declared.

P084 | Rare factor deficiencies and surgical approaches

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Introduction: Rare factor deficiencies (RFD) include fibrinogen defects and factor (F) II, FV, combined FV and FVIII, FVII, FX, FXI, and FXIII deficiencies. Insufficient information is available concerning this patient group, which may present with findings of severe hemorrhage. Mortality and morbidity also increase due to the limited knowledge available concerning diagnostic and therapeutic methods and surgical approaches. We here report demographic features, clinical follow-up, surgical approaches and the treatment of cases with RFD.

Methods: We retrospectively evaluated 37 patients with RFD. Patients' demographic characteristics, age at presentation, type of bleeding at diagnosis, clinical findings, operations performed and surgical approaches were recorded.

Results: Sixty-four points eight percent of the patients were male and 35.2% female. The most common factor deficiency was FVII deficiency (29.7%). Parental consanguinity was determined in 48.6% of cases. Adenoidectomy was performed on 27% of patients with FVII deficiency. Circumcision was performed on 67% of patients with FXI deficiency and 27% with FVII deficiency, 20% with FV deficiency. Fresh frozen plasma (FFP), fibrinogen concentrate or rFVIIa were administered before surgery together with tranexamic acid. No postoperative complications were observed.

Discussion/Conclusion: We wish to emphasize that pre-operative screening is important because of the late diagnosis of asymptomatic cases with RFD. Since the clinical findings of RFDs are not obvious, patients in the preoperative period must be assessed in terms of RFD. We think that this paper will contribute to the management of diagnosis and treatment of RFD and to surgical approaches.

Disclosure of Interest: None declared.

P085 | Drug consumption and cost estimates for different recombinant factor VIII products approved for replacement treatment in patients with hemophilia A in Italy

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Introduction: Since three new recombinant FVIII (rFVIII) have recently been marketed in Italy (octocog-alfa, Kovaltry®; efmoroctocog-alfa, Elocta®; lonoctocog alfa, Afstyla®), the aim of this analysis was to provide an estimate of the annual per patient drug consumption and costs for the different rFVIII available.

Methods: The analysis is focused on prophylaxis as it is recognized as the most effective treatment for the prevention of joint complications. The frequency of administration and the dosage of each drug can vary depending on several factors. The analysis estimated the annual per patient drug consumption (in terms of number of International Units (IUs) administered) and related costs borne by the Italian National Health Service (INHS) using, as a starting basis, the indications approved for each rFVIII currently reimbursed by the INHS. For the purpose of this analysis a patient with an average weight of 70 kg was considered. The average per patient cost was estimated on the basis of the actual selling price borne by Italian facilities. Considering that, as Afstyla® was recently approved at a price higher than the current selling price of all other rFVIII, we conservatively considered its per IU cost to be equivalent to the other marketed drugs.

Results: Considering the dosage and frequency of administration reported in the Summary of Product Characteristics (20-40 IU/kg 2-3 times a week), Kovaltry®, without an increase in the unitary dose per administration, enables a reduced number of administrations per year. On this basis, all other therapies are associated with a higher level of drug consumption than Kovaltry®; in particular, the standard therapy is associated with a + 17% increase in consumption of rFVIII, turoctocog (Novoeight®) +31%, Elocta® +17% and Afstyla® +19%. Regarding the acquisition costs of rFVIII for Italian facilities, as a result of this reduced frequency of administration, Kovaltry® is also associated with the lowest per patient acquisition cost.

Discussion/Conclusion: As a result of the potential reduction in the number of administrations per year without increasing dosages, Kovaltry®, used at approved dosages and frequency of administration, can potentially lead to cost savings, improved therapy compliance and, with a reduced risk of breakthrough bleedings and related complications, enhanced quality of life for patients.

Disclosure of Interest: None declared.

P086 | Haeminnov ethnographic study to improve the management of patients with hemophilia (PWH): description of the methodology

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Introduction: Ethnography, a qualitative method based on observation, allows powerful lessons to be drawn from a small and significant sample of users.

Methods: The innovative scientific approach used in this study involves three main steps: understanding common practice, the creation of ideal experiences to meet identified needs, and the definition of specific offers. Its value is derived from the combination of three areas of expertise: humanities, design and consulting. Although this approach has proven its worth in many areas, this is the first time that it is being used in the context of a project on hemophilia, where it enabled the identification of areas for improvement to focus on in the management of PWH.

Results: First, ten PWHs and their relatives were observed for a total 30 hours of natural observation and interviews. Then they filmed themselves in their daily life, which provided a total of 10 hours of self-observation. In order to gain a better understanding of the major trends and issues in this community, eight caregivers, two health anthropologists and a representative of the French Haemophilia society (AFH) were also interviewed. Two hemophilia centers were also visited. A semiotic analysis allowed studying codes of masculinity in the context of this disease.

Discussion/Conclusion: Overall, five key lessons emerged from the multidisciplinary analyses performed, and four areas of opportunity for the development of innovative solutions in partnership with the AFH and caregivers.

Disclosure of Interest: F. Genre-Volot Consultant for: Roche, R. d'Oiron Consultant for: Roche, M. Makhloufi Consultant for: Roche, M. Raymond Consultant for: Roche, T. Sannie: None declared, B. Debaecker: None declared, A. Guyot Employee of: Roche, A. Pruvot Employee of: Roche, A. Delcourt: None declared.

P087 | Control of variceal bleeding in a patient with severe hemophilia A and factor VIII inhibitors using rFVIIa, aPPC and platelet transfusion

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Introduction: Many patients with hemophilia became infected with hepatitis C virus (HCV) before virus inactivated clotting factors have developed. The complication of cirrhosis is particularly challenging in patients with bleeding disorders, especially those with inhibitors. Bypassing agents that may circumvent the inadequate activation of factor X in classical hemophilia, have demonstrated a high degree of efficacy in life threatening bleedings.

Methods: We report a 49-year-old man with severe hemophilia A complicated by a high titer factor VIII (FVIII) inhibitor (124 Bethesda Units) who presented with hematemesis and hemodynamic compromise.

Results: He was known to have chronic HCV viremia which was recently cleared with sofosbuvir-ledipasvir therapy. After detection of esophageal varices, upper endoscopic interventions were performed annually since 2014. According to the hemophilia treatment care he was on a prophylactic treatment of aPCC with 1500 IU three times a week. PE revealed a small liver and splenomegaly. Initial investigations revealed PT 15s, aPTT 112s. Pancytopenia which detected from the previous investigations was attributed to hypersplenism. He required a four-unit erythrocyte transfusion at presentation. He was managed with fluid resuscitation, blood transfusion, aPCC 100 IU/kg every 12 h, IV glypressin, tranexamic acid and antibiotics. Following investigations revealed Hb 6.3 g/dL, WBC 2400 10^3 µL, platelets 22000 10^3 µL. There was evidence of on-going active hemorrhage so pd-aPCC was withdrawn and activated recombinant human factor VII molecule (r-FVIIa) was administered with a dose of 90 µg/kg every 2 hours. Also he required a two-unit apheresis platelet transfusion. After controlling on-going active hemorrhage the patient underwent endoscopy with variceal sclerotherapy. After endoscopy there was no evidence of bleeding and r-FVIIa was switched to pd-aPCC 80 IU/kg per day to continued to 7 days and then prophylactic aPCC 1500 IU three times a week was initiated again.

Discussion/Conclusion: The management of acute bleeds in hemophilia A patients with inhibitors is challenging. Additional conditions like cirrhosis, splenomegaly and pancytopenia attributing to hypersplenism make management more challenging. In life threatening bleeding in hemophilia patients with persistent inhibitors, treatment of bypassing agents should be considered.

Disclosure of Interest: None declared.

P088 | The relationship between inhibitor development factor VIII with interleukin-10 and tumor necrosis factor alpha genotypes in hemophilia A

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Introduction: Inhibitor development against exogenous factor VIII (component or recombinant) is the major challenging replacement therapy. IL10 and TNF a are 2 factors can affected immune responding of patients to exogenous infused factor. Thus in the present study, we assessed relationship between 2 main gene variation of IL10 (1082 A>G) and TNFa (308 G>A) and risk of inhibition formation in patients with severe Hemophilia A (HA) patients.

Methods: In the case-control, we selected 78 affected HA patients and subsequently divided 2 groups of cases (patients with inhibitor) and control (patients without inhibitor). Titer of factor VIII inhibitor was determined by Bethesda method and was reported as IU. Patients genotyping for IL10 and TNFa gene variation was performed by PCR-ARMS and finally data was analyzed using SPSS version 18 software.

Results: Analysis of TNFa (308 G>A) polymorphism displayed the allele of G/C and G/A polymorphism was found with higher frequency in the inhibitor cohort study. In IL10 analysis (1082 A>G) A/A allele was represent more frequency in patients with alloantibodies.

Discussion/Conclusion: These findings showed that polymorphisms of IL10 and TNFa correlated with developing inhibition of factor VIII in severe hemophilia A.

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P089 | Intracranial bleeding in a female hemophilia patient: molecular analysis of factor 8 and determination of a novel mutation

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Introduction: Although Hemophilia A is typically seen in males, females can be presented as carriers and rarely as patients. The phenotypic expression of the disease in females could result from different mechanisms. Skewed inactivation of the X chromosome leading to inactivation of the wild type X chromosome, numerical and structural

anomalies like Turner syndrome or translocations. In societies where consanguineous marriages are common, female hemophilia patients can be born from a hemophiliac father and a carrier mother.

Methods: 11 months old female patient was admitted to the emergency department with right occipital fracture and epidural hematoma. The father of the patient had severe hemophilia A and the parents were cousins. At admission the laboratory tests were revealed normal CBC and prolonged aPTT. Mixing test showed normal aPTT after mixing. After plasma was collected for further diagnostic tests, Fresh Frozen Plasma (FFP), dexamethasone was administered. Epidural hematoma was drained.

Results: The Factor VIII level was: 0.1%, 35% and 0.5%, of the patient, mother and father respectively. The patient's VWF level was: 128 IU/mL, VWF:Ricof: 110 IU/mL, collagen ADP: 110 sec and collagen epinephrine: 98 sec. In order to detect the molecular etiology, intron 22 inversion was investigated with IS-PCR method and was found to be normal. Karyotyping was 46,XX. Whole Genome Analysis including all exonic regions of F8 gene was made and homozygous c.608T>C (p. L203P) mutation was found. This mutation was not previously reported. After the Factor VIII level was detected pdFVIII 2 × 500 IU/day was administered for 14 days followed by 300 IU/week prophylaxis. Inhibitor screening at 5th and 10th exposure days were negative.

Discussion/Conclusion: The father and the patient had homozygous and mother had heterozygous c.608T>C (L230P) mutation. The clinical situation of our patient as she applied with epidural hematoma requiring surgical intervention and the reality that the family did not apply for prenatal diagnosis before birth, although the father was a hemophiliac married to a probable carrier, pointed out the importance of prenatal diagnosis in regions where consanguineous marriage is common. To sum up, hemophilia A must also be considered in female patients and VWD Type 2N and VWD Type 3 must be considered in differential diagnosis.

Disclosure of Interest: None declared.

P090 | Surgery in hemophilia patients without inhibitors-experience from a Portuguese Hemophilia Centre

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Introduction: Although patients with hemophilia A or B have an increased risk of bleeding following injury, improvements in medical technology and the introduction of Comprehensive Care Centres (CCC) allowed surgical procedures to be safely performed. This study reviews the experience of surgical treatment of hemophilic patients managed in our hospital since 2000.

Methods: A retrospective analysis of 105 consecutive surgical procedures performed at our hospital in 45 patients with Hemophilia A or B since 2000 until nowadays was carried out. Patient demographics, hemophilia severity, factor concentrate (FC) requirements during hospital stay and length of hospital stay were evaluated. The procedures included were all elective, except two that were performed urgently, and 43% were major surgeries (45 out of 105).

Results: Mean age of the patients was 45 yo (14-73), and 22 out of 45 were severe hemophiliacs. An average of 2.36 procedures were performed per patient. All 60 minor procedures were non-orthopedic surgeries (NOS), whereas in the major procedures group 60% (27 out of 45) were orthopedic surgery (OS). Comparing major and minor surgery groups we found significant differences in the mean length of stay (minor: 0.4 days, major: 12 days) and average FC requirements per surgery (minor: 7000 UI, major: 49 650 UI). In the minor procedures group only 2 patients needed more than 20 000 UI per surgery: one with severe HA who underwent circumcision at 15 yo and a moderate HB patient who underwent sacrococcygeal pilonidal sinus surgery. Concerning major surgeries, we found average CF requirements per surgery were significantly higher for OS than NOS (60 500 UI for OS against 33 300 UI for NOS). All patients experienced full recovery after surgery, with no bad outcomes to report.

Discussion/Conclusion: As expected, major surgery requires more CF and longer inpatient stay than minor surgery, but this study also emphasizes, among major surgeries, the significant burden of orthopedic surgery in hemophilia patients. Despite the increased hemorrhagic risk associated with hemophiliac surgeries, the therapeutic weapons currently available allow for a safe surgical approach to these patients, when there is appropriate factor replacement and good support from the hematology team

Disclosure of Interest: None declared.

P091 | Treating acute bleeding in adolescent patients with congenital fibrinogen deficiency: pharmacokinetics and efficacy of a new fibrinogen concentrate

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Introduction: People with congenital afibrinogenemia can experience frequent/severe bleeding episodes (BE). Human fibrinogen concentrate (HFC) can correct the hemostatic defect and arrest bleeding. We

studied the pharmacokinetics (PK) and efficacy of a new highly purified, double virus-inactivated HFC (Octafibrin/Fibryga, Octapharma) in adolescent patients.

Methods: Data were from two multinational, prospective, open-label studies. FORMA-01 studied PK of the new HFC vs. comparator (Hemocomplettan P), surrogate efficacy and safety, after single infusion of 70 mg/kg. Surrogate efficacy was thromboelastometric maximum clot firmness (MCF) in plasma. FORMA-02 assessed hemostatic efficacy on a 4-point objective scale, MCF and safety for on-demand treatment of BE.

Results: Data were available for 8 patients aged 12-17 years with afibrinogenemia. In FORMA-01, mean ± SD PK data (n = 5; 1 patient excluded due to protocol deviation) for new HFC vs. comparator were: AUC_{norm}1.57 ± 0.44 vs. 1.29 ± 0.67 h·kg·g/L/mg; clearance 0.68 ± 0.18 vs. 0.91 ± 0.33 mL/h/kg; $T_{1/2}$ 72.8 ± 16.5 vs. 64.8 ± 11.9 h; incremental *in vivo* recovery 1.95 ± 0.41 vs. 1.52 ± 0.21 mg/dL/(mg/kg). In adults, AUC_{norm} was larger and clearance slower for new HFC vs. comparator (both $P = .0027$). 1 h after infusion of new HFC or comparator, mean ± SD MCF (n = 6) increased from 0 mm to 9.0 ± 2.0 and 8.8 ± 2.6 mm, respectively (9.9 ± 3.3 and 10.4 ± 4.9 mm in adults). In FORMA-02, 2 pediatric patients received new HFC individually dosed for treatment of BE (mean dose 62.8 mg/kg per infusion). Mean MCF increased by 5.5 ± 0.7 mm 1 hour after first infusion (6.6 ± 3.0 mm in adults). In both cases, treatment efficacy was rated excellent. There were no related serious adverse events, no severe allergic or hypersensitivity reactions, no thromboembolic events, and no anti-fibrinogen antibodies were detected.

Discussion/Conclusion: Data from two prospective studies demonstrate the favorable PK, efficacy and safety profile of the new HFC in adolescents with afibrinogenemia. There were no marked differences with new HFC in patients under vs. over 18 years, and PK parameters were broadly comparable vs. comparator HFC in this small group of adolescents. After infusion of new HFC, MCF increased significantly and hemostatic efficacy was rated excellent. No safety concerns relating to the new HFC were identified.

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P092 | Factor IX concentrate expenditure in non-severe hemophilia B

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Introduction: Replacement therapy for hemophilia B patients is administered through on-demand or prophylaxis regimens depending on the severity of the bleeding phenotype which is related to the degree of the FIX defect.

Methods: Retrospective data for a twelve month period of time were obtained from the registries at the Hemophilia Comprehensive Care Centre in Skopje, Macedonia. The amount of F IX concentrate used at a clinical settings as well as concentrate administration prior to minor surgical procedures or ambulatory replacement therapy for the treatment of bleeding episodes were statistically analyzed. No data from transfusion services from other regional transfusion centers in the country were included.

Results: The total number of hemophilia B patients in Macedonia counts 179 with predominant number of mild cases (92.7%). From July 2016 to June 2017, 522 000 IE FIX concentrate were used. In clinical facilities were registered an administration of 193 000 IE. Most of the amount was used for treatment of gastrointestinal (GI) bleeding as well as the rest for joint bleeds (25 500 IE), treatment of dental bleeding (8000 IE) as well as prior to minor surgical interventions (3000 IE). 59.7% was used for home therapy treatment of mainly severe cases of hemophilia. 150 000 IE (28.7%) were used for treatment of severe GI bleeding at a mild hemophilia patient.

Discussion/Conclusion: Significant amount of factor concentrate was used for treating bleeding episodes of non-severe cases of hemophilia which consists 1/3 of the total annual FIX concentrate expenditure on a clinical setting. The atypical bleeding phenotype as well as the need for a prophylactic treatment regimen of non-severe cases, may lead to high factor concentrate expenditures which may become difficult to provide in countries with limited resources of factor concentrates.

Disclosure of Interest: None declared.

P093 | Modeling the impact of factor administration and antithrombin level on thrombin generation

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Introduction: Hemophilia A and B are bleeding disorders characterized by insufficient thrombin generation due to deficiencies in factor VIII and IX, respectively. Intravenously administered replacement factor, given either prophylactically or on-demand, is typically used to support adequate production of thrombin to either prevent or treat bleeds. Fitusiran is a once-monthly, subcutaneously administered investigational RNA interference (RNAi) therapeutic targeting antithrombin (AT) as a means to improve thrombin generation and promote hemostasis in patients with hemophilia A and hemophilia B with or without inhibitors (Pasi KJ et al. *NEJM*. 2017). Patients on fitusiran experiencing a bleed may require treatment with factor replacement; thus, a deeper understanding of the relationship between AT level, factor dosing, and thrombin generation is needed.

Methods: We developed a novel modeling framework that integrates standard half-life factor pharmacokinetics with a quantitative

systems pharmacology (QSP) model describing the coagulation cascade (Nayak S, et al. *CPT Pharmacometrics Syst. Pharmacol.*, 4: 396-405.) to simulate the thrombin generation that patients would experience with single and multiple doses of standard factor treatment at various levels of AT lowering. Using Matlab and the Simbiology Toolbox®, we simulated thrombin generation as a function of time for conditions consistent with the factor dosing guidelines for patients on fitusiran.

Results: Our modeling results suggest that with ≥75% AT lowering (i.e., at target fitusiran pharmacodynamic effect), lower than typical doses of factor VIII (approximately 10 IU/kg) in patients with severe hemophilia A or of factor IX (approximately 20 IU/kg) in patients with severe hemophilia B are sufficient to result in peak thrombin levels that should provide adequate hemostatic effect and minimize risk for thrombosis. This supports the use of reduced factor doses for the treatment of breakthrough bleeding events that may occur during fitusiran therapy.

Discussion/Conclusion: Our integration of pharmacokinetics and a QSP model provides clinical insights and support for guidance on the concomitant dosing of replacement factor to treat breakthrough bleeds while on fitusiran.

Disclosure of Interest: None declared.

P094 | Switching to rIX-FP prophylaxis reduces injection frequency and factor IX consumption: a single centre experience

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Introduction: rIX-FP (IDELVION®) is a long-acting recombinant factor IX (FIX) linking human FIX with recombinant human albumin for the treatment of hemophilia B. Clinical studies with rIX-FP have demonstrated a significantly improved pharmacokinetic profile compared to conventional rFIX and also demonstrated low bleeding rates, with prophylaxis dosing intervals of 7 to 14 days. rIX-FP is now commercially available in a number of European countries and data on the physician and patient experience of using rIX-FP in a real-world clinical setting is needed. Here, we present our experience of switching patients to rIX-FP at the University Clinic Bonn, Germany's largest hemophilia treatment center.

Methods: Ten severe hemophilia B (FIX <1%) patients, receiving either plasma-derived FIX (n = 5) or another recombinant FIX product (n = 5), were switched to rIX-FP based on different medical reasons. Patients were aged 13–61 years, with a median age of 32 years and had 18 joint arthropathies between them. Prior to switching, patients were injecting FIX twice a week (n = 5), three-times per week (n = 2) or every other day (n = 3). All patients were assigned to a 7-day prophylaxis regimen.

Results: To date, we have accrued 8-patient years of experience with rIX-FP with patients being treated for a mean duration of 9.6 months with more than 1 million IU. In these 10 patients, rIX-FP prophylaxis resulted in a 63% reduction in the mean number of annual injections (138 vs. 52 injections per year; $P = .0003$) and a 53% reduction in mean FIX consumption (289 120 IU vs. 135 200 IU; $P = .0002$). rIX-FP demonstrated very good efficacy in prophylaxis with no spontaneous or joint bleeds reported. Only eight bleeds occurred in five patients, all of which were traumatic muscle bleeds that were successfully treated with rIX-FP. rIX-FP was well tolerated with no patients developing inhibitors to FIX or rIX-FP. Patient satisfaction with rIX-FP treatment was high.

Discussion/Conclusion: Switching patients to rIX-FP prophylaxis significantly reduced both injection frequency and FIX consumption whilst offering excellent protection from bleeds.

Disclosure of Interest: G. Goldmann Consultant for: Bayer, Shire, Novo Nordisk, Sobi and Octapharma, Speaker Bureau of: Bayer, Shire, Pfizer, CSL Behring, Novo Nordisk, Sobi and Octapharma, N. Marquardt Consultant for: CSL Behring, Novo Nordisk, Bayer, Pfizer and Swedish Orphan Biovitrum, Speaker Bureau of: Baxalta, Bayer, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum, S. Horneff Consultant for: Bayer and Octapharma and has received travel support from Novo Nordisk, Baxalta and Bayer, C. Klein Consultant for: Roche and Shire and has received travel support from Novo Nordisk, Baxalta and Bayer, J. Oldenburg Grant/Research support from: Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma and Pfizer, Consultant for: Baxter, Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum, Speaker Bureau of: Baxter, Bayer, Biogen Idec, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Swedish Orphan Biovitrum.

P095 | Prophylactic dosing of rIX-FP maintains high observed and steady-state trough fix activity levels in patients with hemophilia B

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Introduction: rIX-FP (IDELVION®), a long-acting fusion protein linking recombinant human Factor IX (FIX) with recombinant human albumin, is used to treat hemophilia B. Maintaining high FIX activity trough levels enables patients to transition from severe to moderate/mild disease states, reducing bleed frequency. Sustained FIX activity levels are critical to achieve persistent pharmacological effects from FIX replacement. This analysis evaluated mean observed and steady-state trough FIX activity levels in previously treated adult and pediatric

patients with hemophilia B (FIX ≤2%) during prophylaxis with rIX-FP in two clinical trials.

Methods: Adults (≥12 years) with hemophilia B received rIX-FP prophylaxis every 7- or 14-days and had trough FIX activity levels measured every 4 weeks before each infusion over a maximum period of ~70 weeks. Pediatric patients (<12 years) received prophylaxis every 7 days and had trough FIX activity levels measured at 4, 12, 24 and 36 weeks. All patients with ≥1 measurement obtained at observed trough were included in the analysis. Steady-state trough FIX activity levels included only FIX trough samples after three consecutive doses on 7-day regimen, and two consecutive doses on 14-day regimen.

Results: In adults, the mean (standard deviation [SD]) observed trough FIX activity levels were 22% (7.7) [n = 45] for the 7-day and 13% (6.8) [n = 18] for the 14-day regimen. The 32 patients receiving 30–50 IU/kg rIX-FP every 7 days had a mean (SD) steady-state FIX level of 21% (6.6) [mean dose = 41.3 IU/kg] and the 16 patients receiving 50-75 IU/kg rIX-FP every 14 days had a mean (SD) steady-state FIX level of 13% (7.3) [mean dose = 73.5 IU/kg]. Pediatric patients (n = 24) receiving rIX-FP every 7 days had a mean (SD) observed trough FIX activity level of 12% (4.5). In the 13 pediatric patients receiving 35–50 IU/kg, mean (SD) steady-state trough FIX activity levels were 14% (4.4). Overall, 96.2% and 97.9% of steady-state trough samples were >5% across all doses and dose intervals in adult and pediatric patients, respectively. The median annualized spontaneous bleeding rate was 0 with all regimens.

Discussion/Conclusion: In keeping with the low median annualized bleeding rates observed in adult and pediatric patients, rIX-FP maintains FIX activity levels with both 7- and 14-day prophylaxis dosing regimens at levels consistent with a mild hemophilia B phenotype.

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P096 | Treatment of factor V deficient patients and perioperative decisions using global hemostatic coagulation assays

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Introduction: Congenital factor V deficiency (FVD) is a rare bleeding disorder with an estimated incidence of 1 in 1 000 000 in the general population. Since the common coagulation tests do not correlate with the bleeding tendency there is an unmet need to predict FVD patients' bleeding hazard prior to surgical interventions.

Aim: Extensive laboratory workup was performed using global coagulation assays, thrombin generation (TG) and rotating thromboelastogram (ROTEM), in order optimize treatment prior to surgical interventions.

Methods: Our cohort included 5 patients with severe (n = 4) and mild FVD. Two patients underwent TG and ROTEM with ex vivo spiking assays of bypass agents and platelets prior to surgical interventions.

Results: All five patients exhibited prolonged PT and PTT, non-dependent on their bleeding tendency. Patient 1, who demonstrated severe bleeding phenotype, underwent surgery treated by combination of low dose APCC (FEIBA) and platelet transfusion. Therapy was guided by global tests (TG as well as ROTEM) results. During the peri- and post-operative period neither excessive bleeding nor any thrombosis was noted. In contrast, TG and ROTEM analysis of patient 4 has lead us to perform the surgery without any blood products' support. Indeed, the patient did not encounter any bleeding.

Discussion/Conclusion: Global coagulation assays may be useful ancillary tools guiding treatment decisions in FVD patients undergoing surgical procedures.

Disclosure of Interest: None declared.

P097 | Periprosthetic bone mineral density after ankle prosthesis. Preliminary observations from two clinical cases

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Introduction: The standard treatment for ankle arthropathy is arthrodesis, but this technique stresses the adjacent joints, while ankle prosthesis maintains the physiological gait. Aseptic mobilization is related to periprosthetic bone loss. Bone Dual X-ray absorptiometry (DXA) has been shown to be an accurate tool for evaluating periprosthetic bone mineral density (BMD) after arthroplasty. Applying a *Metal Removal* software it is possible to quantify bone mass in order to identify early prosthesis mobilization. In our center we have introduced a new application of DXA for ankle periprosthetic analysis and a new post-surgical rehabilitation protocol that allows early weight loading, in order to maintain the ankle bone mass.

Methods: We report here the preliminary observations of two patients who underwent ankle arthroplasty at our hospital. The bone-prosthesis integration was evaluated by means of DXA and x-ray of the ankle joint, with follow-up of 3 months. The first patient (P1) was treated with the classical rehabilitation protocol (immobilization after surgery for 1 month). The second patient (P2) underwent a new rehabilitation protocol, without immobilization of the joint

and with an early rehabilitation program that started on the 3rd postoperative (PO) day. From the 21st PO day, a partial weight load was permitted.

Results: The periprosthetic BMD of P1 was 1.23 g/cm^2 at the tibia and 0.94 at the talus before surgery. At 1 and 3 months after surgery it was 1.11-0.80 and 1.03-0.77 g/cm^2, respectively. The periprosthetic BMD of P2 was 1.43 g/cm^2 at the tibia and 0.97 at the talus before surgery. At 1 and 3 months after surgery it was 1.26-0.95 and 1.6-0.90 g/cm^2, respectively. These preliminary observations support our hypothesis that early rehabilitation may be associated with less bone mass loss than the traditional immobilization scheme.

Discussion/Conclusion: The use of ankle bone densitometry was shown to be a valid tool for evaluating periprosthetic bone mass following an ankle prosthesis. Our preliminary observations suggest that in the rehabilitation of the hemophilic patient with ankle prosthesis, an early mobilization and weight load are desirable, in order to limit loss of function and bone mass. Further investigations are required to evaluate the potential for reducing the risk of aseptic mobilization.

Disclosure of Interest: None declared.

P098 | In vitro characterization of an activated prothrombin concentrate and the effects of individual components in combination with rFVIIa

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Introduction: The mechanism of action of rFVIIa (recombinant activated factor VII) is limited to platelets, whereas activated prothrombin concentrates ([FEIBA®]) restore hemostasis through multiple modes of action and are a composition of many coagulation factors. While both are efficacious bypassing therapies for treatment of bleedings in hemophilia A (HA) patients with inhibitors, only limited knowledge of combining these two therapies is available. The aim with this study was to identify and quantify the individual procoagulant components of [FEIBA®]. In addition, to investigate by thromboelastography (TEG) and thrombin generation test (TGT) the effects of combining [FEIBA®] or the individual components with rFVIIa.

Methods: The concentrations of the various procoagulants in 1 IU of [FEIBA®] were determined using specific Biacore™ assays developed for each individual component. In vitro effects of different combinations of rFVIIa and [FEIBA®] components were measured by TEG in FVIII-inhibited whole blood, and by the Calibrated Automated Thrombogram (CAT) assay in HA plasma. Clinically relevant concentrations of rFVIIa and [FEIBA®] were tested along with combinations of rFVIIa with individual [FEIBA®] components based on experimentally determined values and adjusted to reflect the amount in circulation immediately after a standard dose of 50 IU/mL.

Results: The specifically designed Biacore™ assays allow the detection and quantification of individual components of [FEIBA®]. In the TGT, peak thrombin increased dose dependently for both rFVIIa and [FEIBA®] and when combining rFVIIa and [FEIBA®] an additive effect was observed. In this assay only minimal effects of the key individual components (FII, FIX, FIXa, FX and FXa) with or without rFVIIa were observed. The combination of these five coagulation factors approaches the full response of [FEIBA®]. The studies using TEG closely followed the observations in the TGT.

Discussion/Conclusion: Both [FEIBA®] and rFVIIa showed dose-dependent effects in vitro in HA plasma and in FVIII-inhibited whole blood. Results from both assays suggest additive and not synergistic effects of combining rFVIIa with [FEIBA®] or with the tested individual [FEIBA®] components. When combining FII, FIX, FIXa, FX and FXa the effect approaches the full response of [FEIBA®].

Disclosure of Interest: G. Blouse Employee of: Novo Nordisk A/S, L. F. Larsen Employee of: Novo Nordisk A/S, M. Ezban Employee of: Novo Nordisk. A/S.

P099 | Relationship between prophylaxis regimen, BAY 81-8973 pharmacokinetics and ABR: an analysis of leopold kids data

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Introduction: Individualization of FVIII prophylaxis is important to optimize treatment effectiveness in hemophilia A. This analysis investigated the association between routine prophylaxis with BAY 81-8973 (Kovaltry®) and bleeding outcomes after adjusting for key patient and pharmacokinetic (PK) characteristics.

Methods: LEOPOLD KIDS evaluated safety and efficacy of prophylaxis with BAY 81-8973 in 51 previously treated male children aged ≤12 with severe hemophilia A. Patients received BAY 81-8973 at doses of 25-50 IU/kg either 2×/week (n = 21) or >2×/week (n = 30) and were followed for 6-8 months. Prophylaxis dose and frequency were assigned by investigators. The PK parameters, area under the curve (AUC), half-life, and clearance, were derived from a population PK model and reflect predicted PK values with a dose of 50 IU/kg. Patient characteristics were compared between 2×/week and >2×/week groups using Wilcoxon rank sum or chi-square tests. Negative binomial regression was used to model the association between prophylaxis frequency and annualized number of total bleeds (ABR), first without adjustment, and then adjusting for age, PK parameters and bleed history.

Results: Mean [SD] age was 6.4 [3.0] years. Patients on 2×/week prophylaxis had more bleeds in the last 12 months before study entry (mean [SD]; median = 13.0[16.6]; 6.0 in 2×/week vs. 4.3[5.7]; 1.0 in >2×/week; $P = .027$), and were more likely to have been on demand treatment (38% vs. 10%; $P = .035$). PK parameters were similar between 2×/week and >2×/week groups. Without adjustments, the

ABR during the study was 12% higher among 2×/week group relative to >2×/week group (rate ratio [RR]: 1.12; 95% CI: [0.44, 2.90]; $P = .81$). The ABR was 36% lower among 2×/week group (RR: 0.64; 95% CI: [0.24, 1.70]; $P = .37$) after adjustment for age, AUC and number of bleeds in prior 12 months.

Discussion/Conclusion: ABR was numerically lower but not significantly different between the 2×/week and >2×/week groups after adjustment for age and PK parameters These findings suggest that even among patient groups that are homogeneous with respect to age, PK, and bleed history, further individualization of BAY 81-8973 treatment based on other characteristics may help reduce bleeds even at a lower treatment frequency. Larger real-world studies could be used to verify these findings.

Disclosure of Interest: O. Afonja Employee of: Bayer, A. Shah Employee of: Bayer, M. Sanabria Employee of: Bayer, G. Senatore Employee of: Bayer, S. Rauchensteiner Employee of: Bayer, N. Church Employee of: Bayer.

P100 | Correcting hemophilia using in vivo therapeutic protein production by an encapsulated gene modified allogeneic cell

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Introduction: Current hemophilia therapies require frequent protein infusions yet are unable to adequately address long-term sequelae due to compliance, peaks and troughs and immunogenicity. To overcome these drawbacks alternative delivery methods such as gene therapy are being investigated. The aim of this study is to determine whether the chronic delivery of blood clotting factors by implantation of gene modified cells producing factor is a more controlled viable alternative with significant upside for patients due to elimination of protein administration and better outcomes due to stable production levels.

Methods: We are investigating the secretion of blood clotting factors by a gene modified engineered cell line encapsulated with Afibromer™ polymer chemistry using a combination of in vitro (ELISA and activity assays) and murine hemophilia models.

Results: Proprietary cell line engineered to stably express high levels of hFIX or FVIII and placed in Afibromer™ capsules maintain viability, are contact inhibited and have a long-life span. A time course experiment revealed a rapid secretion of hFIX or FVIII through the capsules. Upon murine implantation hFIX is detected in the plasma at therapeutically relevant levels. We are currently performing long-term expression studies to monitor durable expression of hFIX or FVIII in vivo and also performing efficacy studies in FIX- or FVIII-deficient mice.

Discussion/Conclusion: Taken together, these data confirm the stable clotting factors secretion by our encapsulated engineered cells creating a viable alternative to protein delivery or gene therapy with several important advantages. This platform is amenable to patients suffering from blood disorders requiring chronic therapeutic protein treatment.

Disclosure of Interest: G. Carmona Employee of: Sigilon Therapeutics, L. Barney Employee of: Sigilon Therapeutics, J. Li Employee of: Sigilon Therapeutics, J. Huang Employee of: Sigilon Therapeutics, F. Caballero Employee of: Sigilon Therapeutics, D. Smith Employee of: Sigilon Therapeutics, D. Peritt Employee of: Sigilon Therapeutics.

P101 | Beyond ABR: high fix activity translates into clinical benefits

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Introduction: N9-GP is an extended half-life rFIX designed to achieve high FIX levels. While paradigm™ trials demonstrated safety and efficacy in prophylaxis (PPX) using annualized bleeding rate (ABR) as the standard efficacy measure, ABR may not adequately discriminate the impact of FIX levels.

Methods: In adolescents/adults, patients were blinded/randomized to receive 40 IU/kg (n = 29) or 10 IU/kg (n = 30) once weekly; children (n = 25) received 40 IU/kg once weekly. Post-*hoc* analyses explored peak/trough FIX activities, ABR, target joint (TJ) resolution and mobility.

Results: Mean steady-state peak/trough levels on 40 IU/kg were: age ≤6: 66%/15%; age 7-12: 71%/19%; age 13-17: 83%/24%; age ≥18: 98%/29%. Adolescents/Adults: The median overall/spontaneous ABR on 40 IU/kg and 10 IU/kg was 1.04/0.00 and 2.93/0.97. *In the 40-IU/kg arm:* While ≥90% had preexisting arthropathy/TJs, 69% had no spontaneous bleeds; 59% of 34 spontaneous bleeds occurred in 2 patients with TJ. For 63% on PPX before enrollment, mean ABR was reduced from 7.5 (historical) to 3.3. 67% had no TJ bleeds and most were resolved (90%); 56% of 9 preexisting TJ that developed on standard PPX in 6 patients were bleed-free. EQ5D VAS was improved with 40 IU/kg (mean change 8.2, 9.0 with prior PPX). Fewer patients on 40 IU/kg had any problems with EQ5D mobility (52% baseline vs 24% at end of trial; 47% vs 13% on prior PPX). For 22 completing the ~1-year extension still on 40 IU/kg, 82% were spontaneous bleed-free. Children: Overall median ABR for children was 0.0 (age 0-6) and 2.0 (age 7-12). During the main phase (1+ years)/extension (mean 2.5 years), 83%/75% of younger and 69%/69% of older children remained spontaneous bleed-free. Through the extension, only 21 spontaneous bleeds were reported by 7 patients; one older child with preexisting joint disease had 12 bleeds (57%). ABRs were reduced for 22 children compared with prior PPX (age 0-6: 2.7-0.6; age 7-12: 2.7-1.3). Two children (ages 9 and 11) had preexisting TJ on prior PPX; both resolved during the main phase.

Discussion/Conclusion: N9-GP 40 IU/kg leads to higher FIX activity throughout the once-weekly dosing interval in all age groups. *Post hoc* analyses show the impact of higher FIX activity on remaining spontaneous bleed-free over periods of years. Reductions in ABR, TJ resolution and improved mobility were seen even in patients treated with standard PPX prior to trial enrollment.

Disclosure of Interest: G. Young Consultant for: Novo Nordisk, Speaker Bureau of: CSL Behring, M. Carcao Grant/Research support from: Baxter, Bayer, Biogen, CSL-Behring, Novo Nordisk, Octapharma and Pfizer, Speaker Bureau of: Baxter, Bayer, Biogen, Biotest, CSL Behring, Novo Nordisk, Octapharma and Pfizer, S. Kearney Grant/Research support from: Bayer, Bioverativ, Daiichi Sankyo, Grifols, and Novo Nordisk, Speaker Bureau of: Bayer, Bioverativ and Novo Nordisk, S. Seremetis Employee of: Novo Nordisk Inc, D. Cooper Employee of: Novo Nordisk Inc.

P102 | Patient with hemophilia a carrier developing FVIII inhibitor after recombinant FVIII therapy

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Introduction: Hemophilia A carriers may have low factor FVIII levels although this varies widely. Inhibitor development after factor concentrates may occur in patients with mild or moderate hemophilia, also carriers due to allo-immune response. Eradication of inhibitor requires routine administration of the deficient factor to reset the patient's immune system with or without immunosuppressive therapy, or via the use of bypassing agents.

Methods: We aim to describe a patient with hemophilia A carrier who developed FVIII inhibitor after exposure of recombinant FVIII concentrate.

Results: 73 years old lady with carrier of hemophilia A was referred due to 3 months history of hematochezia. Her medical history included surgery and chemo-radiotherapy for cervix carcinoma 6 years ago. Laboratory tests revealed Hb 8.64 g/dL and prolonged aPTT 55.6 sc, which was corrected after mixing with normal plasma. FVIII level was 1.4% and FVIII inhibitor was negative. Recombinant FVIII was initiated with a dose of 60 IU/kg approximately every 12 hours for 5 consecutive days. Bleeding could not be controlled with the treatment of recombinant FVIII and she required blood transfusions. Prolongation of APTT was gradually worsened to 84.0 sc without any abnormal result with other coagulation tests. Inhibitor development was considered and mixing and inhibitor tests repeated. Mixing test failed to correct aPTT prolongation. FVIII level was 0.1 % and FVIII inhibitor was found 117 BU. Recombinant FVIIa was started with 90 μg/kg every 2 hours with oral tranexamic acid 500 mg three times a day. Methylprednisolone was initiated immediately 1 g intravenously once daily for 3 consecutive days, followed by 2 mg/kg/day for 3 weeks. By the treatment inhibitor level decreased to 4 BU and bleeding was undercontrolled. Immunosuppressive therapy switched to rituximab 375 mg/m^2 weekly to 4 cycles due to advanced age. Two months after administration, full recovery was achieved.

Discussion/Conclusion: Female patients who are carriers of hemophilia A with a low FVIII level are at risk of developing FVIII inhibitor after exposure an intensive treatment. To prevent further bleeding, immunosuppressive therapy should be initiated as soon as possible. Inhibitor development in carriers should be kept in mind. After each exposure to FVIII screening tests for detecting inhibitor should be done.

Disclosure of Interest: None declared.

P103 | Congenital macrothrombocytopenia: is it misdiagnosed?

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Introduction: MYH9-related disease (MYH9-RD) is one of the most frequent forms of inherited thrombocytopenia. It is transmitted in an autosomal dominant fashion and derives from mutations of MYH9, the gene for the heavy chain of non-muscle myosin IIA. Patients present with congenital macrothrombocytopenia with mild bleeding tendency and may develop kidney dysfunction, deafness and cataracts later in life.

Methods: Inherited macrothrombocytopenia represents a heterogeneous group of disorders, tubulin gene defects also may result in macrothrombocytopenia. Tubb1 knockout mice show thrombocytopenia and spherical platelets. Here we report our study screening macrothrombocytopenia at schools which are specialized for children with deafness for detecting macrothrombocytopenia.

Results: One hundred seventy two children with deafness were enrolled in the study (92 male, 80 female) with a median age 11.8 (4-18.5). Eleven of the children with MPV > 10 fL and seven children with platelet count <150 000/mm^3 (six with MPV > 10 fL) had undergone for whole genome sequencing for macrothrombocytopenia related disorders. Single nucleotide polymorphisms Q34P and R307H were found at TUBB1 gene. Q34P were found at four children and R307P were found at three children. Q34P and R307H were found together at two children.

Discussion/Conclusion: In conclusion, awareness of this condition will reduce the risk of misdiagnosis and the potential for inappropriate treatment of affected children with macrothrombocytopenias, which is important, given that congenital macrothrombocytopenia is a common and underdiagnosed. Especially kidney dysfunction, deafness and cataracts must be questioned at patients with chronic thrombocytopenia and TUBB-1 mutations must be in differential diagnosis when there is treatment failure at immune thrombocytopenia. The precise

molecular mechanisms will not only advance our classification and diagnosis of congenital macrothrombocytopenias, but also our comprehensive understanding of megakaryopoiesis and platelet genesis.

Disclosure of Interest: None declared.

P104 | Application of pediatric bleeding score (ISTH-BAT) in children with von Willebrand disease (preliminary study)

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Introduction: Von Willebrand disease (vWD) is the most common inherited bleeding disorder caused by quantitative or qualitative defects in von Willebrand factor (vWF). The patients most frequently suffer from mucocutaneous bleedings but clinical expression is heterogeneous with a large inter- and intra-individual variability of symptoms. In general, the frequency and severity of bleeding phenotype is associated with the type of vWD and the level of functional vWF. The aim of this study was to evaluate the frequency and severity of bleeding manifestations in children with vWD, applying the pediatric bleeding score and to investigate the correlations with the laboratory results.

Methods: Sixty nine children, aged 1-18 years and diagnosed with vWD were included in the study. Bleeding severity and frequency were determined using the International Society of Thrombosis and Haemostasis Bleeding Assessment tool (ISTH-BAT) with supplementary pediatric-specific bleeding symptoms (umbilical stump bleeding, cephalohematoma, cheek hematoma, conjunctival bleeding, postcircumcision and postvenipuncture bleeding) and the total score being rated from 0 to 56. The cause of referral and the bleeding score (BS) of children and their parents were recorded, during interviews.

Results: The mean age of children with vWD was 8.4 ± 4.7 years and 55.7% of them were girls. At first visit, the age of boys was statistically significantly lower than the age of girls (6.6 ± 4.3 vs 9.8 ± 4.6, *t*-test, $P < .05$). In total, 211 visits for clinical and laboratory investigation were recorded, with a mean number of 3 ± 1 visits per patient. The BS of mothers were significantly higher than those of fathers (Wilcoxon test, $P < .05$). In 38.4% of children's visits a zero BS was recorded. The BS had statistically significant negative correlation with the levels of FVIII ($r = -.300$), Rcof ($r = -.329$) and vWFAg ($r = -.309$) ($P < .01$) and a better correlation with FVIII with negative predictive value of 96.7%. Moreover, ROC (Receiver Operating Characteristic) analysis showed that ISTH-BAT had a high resolution to predict FVIIIc<50%, RCOF<40% and vWFAg<50% (all $P < .01$). The analysis also showed that the best value of the BS giving the best combination of sensitivity and specificity was 3.

Discussion/Conclusion: The pediatric ISTH-BAT could potentially be used as a routine tool for assessing hemorrhagic events (bleeding phenotype) in children with vWD.

Disclosure of Interest: None declared.

P105 | Concizumab exposure-response modeling in hemophilia A patients

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Introduction: Concizumab enhances thrombin generation (TG) potential by inhibiting tissue factor pathway inhibitor (TFPI). explorer™3 (NCT02490787), a phase 1b, double-blind, multiple-dose escalation trial of subcutaneously administered concizumab (0.25, 0.5, 0.8 mg/kg Q4D) in severe hemophilia A (HA) patients without inhibitors, assessed concizumab safety, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity. No safety concerns were raised and a PK/PD relationship among concizumab dose, unbound TFPI and TG was confirmed. We present post-hoc PK/PD analyses to determine the association between concizumab exposure and PD markers.

Methods: Unbound TFPI predictions were generated with an estimated exposure-response (E_{max}) model between concizumab and unbound TFPI. Concizumab concentration at time of bleed was predicted using a PK model. Unbound TFPI level at time of bleed was predicted using estimated concizumab concentration and the unbound TFPI model. The PK model was based on available data for clinically relevant doses of concizumab. Plots of unbound TFPI and peak TG vs concizumab concentrations were constructed based on explorer™3 observations.

Results: A dose-dependent, non-linear increase in concizumab exposure was shown. Dose-dependent within-patient concizumab concentration variability was observed. In higher dose cohorts, large between-patient and within-patient variability were observed. The PK model predicted once-daily dosing would minimize within-patient PK variability by minimizing the peak-to-trough differences and the influence of absorption variability. A tight PK/PD relationship between concizumab exposure and unbound TFPI was shown. A correlation between bleed frequency and concizumab concentration was shown, with least frequent bleeding for exposures >100 ng/mL and no apparent effect for exposures <100 ng/mL.

There was a strong correlation between concizumab concentration and peak TG: concizumab >100 ng/mL re-established TG potential to within normal range.

Discussion/Conclusion: A clinically relevant prophylactic effect for HA patients without inhibitors was noted at estimated concizumab exposure levels >100 ng/mL. At these levels, TG potential was mainly within normal range. Thus, the phase 2 concizumab program will target an exposure of ≥100 ng/mL, with a once-daily, efficacy-based, individual, optional dose-escalation regimen to reduce exposure variability.

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P106 | Arthroscopic treatment of anterior ankle osteophyte in patients with hemophilia

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Introduction: Joints of patients with hemophilia is prone to bleeding. The diagnosis of anterior pinch syndrome is characterized by pain and limitation in dorsiflexion in the anterior region of the ankle.

Objective: Evaluate the arthroscopic treatment for painful ankle arthropathy with mobility restriction by an anterior osteophyte compared to open surgery.

Methods: Surgery were performed in 28 patients with 30 ankles presented anterior ankle osteophyte with pain and functional limitation of the joint. The preoperative AOFAS score was taken. The days of hospitalization, days of continuous infusion and the required bolus of factors for the surgery were evaluated. Complementary studies were performed where the lesion was evident. A group of 6 patients were operated between 2008 and 2010 with conventional open surgery and the remaining 22 patients underwent ankle arthroscopy, In all patients anterior osteophyte were resected. They were given 6 weeks of postoperative discharge. Six months postoperative AOFAS score was again taken to evaluate the evolution.

Results: According to the AOFAS score, there were significant differences between preoperative 43.9 and postoperative 74.4-. In all patients (open surgery and those who underwent arthroscopic surgery) pain decreased and they were able to return to their daily activities. Statistically significant differences were found between the group of patients operated through open and arthroscopic surgery with regard to days of continuous infusion and the requirements of continuous infusion of factors.

Discussion/Conclusion: The arthroscopic treatment is a technique that allows a small approach and a shorter surgical time than open surgery with less requirement of factors, being this a benefit for the hemophilic patient

Disclosure of Interest: None declared.

P107 | Complications of ankle arthroscopy synovectomy

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Introduction: The arthroscopic synovectomy in PWH, with impingement between the tibia and the astragalus has advantages over the open surgery: is less traumatic, painful and facilitates rehabilitation. The objective of this work is to show the complications of this procedure in our treatment group.

Methods: Surgery were performed in 28 patients with 30 ankles that presented anterior ankle osteophyte. Arthroscopy synovectomy was performed in all cases.

Results: The 93% of the cases, showed good evolutions without adverse effects. We observed two (7%) complications: one, was observed in a 26-year-old patient that 6 months after surgery consulted for a tumor that throbbed in the anterior face of the ankle. The ultrasound showed a pseudoaneurysm of the anterior tibial artery. The second case, was a 30 year-old patient with advanced ankle hemophilic arthropathy, intra-articular cysts and marked osteophytes. Two weeks after surgery, abruptly, the patient lost ankle mobility. Both patients were operated again. In the first patient, an artery stent was placed in the anterior tibial artery. The second patient, a bone fragment of intra articular cartilage blocked the joint movement. This patient was surgically treated and the fragment was removed and mobility was recovered.

Discussion/Conclusion: To avoid arterial pseudo aneurysm, it´s appropriate to perform a preoperative Doppler ultrasound to see the relation of the anterior tibial artery to the arthroscopic portals. To avoid joint blockage by free fragments, an abundant joint wash must be performed before the arthroscopic procedure is completed. Both complications were quickly detected and treated.

Disclosure of Interest: None declared.

P108 | Platelet rich in fibrin (PRF) in hemophilia

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Introduction: Platelet-rich plasma (PRP) is a platelet-rich fraction of plasma is a source of growth factors to facilitate tissue repair and regeneration. Choucroum et al have described a technique for producing PRF without exogenous additives. This material placed in the surgical wound of the patients would fulfill 3 functions: biodegradable membrane that would guide the regeneration of tissues; biodegradable scaffolds for tissue engineering; reservoir of growth factors in PRP gel form, which would act as tissue regenerator and bone inductor. Use it as a hemostatic plug in the surgery area. The aim of this study is to observe the feasibility of using PRF in PWH.

Methods: For PRF preparation, venous blood is obtained without any anticoagulant and immediately centrifuged at 3000 rpm for 10 minutes. The biological steps of this centrifugation involve that the circulating blood thrombin turns fibrinogen into fibrin: this fibrin then places at the centre of the test tube. The PRF obtained will be used in two ways: a part of it is used as a filling material, with a gelatinous consistency and an amorphous shape; the remaining part is shaped in order to form a resistant fibrin membrane which can be transfer. Two hemophilia type A severe patients were treated. The average age was 42 years old (41-43). One had an elbow pseudotumor without inhibitor and the other a varus arthrosis of the knee with inhibitor, that was submitted to a valgus osteotomy. In both, post- surgical pseudotumor and osteotomy beds, were filled with PRF.

Results: We have not observed any difficulty in the preparation and use of PRF, since the biologists have made their learning curve for PRF preparation. Both patients did not present hematoma in the wound and evolved favorably of their pathology which originated the surgery.

Discussion/Conclusion: We consider that PRF should be used in hemophilia for its properties and because is it simple and low cost treatment.

Disclosure of Interest: None declared.

P109 | Total bilateral knee replacement with flexion anchylosis in PWH. Technical tips

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Introduction: Limitation of movement and flexion deformity makes difficult to perform knee replacement. This situation is common in the patient with hemophilia. Anchylosis more than 90° flexion makes TKR procedure more complex. The extensor apparatus of the knee has bone and fibrous adhesion which makes the release of the extensor apparatus very difficult. There are no descriptions that explain how to proceed in these patients. The objective of this work is to describe the surgical steps necessary to achieve TKR in anchylosis more than 90° in PWH

Methods: Patient with 37 years old with 90° right knee, and 85° left knee of flexion anchylosis, 4 years of evolution. The patient use wheelchair for displacement. Patient received VIII factor bolus before performing the procedure. Technical procedure: 1) Anterior approach centered on the knee, 2) Exposure of the extensor apparatus, 3) Osteotomy of anterior tibial tubercle, 4) Patellar osteotomy in the bone union with the articular surface. In this way the extensor apparatus is released and all adhesions can be removed from to the nearby tissues. 5) The osteotomy of the tibial plate is performed 0.5 cm from the articular surface. This osteotomy is performed without any guidance and the direction of the saw is parallel to the tibial surface. Then the knee can be flexed 120°, 6) The fixation of the tibial plate is separated from the femoral by means of the electro scalpel and osteotomo. Once the tibial fragment is resected, the femoral condyle is exposed free to continue the usual technique with the femoral guides, 7) With the knee in flexion of 120° the tibia is carried forward and the osteotomy performed in tibia is exposed and the conventional guides can be used.

Results: Both knees were operated and TKR could be performed with this technique. Six weeks after the procedure, both knees reached 90° of flexion and 0 and −10 of extension, right and left respectively; the patient also can stand up and start walking rehabilitation plan.

Discussion/Conclusion: This surgical technique is| describe for the TKR with 90 ° knee anchylosis in PWH. This technique may facilitate the practice for surgeons that perform articular replacement in PWH.

Disclosure of Interest: None declared.

P110 | Von Willebrand disease and factor XI deficiency: report of two cases

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Introduction: Von Willebrand disease (vWD) is a common, inherited, genetically and clinically heterogeneous hemorrhagic disorder caused by a deficiency or dysfunction of the protein termed von Willebrand factor (vWF). Factor XI (FXI) is a plasma glycoprotein that participates in the contact phase of blood coagulation (ie, the intrinsic pathway). Combined deficiency of VWF and FXI is an extremely rare condition. We report of two cases with VWD plus FXI deficiency.

Methods: Case 1. A 4 year-old girl presented with traumatic epidural hematoma. There was a history of easy bruising. The parents were third degree relatives. Complete blood count (CBC), and prothrombin time (PT) were normal, activated partial thromboplastin time (aPTT) was increased (45 sn) and the mixing test was negative. Coagulation factor studies revealed that FVIII:C 11%, VWF ag: 19%, VWF: RCo

23%, consistent with VWD type I. Coagulation factor concentrates including VWF and FVIII were applied, but bleeding control failed. Other factor levels were measured, and FXI level was found decreased (28%). Human factor XI concentrate was not found in our country. The bleeding was controlled using factor concentrate (VWF+FVIII) plus fresh frozen plasma. The patient diagnosed with combined VWD and FXI deficiency. Genetic studies planned.

Results: Case 2. A 18 month-old boy was admitted to our hospital with complaint of epistaxis since last 12 months. The parents were second degree relatives. Complete blood count (CBC), and prothrombin time (PT) were normal, activated partial thromboplastin time (aPTT) was increased (44 sn) and the mixing test was negative. Coagulation factor studies revealed that FVIII:C:20%, VWF ag: 12%, VWF:RCo: 31%, FXI: 28%. Other factor levels were in normal range. The patient diagnosed with combined VWD type I and FXI deficiency. Genetic studies planned.

Discussion/Conclusion: Combined factor deficiencies are rare in childhood. Some difficulties can be experienced during the diagnosis. VWD combined with FXI deficiency is extremely rare entity in childhood. VWF and FVIII containing preparats plus FXI containing preparats were convenient for replacement therapy in these patients. However, it is difficult to obtain of FXI products. In this situations, fresh frozen plasma can be used instead of FXI products. In cases where the bleeding has not been controlled despite appropriate replacement therapy, combined factor deficiencies should be kept in mind.

Disclosure of Interest: None declared.

P111 | Generation of coagulation factor VIII or IX knockout rabbits using the CRISPR/Cas9 system

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Introduction: Hemophilia is an inherited genetic disorder that impairs the ability of blood coagulation, a process needed to stop bleeding. Animal models for hemophilia are important for improved understanding of the pathophysiology of bleeding disorders and for evaluating therapeutic drugs. However, genetically engineered mice models for hemophilia have little or no apparent spontaneous bleeding and hemarthrosis, indicating that hemophilic model mice have differences from human patients and limitations therefrom. In this study, we generated coagulation FVIII or FIX knockout rabbit strains using the CRISPR/Cas9 system, which mimicked hemophilia A or B disease, respectively.

Methods: To generate hemophilic rabbits through FVIII or FIX gene disruption, a set of two sgRNAs and in vitro transcribed Cas9 mRNA for each gene targeting was prepared and microinjected into the cytoplasm of pronuclear stage zygotes. To determine the mutations of FVIII or FIX introduced by the CRISPR/Cas9 system in knockout rabbit pups, genomic DNA sequencing was performed. To evaluate whether the knockout rabbits have hemophilic properties, we performed global coagulation assays, such as activated partial thromboplastin time (APTT), modified prothrombin time (mPT) and thrombin generation assay (TGA).

Results: The efficiency of CRISPR/Cas9-mediated FVIII or FIX gene targeting reached 82% and 68.2%, respectively, after embryo transfer. Insertions and deletions (indels) were detected between two sgRNA target sites in FVIII or FIX gene knockout rabbits. Indels caused gain or loss of amino acids which is associated with hemophilia A or B disease. Compared with normal rabbits, the FVIII or FIX knockout rabbits showed prolonged APTT and reduced thrombin formation, just as in the hemophilia phenotypes.

Discussion/Conclusion: In this study, we have successfully generated FVIII or FIX gene knockout rabbits using CRISPR/Cas9 system with high efficiency and our hemophiliac rabbits by FVIII or FIX gene disruption will be very useful for preclinical studies and finding new therapeutic drugs, which may improve to hemophilia patient treatment.

Disclosure of Interest: None declared.

P112 | The surgeries in hemophilia A patients with inhibitors

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Introduction: Inhibitors are the most serious complication of hemophilia therapy. Inhibitors significantly increase morbidity and also lower "quality of life" in hemophilia patients. Treatment of inhibitors and also surgeries in hemophiliac patients with inhibitors are difficult and extremely expensive and sometimes could be life threatening. In this retrospective study, we aim to report that our surgical experiences in 18 hemophilia patients with inhibitors

Methods: We retrospectively reviewed medical records of hemophiliac patients with inhibitors who need major or minor surgery between 2001 and 2017. We used rFVIIa at the dosage of 90 mg/kg every 2 hours in 7 patients in nine surgical procedures. Activated prothrombin complex concentrates (aPCC) was given a loading dose of 75 U/kg and followed by 150 U/kg/day in two divided doses every 12 hour in 11 patients in 21 surgical procedures.

Results: During this period, 30 surgical procedures were performed in 18 hemophilia patients with inhibitors, age ranging from 5 months to 24 years with a average of 12 years. One intracerebral and subdural hematoma drainage, 6 circumcision, 1 cataract extraction, 4 port a cath insertion (CVAD replacement), 1 tonsil cauterizing and clot aspiration with bronchoscopy, 9 dental therapy and 5 radioisotope synovectomies were performed. 1 inguinal hernia operation and

circumcision, and 1 percutaneous nephrolithotomy, 1 open flexor tenotomy for hammer toes were performed. Only one patient with intracranial bleeding died postoperative period. There were no thromboembolic complications. Blood transfusion was given in 3 patients.

Discussion/Conclusion: Surgical procedures in hemophilia patients with inhibitors can present a challenge during and after surgeries because of the increased risk for bleeding complications and the potential difficulty in controlling bleeding. So, these patients need comprehensive and experienced hemophilia care centers. These centers approach ideally incorporates a number of specific pre-, intra-, and postoperative objectives for these patients undergoing surgery for safe surgical procedures.

Disclosure of Interest: None declared.

P113 | The effect of inhibitors and immune tolerance induction treatment on quality of life for adult patients with severe hemophilia; the chess study

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Introduction: Inhibitors pose a significant burden to hemophilia patients. The aim was to describe the effect of inhibitors and treatment with immune tolerance induction (ITI) on the quality of life (QoL) of severe hemophilia patients.

Methods: This study utilized data from the CHESS (Cost of Haemophilia across Europe: A Socioeconomic Survey). The sample size was 541 patients, aged 18-88, who completed the Patient Self-Completion Form. Subgroups were defined based on: diagnosis of inhibitor, history of inhibitor (first-ever/recurrent), timing of inhibitor diagnosis (currently diagnosed, first-ever inhibitor; currently diagnosed, recurrent inhibitor; previously diagnosed, first-ever inhibitor; previously diagnosed, recurrent inhibitor), and ITI administration (use of conventional factors in current; previous - unsuccessful/discontinued; previous - successful attempts). QoL was measured with EQ-5D. Descriptive analyses are presented as n (%)/mean (SD).

Results: In total, 94 (17%) patients were diagnosed with first-ever (n = 67) or recurrent (n = 27) inhibitor. Inhibitor diagnosis was associated with lower QoL for all age groups vs patients without inhibitors (n = 447) (overall score of 0.61 (0.36) and 0.79 (0.25), respectively). The highest QoL score was recorded for patients previously diagnosed with first-ever, currently resolved inhibitor (0.68 (0.30), n = 54); followed by patients currently diagnosed, with first-ever inhibitor (0.58 (0.41), n = 13); patients previously diagnosed, with recurrent inhibitor, currently resolved (0.57 (0.40), n = 14); and patients currently diagnosed, with recurrent inhibitor (0.35 (0.44), n = 13). Of the patients with current inhibitors (n = 26), 85% had moderate or extreme pain/discomfort, and 77% were moderately or extremely anxious/depressed (based on EQ-5D domains). Ongoing ITI administration (n = 9) was associated with a utility score of 0.22 (0.55), while patients who have had a successful ITI in the past (n = 25) reported a score of 0.69 (0.31).

Discussion/Conclusion: Inhibitors, especially if recurrent, are associated with low QoL. Pain and anxiety, in specific, comprise an important burden for inhibitor patients. Although ongoing ITI administration is a burden on these patients, successful ITI treatment and inhibitor eradication is related to a higher QoL, highlighting the need for more effective ITI treatment that can resolve inhibitors faster.

Disclosure of Interest: P. Kritikou Shareholder of: Sobi, Employee of: Sobi, D. Noone Employee of: HCD Economics, K.-J. Myren Shareholder of: Sobi, Employee of: Sobi, J. O'Hara Employee of: HCD Economics. The original data collection in CHESS was funded by Sobi, Bioverativ, and Novo Nordisk.

P114 | Associated impact of activity impairment on clinical and patient-centric outcomes in severe hemophilia

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Introduction: To explore the relationship between clinical manifestations and patient-centric outcomes in severe hemophilia using real world observational data.

Methods: Data were drawn from the 'Cost of Haemophilia across Europe - a Socioeconomic Survey' (CHESS) dataset, a cost-of-illness assessment in severe hemophilia A and B across five European countries (France, Germany, Italy, Spain, and the UK) conducted in 2015. Physicians provided clinical and sociodemographic information for 1285 adult patients, 552 of whom completed corresponding questionnaires covering expenditure and psychosocial impact. Activity impairment (AI) was calculated using the General Health Work Productivity and Activity Impairment (WPAI), measuring impact on a patient's ability to perform daily activities. Impairment was segmented approximately into quartiles relevant for comparison. Outcomes were compared between patients with no reported AI (0% impairment; NI) and AI >40% (>40). Relationships between AI and chronic pain (4-level physician-reported score: none, mild, moderate, severe); anxiety and depression comorbidities; incidence of target joints; HRQOL derived from EQ-5D index scores; and replacement therapy strategy (prophylaxis/on-demand) were assessed. AI and EQ-5D index scores were compared against population norms derived from US-based and UK-based studies, respectively.

Results: AI was derived from 541 patients; EQ-5D index scores were calculated for 534 patients. Anxiety was reported in 5% of the NI cohort versus 25% in the >40 cohort; depression 7% to 23%; mean target joints ranged from 1.07 (standard deviation 1.17) to 1.82 (1.88). Pain scores ≤1 (none, mild) were reported in 95% of NI

cohort versus 47% of >40 cohort. Pain scores of 2 or 3 (moderate, severe) were reported in 5% of NI cohort versus 53% of >40 cohort. EQ-5D index scores were 0.93 (0.14) in NI and 0.56 (0.33) in >40 versus population norms between 0.94 and 0.96. Patients receiving prophylaxis therapy regimens reported 34% AI; primary on-demand was 38%, and secondary on-demand was 38%, versus normative AI of 22%.

Discussion/Conclusion: The results show a clear relationship between AI, HRQOL, and determinant clinical outcomes. The WPAI is a potentially sensitive tool to capture important real world patient outcomes. Further research is required to consider potential confounding factors such as age, demographics, and other clinical variables.

Disclosure of Interest: None declared.

P115 | Associated impact of work impairment on clinical and patient-centric outcomes in severe hemophilia

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Introduction: To explore the relationship between clinical manifestations and patient-centric outcomes in severe hemophilia using real world observational data.

Methods: Data were drawn from the 'Cost of Haemophilia across Europe - a Socioeconomic Survey' (CHESS) dataset, a cost-of-illness assessment in severe hemophilia A and B across five European countries (France, Germany, Italy, Spain, and the UK) conducted in 2015. Physicians provided clinical and sociodemographic information for 1285 adult patients, 552 of whom completed corresponding questionnaires covering expenditure and psychosocial impact. Work productivity loss (WPL) was calculated using the General Health Work Productivity and Activity Impairment (WPAI), as a function of working time missed and level of impairment while working. Impairment was segmented approximately into quartiles relevant for comparison. Outcomes were compared between patients with no reported WPL (0% impairment; NI) and WPL >40% (>40). Relationships between WPL and chronic pain (4-level physician-reported score: none, mild, moderate, severe); anxiety and depression comorbidities; incidence of target joints; HRQOL derived from EQ-5D index scores; and replacement therapy strategy were assessed. WPL and EQ-5D index scores were compared against population norms derived from US-based and UK-based studies, respectively.

Results: WPL was derived from 239 employed patients; EQ-5D index scores were calculated for 534 patients. Anxiety was reported in 6% of the NI cohort versus 24% in the >40 cohort; depression 3% to 11%; mean target joints ranged from 0.90 (standard deviation 1.11) to 1.56 (1.10). Pain scores ≤1 (none, mild) were reported in 97% of NI cohort versus 60% of >40 cohort. Pain scores of 2 or 3 (moderate, severe) were reported in 3% of NI cohort versus 40% of >40 cohort. EQ-5D index scores were 0.90 (0.18) in NI and 0.69 (0.19) in >40 versus population norms between 0.94 and 0.96. Patients receiving prophylaxis therapy regimens reported 23% WPL; primary on-demand was 21%, and secondary on-demand was 30%, versus normative WPL of 15%.

Discussion/Conclusion: The results show a clear relationship between WPL, HRQOL, and determinant clinical outcomes. The WPAI is a potentially sensitive tool to capture important real world patient outcomes. Further research is required to consider potential confounding factors such as age, demographics, and other clinical variables.

Disclosure of Interest: None declared.

P116 | Plasma derived FVIII ITI outcomes in two children with hemophilia A and high titer inhibitors

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Introduction: Management of high titer inhibitors involves eradication of the inhibitor by immune tolerance induction (ITI) using the same recombinant FVIII (rFVIII) used for treatment. In standard UK practice, plasma derived FVIII (pdFVIII) is used as second line therapy when the initial ITI regimen is ineffective.

Methods: We selected patients with severe hemophilia A and inhibitors treated with a specific pdFVIII (Optivate) and compared their outcomes.

Results: Patient 1 presented to our centre at the age of 7 years with hemarthrosis in the left knee. He was an illegal immigrant into UK with a diagnosis of severe hemophilia A and no access to routine medical care. His first exposure to rFVIII was 6 days treatment at another centre in UK. He was treated on a compassionate basis with rFVIII but obtained poor clinical response and was confirmed to have an inhibitor (4.2 BU/mL). He had received cryoprecipitate in Nigeria and we were offered a fixed supply of pdFVIII (Optivate) on a humanitarian basis. He commenced ITI 3 years from inhibitor diagnosis, starting on a dose of 66 iu/kg twice daily. His historic peak titer was 289 BU/mL and titer at start of ITI was 11 BU/mL. His inhibitor rose to 133 BU/mL on ITI but became negative in the third month. Complete tolerance was achieved 2 years from ITI start. Patient 2 was diagnosed with severe hemophilia A after developing a cephalhematoma following a normal delivery. He was treated with rFVIII for 5 days followed by on demand treatment. Inhibitor to FVIII was diagnosed at the age of 23 months. The family are Nigerian in origin with no family history of inhibitors. He commenced ITI with rFVIII with a historic peak titer of 253 BU/mL. The titer at start of ITI was 69 BU/mL and this peaked to 970 BU/mL on ITI. He switched to pdFVIII (Optivate) a year later and on a dose of 100 iu/kg twice daily, the inhibitor titer reduced to 69 BU/mL and 14 months later he received a course of Rituximab. Two years from pdFVIII (Optivate) ITI commencement, his inhibitor titer is 2.4 BU/mL with a significant reduction in bleeding episodes.

Discussion/Conclusion: We have seen positive outcomes with pd-FVIII (Optivate) ITI in both our patients with poor prognostic markers for ITI success. Whilst our first patient was ITI naïve and attained complete tolerance on first attempt, our second patient received rescue ITI resulting in significant reduction in breakthrough bleeding.
Disclosure of Interest: None declared.

P117 | Recombinant von willebrand factor (rVWF) administration: dosing considerations and rapid stabilization of endogenous plasma FVIII levels in patients with severe von Willebrand disease

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Introduction: We analyzed prospective clinical trial data to better inform dosing decisions related to rVWF treatment and the pharmacodynamic effect of administering rVWF on endogenous FVIII coagulant activity (FVIII:C).
Methods: Two ph3 clinical trials were included in this post-hoc analysis: an on-demand (NCT01410227) and an elective surgery (NCT02283268) study. All patients had severe VWD. Patients who received rVWF alone (doses of 50 or 80 IU/kg VWF:RCo) were included in the analysis of mean endogenous FVIII:C over time and proportion of patients with FVIII:C > 40 IU/dL and >60 IU/dL at specific time points.
Results: This analysis included 25 patients (12 female/13 male; 19/25 with type 3 VWD) treated with rVWF 50 IU/kg VWF:RCo and 15 (9 female/6 male; 11/15 with type 3 VWD) treated with 80 IU/kg VWF:RCo. Treatment with rVWF alone resulted in rapid and sustained increases in endogenous FVIII:C, regardless of VWD type. Among 36 patients with preinfusion FVIII:C level <40 IU/dL, mean time to reach 40 IU/dL FVIII:C was 5.1 h (range: 0.8-11.5) overall and 5.6 h (range: 1.6-11.5) in patients with type 3 VWD. Patients with type 1, 2A, and 2B seem to have achieved the 40-IU/dL level faster (1.5, 4.2, and 0.8 h, respectively). Mean FVIII:C levels were 18.8 IU/dL (range: 4.0-69.8) as early as 30 min postinfusion, 56.6 IU/dL (range: 8.0-116.8) 6 h after infusion, and 98.2 IU/dL (range: 51.9-177.7) 24 h after infusion. Levels in patients with type 3 VWD were 10.9 IU/dL (range: 4.0-24.1) 30 min postinfusion, 48.6 IU/dL (range: 8.0-108.3) 6 h after infusion, and peaked at 103.8 IU/dL (range: 53.0-178.0) after a mean of 29.1 h (11.0-48.1) postinfusion. At 6 h after administration of rVWF alone, 70% (28/40) of overall and 63.3% (19/30) of patients with type 3 VWD had FVIII:C > 40 IU/dL and 47.5% (19/40) and 33.3% (10/30), respectively, had FVIII:C > 60 IU/dL.
Discussion/Conclusion: Treatment with rVWF alone results in rapid stabilization of endogenous FVIII:C. A rise in FVIII:C to hemostatically effective levels was reached in the majority of patients within 6 h, and sooner in patients with higher baseline FVIII:C levels. These data may help physicians decide whether and when exogenous rFVIII is required at the first dose of rVWF, and provide additional information on the timing of the endogenous FVIII rise in patients with different VWD types.
Disclosure of Interest: J. Gill Grant/Research support from: Shire, CSL Behring, Consultant for: Shire, Bayer, CSL Behring, Speaker Bureau of: Shire, Bayer, CSL Behring, P. Mannucci: None declared, M. Ragni Grant/Research support from: Alnylam, Shire, Biogen [Bioverativ], Biomarin, CSL Behring, Novo Nordisk, Pfizer, Sangamo, SPARK, Opko, Vascular Medicine Institute, Consultant for: Alnylam, Shire, Biogen [Bioverativ], Biomarin, Paid Instructor at: Alnylam, Shire, Biogen [Bioverativ], Biomarin, Speaker Bureau of: Medical and Scientific Advisory Board, NHF; Foundation Women & Girls Blood Disorders Medical Advisory Board [FWGBD], Blood Products Advisory Committee, Food & Drug Administration [BPAC], G. Castaman Grant/Research support from: Pfizer, CSL Behring, Speaker Bureau of: Pfizer, Sobi, Shire, CSL Behring, Kedrion, Novo Nordisk, F. Peyvandi Consultant for: Freeline, Kedrion, Biopharma, LFB, Octapharma; member of an advisory board Ablynx, F. Hoffmann-La Roche, Paid Instructor at: Ablynx, Bayer, Grifols, Novo Nordisk, Sobi, B. Ploder Employee of: Shire, A. Novack Employee of: Shire, P. Chen Employee of: Shire, A. Sytkowski Employee of: Shire, B. Ewenstein Employee of: Shire.

P118 | Does ADAMTS13 influence the bleeding phenotype in patients with von Willebrand disease?

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Introduction: The bleeding phenotype of von Willebrand disease (VWD) varies between patients and can only partly be explained by von Willebrand factor (VWF) parameters. By cleaving large VWF

multimers into smaller, less active multimers, A Disintegrin-like and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) is an important regulator of VWF activity. We therefore investigated if ADAMTS13 is associated with the bleeding phenotype in VWD.

Methods: We measured ADAMTS13 activity using the FRETS-VWF73 method in 638 VWD patients in the nationwide cross-sectional 'Willebrand in the Netherlands' (WiN) Study and 36 healthy controls. The bleeding phenotype was assessed using the Tosetto bleeding score and by determining the bleeding incidence during a 1-year period. Comparisons between groups were made with unpaired t-test or ANOVA, and associations were tested with linear regression.

Results: ADAMTS13 activity was similar in VWD patients (mean 109% ± 20.6% (SD)) and healthy controls (110% ± 19.7%). ADAMTS13 activity was higher in type 3 VWD patients (121% ± 22.3%) than in patients with type 1 (110% ± 20.2%) or type 2 VWD (106% ± 20.4%), $P < .01$. ADAMTS13 activity did not differ between type 2 subtypes ($P = .15$). ADAMTS13 activity decreased by 2.1% for every 10 year age increase (95% confidence interval (CI) 1.2% to 2.9%) in the VWD patients. After adjusting for age and sex, VWF propeptide, but not VWF antigen or activity, was associated with ADAMTS13 activity (8.4% ADAMTS13 activity decrease per 10 U/dL VWF propeptide increase, 95% CI 5.1% to 11.7%). ADAMTS13 activity was not associated with the Tosetto bleeding score, also after adjusting for age and sex (0.0 change in bleeding score per 10% ADAMTS13 increase, 95% CI −0.2 to 0.3). Furthermore, ADAMTS13 activity did not differ between VWD patients who had a bleeding during a 1-year period and those who had not (mean difference −1.4%, 95% CI −4.9% to 2.1%).

Discussion/Conclusion: In the first ever study on ADAMTS13 and bleeding, variations in ADAMTS13 activity were not associated with the bleeding phenotype in a large cohort of VWD patients.

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P119 | Quality of life and satisfaction of children and adults with severe hemophilia A treated with turoctocog alfa pegol

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Introduction: Hemophilia A treatment-related issues impact patients' quality of life (QOL) and treatment satisfaction (TS). QOL and TS data of children and adults with severe hemophilia A treated with turoctocog alfa pegol, a novel recombinant factor VIII (rFVIII) product with extended half-life which allows for less frequent dosing, are reported.

Methods: Children (ages 13-16) and adults (ages ≥ 17) with severe hemophilia A participating in the non-randomized Phase III pathfinder™2 trial were treated with 50 IU/kg turoctocog alfa pegol as prophylaxis (PPX) or on-demand (OD) for up to 27 months. QOL was assessed using hemophilia-specific QOL questionnaires (Haemo-QoL: completed by children and their parents; Haem-A-QoL: completed by adults). TS was assessed using the Haemophilia Satisfaction questionnaire (Hemo-Sat) by adults or the child's parent. All scores ranged from 0-100, lower score reflecting better QOL or higher TS. Changes in mean scores from baseline (BL) to the end of the trial (EOT) were assessed.

Results: All children (n = 16) were in the PPX arm. 157 adults were in the PPX arm and 11 in the OD arm. At BL, children had a good QOL as reported by the children's Haemo-QoL total score (18.5 ± 9.6) and by their parents' total score (25.3 ± 11.9). Over the trial, children maintained their QOL (no change in scores) and parents reported improvement for their children in the 'Physical Health' (−10.7 ± 25.0) and 'Others' (−13.5 ± 18.3) domains. At BL, adults reported an average QOL with a mean Haem-A-QoL total score of 40.6 ± 16 for the OD arm and 30.8 ± 16.5 for the PPX arm. There were no significant differences in QOL between treatment arms, however adults in the PPX arm had significant improvements during the trial in 'Physical Health' (−8.4 ± 18.1, $P < .0001$), 'Feeling' (−3.5 ± 17.7, $P = .016$), 'View' (−2.9 ± 17.9, $P = .048$), 'Work' (−4.7 ± 17.7, $P = .003$) and the Haem-A-QoL total score (−2.3 ± 8.9, $P = .002$). Parents and adults reported high levels of TS with turoctocog alfa pegol in all Hemo-Sat domains at EOT.

Discussion/Conclusion: Adults treated prophylactically with turoctocog alfa pegol reported significant improvement in several key Haem-A-QoL areas and total score. Parents reported improvement in the 'Physical Health' and 'Others' domains for their child, while children did not report differences. Parents and adults were satisfied with turoctocog alfa pegol.

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P120 | Emicizumab prophylaxis and health-related outcomes in persons with hemophilia a (PwHA) with inhibitors: HAVEN 1 study

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Introduction: PwHA with inhibitors (PwHAwI) to FVIII replacement therapies often experience decreased health-related (HR) outcomes due to burden of both disease and treatment. Emicizumab, a recombinant, humanized, monoclonal antibody, restores hemostasis by bridging FIXa and FX. In a randomized, Phase 3 study in PwHAwI (HAVEN 1; NCT02622321), annualized bleed rate (95% CI) was 2.9 (1.69; 5.02) with once-weekly (QW) subcutaneous emicizumab prophylaxis (Px) vs 23.3 (12.33; 43.89) in pts with no Px (only episodic bypassing agents [BPAs]; $P < .001$). This bleed reduction was associated with improvements in HR outcomes. We report detailed HR outcomes with emicizumab Px in HAVEN 1.

Methods: PwHAwI age ≥12 year previously on BPAs were randomized to receive emicizumab Px (n = 35) or no Px (n = 18). Pts on prior BPA Px received emicizumab Px (n = 49). HR outcomes included: HRQoL in terms of Haem-A-QoL (age ≥18 year), Haemo-QoL-SF (age 12-17 year); health status with the EQ-5D-5L index utility score (IUS) and EQ-VAS (visual analog scale); missed work/school days; days hospitalized. Clinically meaningful improvements: for Haem-A-QoL −7 (Total score) and −10 ('Physical Health' [PH]); for EQ-5D-5L: +7 (EQ-VAS) and +0.07 (IUS).

Results: The difference in adjusted mean scores favored emicizumab vs no Px at Wk 25: 22 for Haem-A-QoL PH score ($P = .003$), 14 for Haem-A-QoL Total score ($P = .002$), −9.7 for EQ-VAS ($P = .017$), and −0.16 for EQ-5D-5L IUS ($P = .001$). A greater proportion of emicizumab pts had clinically meaningful improvements at Wk 25 in Haem-A-QoL Total Score (52 vs 7%) and PH score (72 vs 29%), EQ-VAS (57 vs 19%) and IUS (50 vs 13%) vs no Px. Mean proportion missed work days was 7 vs 13% and mean (SD) number days hospitalized was 1.2 (5.0) vs 5.2 (10.0) with emicizumab Px vs no Px, respectively. In pts on prior BPA Px, mean change from baseline at Wk 25 on the Haem-A-QoL was −17 (Total score) and −22 (PH Score); on the Haemo-QoL-SF was −10 (Total score) and −21 (PH Score); and 9.2 (VAS) and 0.11 (IUS) on the EQ-5D. In this Arm, mean proportion of missed work and school days was 3 and 5%, respectively, and mean (SD) days hospitalized was 0.8 (2.8).

Discussion/Conclusion: In PwHAwI, emicizumab QW provided substantial reduction in bleeding and statistically significant and clinically meaningful improvements in HRQoL outcomes and health status. This was seen in pts previously on episodic or prophylactic BPA treatment.

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P121 | Simultaneous thrombin and plasmin generation in patients with plasminogen or plasminogen activator inhibitor type 1 deficiency

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Introduction: Deficiencies of plasminogen and plasminogen activator inhibitor type 1 (PAI-1) are rare disorders of fibrinolysis. Conventional laboratory assays of fibrinolysis lack specificity and validation. Moreover, correlation to clinical symptoms is weak. In this study, the potential of simultaneous measurement of thrombin and plasmin generation is illustrated in patients with deficiencies of plasminogen and PAI-1.

Methods: The Nijmegen Hemostasis Assay was used to simultaneously measure thrombin and plasmin generation as a derivative of the hemostatic balance in 5 patients with plasminogen deficiency and 10 patients with a PAI-1 deficiency. Thrombin and plasmin generation parameters were subdivided by initiation (lag-time and thrombin peak time), propagation (thrombin peak height and area under the curve (AUC)), and termination (fibrin lysis time, plasmin peak height and plasmin potential). All parameters are expressed as a percentage compared to normal pooled plasma of 10 healthy individuals.

Results: None of the patients with plasminogen deficiency had a thrombotic event. They all had ligneous conjunctivitis and/or gingivitis. Overall, these patients had a normal initiation, but propagation was enhanced (median AUC 143%, $P < .05$). Termination showed no plasmin generation in all patients (median plasmin peak height 15%, $P < .001$, and plasmin potential 28%, $P < .001$). All patients with a PAI-1 deficiency had a hemorrhagic diathesis. In these patients initiation was normal but propagation of thrombin generation decreased (median thrombin peak 74%, $P < .005$), with normal AUC (109%). Overall, the termination was enhanced with a shortened fibrin lysis time (median 72%, $P < .001$). There was a large variation in plasmin generation, with plasmin peak height ranging from 47% - 138% (median 94%) and plasmin potential 36% - 155% (median 83%). All of these patients had a complete absence of PAI-1 activity and antigen level.

Discussion/Conclusion: For the first time, simultaneous measurement of thrombin generation and plasmin generation was measured in patients with a plasminogen deficiency and PAI-1 deficiency. The only major difference between the two populations, apart from plasmin generation, is propagation of coagulation, potentially explained by the formation of plasmin. Subsequent studies are needed to determine the clinical relevance and correlation with the bleeding phenotype.

Disclosure of Interest: None declared.

P122 | Whole exome sequencing in patients with a bleeding tendency

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Introduction: Bleeding assessment tools and conventional laboratory assays in patients with a hemorrhagic diathesis are time consuming, expensive and often inconclusive. Next generation sequencing techniques could contribute to the diagnostic path of bleeding disorders.

Methods: Whole exome sequencing (WES) was incorporated in the routine diagnostic pathway of patients with thrombocytopenia (defined as a platelet count $<150\times10^9$/L with or without a platelet function disorder, group A, n = 14), platelet function disorders (defined as abnormal platelet aggregation with normal platelet count, group B, n = 13) or an unexplained bleeding tendency (group C, n = 29). A panel of 136 OMIM (Online Mendelian Inheritance in Man) genes involved in thrombosis and hemostasis was conducted, and if negative, further analysis with open exome performed.

Results: Twelve variants were detected in 11 patients from a total of 56 patients (20%). The highest incidence of solved cases was observed in group A (21%) with causative mutations in *MYH9* (2 cases) and *SLFN14*, causing a MYH9 associated bleeding phenotype and autosomal dominant bleeding disorder platelet-type 20, respectively. One variant of unknown significance (VUS) was found in *GFI1B*, and two carrierships of autosomal recessive disorders in *CD36* and *FGG*. In group B, one case was solved with a causative mutation (8%) in *P2RY12*, causing bleeding disorder platelet-type 8. A VUS was identified in *VWF*. In group C, one case was considered solved (3%) due to combined carriership of *F7* and *F13A1* mutations. Two patients were carriers of respectively *GP1BA* and *MPL*. Two heterozygous VUS in one patient in *NBEAL2* were not considered causative as segregation analysis showed that these variants were not compound heterozygous. Open exome analysis was performed in 37 cases out of 49 unsolved cases, and identified one likely pathogenic variation in a candidate gene. There were two unsolicited findings reported to patients: one mutation in RET (multiple endocrine neoplasia) and one in FH (hereditary leiomyomatosis and renal cell cancer).

Discussion/Conclusion: Based on our findings, we conclude that WES can contribute to a better explanation of bleeding phenotypes. Incorporating WES in the diagnostic path of patients with an unexplained bleeding tendency will result in the discovery of novel genes

that predispose to bleeding and therefore will lead to a better understanding of a bleeding phenotype.

Disclosure of Interest: None declared.

P123 | Heterogeneous landscape of RUNX1 related disorder: four families with inherited thrombocytopenias and novel genetic variants in RUNX1 associated to relevant clinical complications

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Introduction: Familial platelet disorder with propensity to myeloid malignancy (FPD/AML) is a rare autosomal dominant (AD) disease, characterized by thrombocytopenia and/or platelet functional defects. and an important increased risk of myeloid neoplasms, such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). The goal of our study was: to assess the clinical, platelet phenotype and their genetic defect of 4 unrelated families with *RUNX1* related thrombocytopenia (*RUNX1*-RT) in our cohort of 82 consecutive unrelated probands with IPDs.

Methods: We studied 5 patients from 4 unrelated families presenting with lifelong thrombocytopenia with normal platelet size. Clinical records were reviewed and bleeding scored with ISTH-BAT. Platelet phenotyping included peripheral blood smear and platelet aggregation. Patients DNAs were analyzed by HTS using a 72-gene panel related to IPDs. Causative variants were elucidated after a workflow algorithm filter previously reported (Bastida JM et al. Haematologica. 2017).

Results: The median age was 28 years old (1-54), median platelet counts was $90 \times 10^3/mm^3$ ($35\text{-}108 \times 10^3/mm^3$) and bleeding score was 3 (2-5). Family 1 (F1) showed an AD thrombocytopenia (P1, P2, brother and their mother) and a extremely history of hematologic malignancies: one brother underwent to allogeneic transplant from unrelated donor due to a high-risk MDS del(7q) and one daughter of P1 died at the age of 13 years old due to a refractory AML. In F2, a lifelong thrombocytopenia, bleeding and family history of breast cancer was characteristic; but, in F3, only a lifelong thrombocytopenia was referred. Finally, P5 showed mental retardation, corpus callosum hypoplasia, facial and cardiac abnormalities and severe thrombocytopenia. HTS revealed three novel variants affected to *RUNX1:* F1: p.Thr196Ala, P3; p.Asn159Ser, and P4:p.Gln268*; and one sporadic germ line *RUNX1* deletion involving chromosome 21q22. The missense variants affected to runt homology domain may lead to dominant-negative effects.

Discussion/Conclusion: HTS facilitates genetic confirmation of FPD/AML diagnosis, and may help investigating phenotype-genotype relationships in this heterogeneous landscape. An earlier diagnosis of this disorder improves the genetic counseling and appropriate therapeutic management.

Disclosure of Interest: None declared.

P124 | Evaluation of adherence to standard and PK tailored prophylaxis in an hemophilia A population

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Introduction: Prophylaxis treatment in hemophilia A (HA) patients should be tailored based on bleeding phenotype, physical activity, musculoskeletal status and FVIII pharmacokinetics (PK). Adherence is one of the main limitations to reach zero bleeds. Our main aim is to describe the effects of PK guided prophylaxis on an HA population in terms of clinical outcomes, FVIII consumption and adherence to treatment.

Methods: The analysis was performed on a population of 11 patients with severe and moderate HA. Clinical data included age, weight, *F8* mutation and FVIII basal level. Patients were all receiving rFVIII prophylactic treatment. PK parameters were determined using the online medical device myPKFiT. Prophylaxis regimens were adjusted to maintain a FVIII trough level above 2 or 3 %, depending on their physical activity (Broderick bleeding risk scale) and joint status (Hemophilia Joint Health Score). Standard (based on weight, bleeding phenotype and lifestyle) and PK-guided prophylaxis regimens were recorded. Clinical outcomes (annual joint bleeding rates) and FVIII annual consumptions (provided by hospital pharmacy) were documented during the standard and PK tailored prophylaxis periods.

Results: PK parameters showed high variability between patients, with a FVIII half-life ranging from 7.7 to 14.8 hours. Prophylaxis regimen was modified (FVIII dose and/or frequency of infusion) in 6 patients after PK analysis with myPKFiT. PK tailored prophylaxis led to the reduction of AJBR in 4 patients. The other 7 patients had zero AJBR during both prophylaxis regimens. However a clear discrepancy between the theoretical (calculated based on prescribed prophylactic regimen) and real FVIII annual consumption (based on pharmacy records) was found in 4 patients. These differences were reduced during the PK guided prophylaxis period. More detailed information will be included in tables.

Discussion/Conclusion: Prophylaxis protocols should be tailored considering the patient clinical and lifestyle features. Adherence to treatment must be evaluated and promoted in those patients in order to reach zero bleeds and avoid joint disease. In our experience, the use of myPKFiT graphs as an educational tool have contributed to increase adherence. It is also relevant the multidisciplinary collaboration between professionals involved in HA patients treatment to determine and improve compliance levels.

Disclosure of Interest: None declared.

P125 | Online course of pharmacokinetic monitoring in hemophilia with application in the clinical practice

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Introduction: Individual pharmacokinetics profiling (iPK) in hemophilia has become a useful tool to individualize prophylaxis in each patient. Exploiting the potential of iPK requires education of physicians to the use of PK population models in their routine clinical practice. The aim of this initiative is to provide theoretical bases to introduce hematologists in the use of WAPPS-Hemo platform in the personalization of hemophilia therapy.

Methods: We performed an online theoretical and practical course, in which each participant could access the virtual content of four of the modules. The virtual academic platform included interactive video classes, scientific bibliography and real practical cases. Each teaching module was composed of a masterclass talk by one of the teachers along with scientific articles complementing each presentation. Furthermore, a permanent forum was provided for interactive consultations, comments and suggestions from participants. The Bayesian PK tool employed was WAPPS-Hemo, a Web-Accessible Population PK Service for all existing factor concentrates. The 4 modules were: (1) Introduction to PK analysis and population PK models. (2) Presentation of the WAPPS-Hemo platform, applications and clinical utility. (3) Independent exploration by participants of the platform by working on their own patient data. (4) Interactive questions and answers regarding the use of the platform. The expected duration of the course is 22 hours. The course material is available in English and Spanish. The course realization was made possible by an educational contribution from Bayer Healthcare.

Results: The course was piloted in Colombia. Two hundred seventy health professionals' specialists and experts in the management of patients with hemophilia participated in the course. Experts in PK monitoring from McMaster University (Canada) and Hospital La Fe (Spain) thought the course. Participants received a certification of the training course issued by McMaster University in Canada once the course had finished and passed the written test.

Discussion/Conclusion: Bayesian estimate allowed to know the individual PK profile and could be a useful tool to individualize prophylaxis. The positive feedback provided by participants to the first edition of the course makes us consider performing further editions in Colombia and in other countries.

Disclosure of Interest: None declared.

P126 | Individualization of prophylaxis with recombinant factor VIII in severe or moderate hemophilia A

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Introduction: Knowledge of the individual's pharmacokinetics (PK) using Bayesian analysis with 2-3 samples could help to individualize prophylactic therapy with recombinant factor VIII (rFVIII) in severe or moderate hemophilia A patients (HA) & minimize the risk of bleeding.

Methods: Retrospective study in HA with Advate® prophylaxis from January 2014 to September 2017. A Bayesian model (myPKFit® 2.0) was employed to get individual PK profile using FVIII trough levels retrospective data. PK parameters analyzed were: clearance (Cl); steady state volume (Vss); half-life ($t_{1/2}$); trough level at 48 & 72 h (TL); & time to reach rFVIII levels <1% (T1%). Kruskal-Wallis test (R®) was used to compare PK parameters & clinical variables: age, dose/kg, annualized joint bleeding rate (AJBR), Gilbert score.

Results: Eighteen patients were analyzed. Mean age was 36.7 years (SD: 13.3; range 16-70) & 144 PK monitoring were made. Mean PK values (SD) were: Cl 3.0 (0.6) mL/h/kg; Vss 52.2 (7.3) mL/kg; $t_{1/2}$ 13.9 (2.5) hour; TL at 48 h 4.6 (2.7) IU/dL, TL at 72 h 1.7 (1.5) IU/dL and T1% 75.8 (17) hour. The median dose/kg was 62.4 (12.9) IU/kg/week & mean Gilbert score of 17 (12.1). Along the last year, 7 patients (38.9%) reported joint bleeds (JB), with a mean of 0.6 JB/patient/year, instead prophylaxis. A significant association between AJBR & $t_{1/2}$ was noted ($P = .017$) when $t_{1/2}$ was categorized in short (p75 15.4 h). We observed in 3 patients JB were related to low TL48 (TL72 were not evaluable) & short $t_{1/2}$ (#1: $t_{1/2}$ 10.2 hour, TL48 0.8 IU/dL; #7: $t_{1/2}$ 11.8 hour, TL48 2.9 IU/dL; #9: $t_{1/2}$ 11.3 hour, TL48 1.9 IU/dL). However, several JB were reported in 3 patients

with high Gilbert score & severe arthropathy (Gilbert #11: 28, #13: 23; #17: 36), whereas their estimated TL & $t_{1/2}$ were appropriated (#11: $t_{1/2}$ 14.1 hour, TL48/72 5.4 & 1.7 IU/dL; #13: $t_{1/2}$ 16.5 hour, TL48/72 9.4 & 3.4 IU/dL; #17: $t_{1/2}$ 16.5 hour, TL48/72 6.6 & 2.4 IU/dL).

Discussion/Conclusion: Bayesian estimate with myPKFit® allows to know the individual PK profile & could be a useful tool to individualize prophylaxis, along with physical activity & bleeding pattern. Patients with short $t_{1/2}$ are more prone to bleeding & a personalized prophylaxis would be adequate, although other factors such as articular state also influence the AJBR. We are running a personalized 1-year program to identify & treat the causes of poor bleeding control in HA on prophylactic therapy.

Disclosure of Interest: None declared.

P127 | Correlation of factor levels with bleeding phenotype in non-severe hemophilia

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Introduction: Hemophilia is categorized into severity groups (severe-, moderate- and mild hemophilia) based on the basal activity levels of the factors VIII (FVIII) or -IX (FIX). This categorization is expected to be in accordance with the severity of the bleeding phenotype. Our study aimed at quantifying the association between the severity of the bleeding phenotype and FVIII or FIX basal activity levels in a cohort of non-severe hemophilia A (HA) and -B (HB) patients, respectively.

Methods: Patients at 3 hemophilia treatment centers in Austria were recruited for this study (Medical University of Vienna, Medical University of Innsbruck and the Red Cross Center of Linz). Patients with non-severe hemophilia, defined as having a baseline FVIII/FIX activity of >1 to 40%, were eligible. Detailed data on the history of bleeding episodes were collected via direct patient consultations and search of the hospital databases. The bleeding history also included the time period before the diagnosis of hemophilia had been established. This information was then used to quantify the bleeding phenotype with the Bleeding Assessment Tool of the International Society on Thrombosis and Haemostasis (ISTH-BAT).

Results: Seventy-two (78%) patients with HA and 20 (22%) patients with HB were enrolled (median age 51.5 years, range 19-80). The median levels of FVIII were 12% [range: 1.5%>39%] in HA, and the median levels of FIX were 12% [2%>25%] in HB. The median ISTH-BAT score was 10 points [0-28] overall, 10 [0-28] points in HA, and 8 [1-20] points in HB, and did not differ significantly between HA and HB ($P = .65$). Lower basal factor levels correlated with a higher ISTH-BAT score (Spearman's rho = −0.31, $P = .003$). In linear regression, a 1% increase in basal factor levels was associated with a 0.2 point decrease in the ISTH-BAT ($\beta = -0.20$, 95%CI: −0.33-(−0.07), $P = .003$). This association was similar in HA and HB patients (p for interaction = 0.63). However, basal factor levels explained only 10% of the variation in the ISTH-BAT ($R^2 = 0.10$ for both HA and HB patients).

Discussion/Conclusion: We observed a weak but significant correlation between basal FVIII/IX level and the bleeding severity, as expressed by the ISTH-BAT score. This correlation only explained 10% of the bleeding phenotype. This data are consistent with the concept that there are other yet-to-be-explored determinants of the bleeding phenotype beyond basal factor levels in both HA and HB patients.

Disclosure of Interest: None declared.

P128 | Physical activity and health outcomes in severe hemophilia a patients on prophylaxis with conventional rFVIII vs rFVIIIFc

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Introduction: Achieving appropriate physical activity (PA) and bleed control are critical to maintaining joint health and overall health in hemophilia patients. But few have assessed these outcomes across patients on prophylaxis with rFVIII vs. extended half-life (EHL) product rFVIIIFc. This study assessed patient-reported changes in PA participation and bleeding frequency over time among severe hemophilia A patients on the two types of prophylaxis.

Methods: A retrospective chart review was conducted on 201 severe hemophilia A patients receiving rFVIII or rFVIIIFc at Hemophilia Treatment Centers (HTCs) or non-HTC hematology clinics across the US from 2014-2015. Eligible patients included males aged 6-35 years with severe hemophilia A, were on rFVIII/rFVIIIFc prophylaxis continuously for ≥6 months, had no inhibitors, and did not participate in any hemophilia treatment-related clinical trials during the study period. Data on demographic/clinical characteristics, treatment and PA participation (e.g., walking, running, swimming, etc.) were collected from annual comprehensive exam visits and compared using chi-square or t-test for baseline and Wilcoxon rank-sum test for outcomes.

Results: Of 201 patients, 105 were children aged 6-17 years (67 on rFVIII and 38 on rFVIIIFc) and 96 were adults aged 18-35 years (51 on rFVIII and 45 on rFVIIIFc), representing 13 HTC and 3 non-HTC sites.. The rFVIII and rFVIIIFc groups were similar across all relevant demographic and baseline clinical characteristics. Weekly (wk) frequency and duration of participation in PA increased in 2015 across all groups compared to 2014. However, the mean increase tended to be higher for those on rFVIIIFc than those on rFVIII (Mean

frequency: +1.19/wk, $P = .03$ in children; +1.16/wk, $P = .33$ in adults; Mean duration of participation: +44.46 minutes/wk, $P = .26$ in children; +59.96 minutes/wk, $P = .06$ in adults). Reductions in annualized bleeding rate (ABR) during the study period were larger for adults on rFVIIIFc compared to rFVIII (Total bleeds: −0.72, $P = .001$; Spontaneous bleeds: −0.83, $P = .001$). Similar pattern was observed for children for total bleeds, though not statistically significant (−0.43, $P = .87$).

Discussion/Conclusion: This study shows that severe hemophilia A patients, particularly adults on rFVIIIFc prophylaxis, reported an increase in physical activity and lower ABR compared to those on rFVIII prophylaxis.

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P129 | Case report: a successful pregnancy in hemophilia A

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Introduction: Female carriers of Hemophilia A may, in exceptionally rare circumstances, manifest a severe bleeding phenotype due to extremely skewed lyonization. Owing to its rarity, there is limited evidence in literature to guide the optimal management of the obstetric challenges this poses. This includes uncertainty regarding the effects of FVIII deficiency on the maintenance of feto-placental viability, prenatal diagnosis of hemophilia and intra- and postpartum care of both mother and child.

Methods: We describe our experience in the obstetric care of a 21-year-old lady with severe Hemophilia A due to skewed lyonization, with a baseline factor VIII (FVIII) levels of <2%.

Results: Three weekly prophylactic injections of 3000 I.U. Refacto (FVIII) were used throughout the pregnancy, which maintained a trough FVIII level no lower than 4%. Prenatal diagnosis was in concordance with the patient's choice after genetic counseling. A non-invasive approach was preferred with gender identification via ultrasound and postnatal neonate blood sampling for FVIII levels. Successful vaginal delivery was facilitated by a multidisciplinary team involving obstetric specialists, hematologists and pediatricians, resulting in the birth of a healthy baby boy with normal FVIII levels postnatally.

Discussion/Conclusion: Our experience suggests maintaining FVIII levels with a trough of no less than 4% in facilitating a viable placenta and fetus in a young female hemophiliac with a bleeding phenotype. A multidisciplinary approach with prior agreed individualized care plan was vital in the successful vaginal delivery of a live birth.

Disclosure of Interest: None declared.

P130 | Turkish pup registry and national data for inhibitor rates; rodin and sippet effects on hemophilia care

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Introduction: Inhibitor development is the most important complication of severe hemophilia-A (sHA) treatment and Previously Untreated Patients (PUP) are the most risky patient group. Purpose of this study was founding inhibitor rate in PUP patients for last four years of period which 3rd generation Rec-FVIIIs were initiated in Turkish market. Observation for Rodin and SIPPET effect for product selection was planned as well.

Methods: As Hemophilia Subcommitee of Turkish Hematology Association, Turkish PUP Registry and Inhibitor Study Group was established. Inhibitor development was monitored by this retrospective registry. Totally 39 centers sent data by CRF forms. Only sHA (FVIII<1%) and birth date after 2014 were evaluated. Patients from Clinical trials and <5 EDs were excluded. Totally 153 PUP patients (Rec-FVIII: 94 and PD-FVIII: 43 and combined: 16) were evaluated.

Results: Inhibitor rate was calculated after completion for 10th-20th-50th EDs. Totally 20 inhibitors were reported and 13 of them (12 HR and 1 LR) with Rec-FVIIIs whereas only five patients were (2 HR and 3 LR) with PD-FVIIIs. Another two patients used combination had inhibitor (1 HR and 1 LR) as well. Most inhibitor patients had serious risk factors. Inhibitor rate was 4% for Rec-FVIIIs and 3% for PD-FVIIIs after 10 EDs for 130 PUP patients. Rate was 10% for Rec-FVIIIs and 8% for PD-FVIIIs after 20 EDs for 116 patients. HR inhibitors were superior in Rec-FVIIIs than PD-FVIIIs as 7% vs. 4%. For 50 EDs, HR inhibitor rate was still above in Rec-FVIIIs as 20% vs. 14% for 94 patients. Advate was the most preferred product (n = 44). Others were Refacto (n = 33) and Factane (n = 12). Inhibitor rates for single products after 50 EDs were 17% for Advate, 22% for Refacto and 11% (1/9) for Kogenate. For PD-FVIIIs, HR inhibitor rate was close to 10%. As of 2016, significant changes were observed. PD-FVIIIs were more preferred than Rec-FVIIIs (22 vs. 9 pts).

Discussion/Conclusion: PD-FVIIIs seems more safer products in respect of inhibitor development than Rec-FVIIIs. Superiority was more prominent in HR inhibitors. However, only 62% of cohort has completed 50 EDs. We plan to extend data collection after the end of 50 EDs for most patients as final evaluation. Rodin effect was clearly

observed and Kogenate was <10% of Rec-FVIII options. SIPPET effect on Turkish hemophilia care also observed that as of 2016, the most preferred products are PD-FVIIIs for PUPs.

Disclosure of Interest: K. Kavakli Grant/Research support from: Pfizer, Bayer, Shire, Novo Nordisk, Consultant for: Novo Nordisk, Bayer, Shire, Pfizer, LFB, Speaker Bureau of: Novo Nordisk, Shire, Bayer, Pfizer, A. Unuvar: None declared, C. Balkan Consultant for: Novo Nordisk, Bayer, Shire, Pfizer, Speaker Bureau of: Novo Nordisk, Bayer, Shire, Pfizer.

P131 | Pharmacokinetics (PK) simulations of different treatment regimens with rFVIIIFc and rFVIII - economic impact from a german perspective

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Introduction: rFVIIIFc has similar incremental recovery and volume of distribution but reduced clearance compared to rFVIII, which translates into a 1.5-fold extension in elimination half-life and time to trough. The aim of this study was to perform simulations based on population PK modeling to illustrate differences in factor levels, troughs, area under the curve (AUC), factor consumption and economic impact between different prophylactic dosing regimens with rFVIII and rFVIIIFc.

Methods: All simulations were based on mean population PK estimates for rFVIIIFc (Elocta®) and rFVIII (Advate®), respectively, in a 73 kg severe hemophilia A patient. These estimates were developed using population PK analysis of individual patient data from phase 1/2a and phase 3 studies of rFVIIIFc. The economic impact was calculated based on the official prices for rFVIIIFc (0.94€/IU) and the lowest priced rFVIII (0.83€/IU) product in Germany. Three simulated treatment scenarios are presented here based on local treatment practices.

Results: Scenario one compared outcomes using the same regimen for rFVIIIFc and rFVIII: 3× per week dosing at 2500 IU (103 IU/kg/week). rFVIIIFc was associated with 55% greater AUC and 3-5 times higher troughs compared to rFVIII. In order to achieve similar trough and AUC as rFVIIIFc, rFVIII would need 3500 IU every other day (EoD) and 63% higher consumption (168 IU/kg/week). Scenario two compared different regimens of rFVIII and rFVIIIFc, targeting a trough of 3 IU/dl. rFVIII required EoD dosing at 2500 IU (120 IU/kg/week) whereas rFVIIIFc could be dosed 3× per week at 2000 IU (82 IU/kg/week). The rFVIII regimen resulted in 46% higher consumption and 28% higher costs. In scenario three, rFVIII EoD at 2500 IU (120 IU/kg/week) was compared with rFVIIIFc every 3rd day at 3000 IU (96 IU/kg/week). In this simulation the rFVIII regimen achieved a trough of 3 IU/dl with 25% higher consumption. The rFVIIIFc regimen achieved a trough of 4.4 IU/dl and 20% greater AUC.

Discussion/Conclusion: Simulations suggest that higher troughs and AUC of FVIII are achievable with fewer injections and lower weekly consumption with rFVIIIFc than with conventional rFVIII. Scenario three showed that the dosing interval for a high trough (3 IU/dl) patient on EoD rFVIII could be extended with rFVIIIFc, achieving better protection based on higher AUC and trough levels while reducing cost from a German perspective.

Disclosure of Interest: K.-J. Myrén Shareholder of: Sobi, Employee of: Sobi, P. Gozzi Shareholder of: Sobi, Employee of: Sobi, F. Zucca Shareholder of: Sobi, Employee of: Sobi, S. Lethagen Shareholder of: Sobi, Employee of: Sobi.

P132 | Anticoagulation in patients with bleeding disorders: preliminary results of a multicentre cross-sectional study in Germany

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Introduction: Thromboembolic complications are rare in patients with bleeding disorders (PWBD), but due to the improved life expectancy of PWBD atrial fibrillation (AF), heart valve replacement and venous thromboembolism (VTE) become more common. Whether anticoagulation, which would be indicated in the normal population, is necessary and safe in PWBD, is not clear.

Methods: Retrospective data collection from patient charts of PWBD (Hemophilia A (HA) and B (HB) all severities, von Willebrand disease (VWD) with activity < 30%), including type, severity, treatment of the bleeding disorder, co-morbidities and disease with indication for anticoagulation and its treatment.

Results: So far, 27 male PWBD, median age 71 years (range 29-90), from 7 hemophilia centers in Germany have been included. 19 had HA (8 severe, 3 moderate, 8 mild), 5 HB (1 severe, 4 moderate) and 2 had VWD, 1 HA and VWD. 64% had a clinically significant bleeding phenotype (> 2 spontaneous joint or muscle bleeds, organ-, or GI-bleeding). Indications for anticoagulation were AF (n = 19, median CHA_2DS_2VASc Score 3 (range, 1-6)), VTE (n = 4, 3 after surgery with intensive replacement of clotting factors), 3 mechanical heart valves and 1 arterial thrombosis. 9 patients received anticoagulation (2 vitamin K antagonists, 4 low molecular weight heparins, 2 apixaban, 1 rivaroxaban), 5 for AF, 2 for mechanical heart valve replacement, and 2 for VTE. Of these 9 patients 4 had mild, 2 moderate and 1 severe hemophilia. 4 PWBD (mild and moderate HA) received low dose Aspirin, 3 for AF, 1 for arterial thrombosis without additional factor replacement. In 2 patients with VWD (activity 13 and 17% respectively) and 1 patient with mild hemophilia, prophylactic factor replacement was initiated

with anticoagulation. Main reason for not initiating anticoagulation was bleeding risk in PWBD, second was expected lower event rate.

Discussion/Conclusion: The majority of PWBD is not treated with long-term anticoagulation despite having a disease with indication for anticoagulation. To evaluate risk for thrombotic events and bleeding risk with anticoagulation in this specific population, a prospective study is needed.

Disclosure of Interest: None declared.

P133 | The fibres study: a phase 3, non-inferiority, randomized comparison of a new fibrinogen concentrate vs. cryoprecipitate for treating acquired hypofibrinogenemia in bleeding cardiac surgical patients

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Introduction: Cardiac surgery involving cardiopulmonary bypass (CPB) is associated with coagulopathy and excess bleeding. Acquired hypofibrinogenemia (plasma fibrinogen <1.5-2.0 g/L) is a primary causative factor. Randomized trials evaluating the use of fibrinogen supplementation with cryoprecipitate vs. fibrinogen concentrate in this setting are needed.

Methods: FIBrinogen REplenishment in Surgery (FIBRES) is a prospective, multi-centre, randomized (1:1), active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients with clinically significant bleeding due to acquired hypofibrinogenemia (NCT03037424). The primary objective is to determine if the efficacy of a new fibrinogen concentrate (Octafibrin/Fibryga, Octapharma) is non-inferior to cryoprecipitate. Patients will receive 4 g fibrinogen concentrate or 10 units of cryoprecipitate (dose-equivalent to 4 g) each time fibrinogen supplementation is ordered within 24 hours after CPB; all randomized patients will receive fibrinogen supplementation as clinically indicated. The primary outcome is total allogeneic blood products (ABPs; red blood cells, pooled/apheresis platelets, plasma) administered within 24 hours. Secondary outcomes include ABPs administered within 7 days, major bleeding within 24 hours, fibrinogen levels, and adverse events (AEs) and serious AEs within 28 days. Patient consent prior to treatment is waived, and the study will include 1200 patients; using a 20% non-inferiority margin and assuming a drop-out rate of ~10% after randomization, ≥550 patients/group will provide >80% power. Interim analysis will include 600 patients. The pragmatic study design and treatment algorithm align with standard practice, aiding adherence and clinical relevance.

Results: FIBRES is expected to complete in late 2018, with results available in early 2019.

Discussion/Conclusion: FIBRES is the largest randomized comparison of fibrinogen concentrate and cryoprecipitate in cardiac surgery patients undergoing CPB, an under-studied, high-risk population. Non-inferiority of the new, highly purified fibrinogen concentrate would support its use in acquired hypofibrinogenemia. The results from FIBRES are likely to improve care for cardiac surgical patients experiencing significant bleeding.

Disclosure of Interest: K. Karkouti Grant/Research support from: Octapharma, Consultant for: Octapharma.

P134 | Characterization of medical healthcare utilization among prophylaxis hemophilia A patients using a commercially-insured and medicare advantage population claims database

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Introduction: As the hemophilia treatment landscape continues to evolve, emphasis has been placed on better characterization of the medical healthcare resource utilization (HRU) impact associated with members on prophylaxis therapy, as well as novel, extended half-life (EHL) therapies. Within hemophilia A, limited studies have used a claims-based algorithm to quantify the real-world HRU of prophylaxis treatment and EHLs on the medical benefit.

Methods: This retrospective analysis used Aetna's fully-insured US Commercial and Medicare Advantage pharmacy and medical claims database records from 1/1/14-1/31/17. Hemophilia A patients were defined as > 1 ICD code for hemophilia A and > 1 claim of Factor VIII therapy (J-code/NDC). Prophylaxis was defined as a factor VIII therapy frequency of 0.5-1.5 claims per month, and medical HRU was then characterized in this population, including a subgroup comparison of EHL and conventional factor therapies. Due to timing of this analysis, ELOCTATE presumably represents the majority of EHL utilization.

Results: Of 324 treated hemophilia A patients identified, 164 (50.6%) patients were treated with prophylaxis regimens - 10 of whom used EHLs. Main medical cost-drivers per-patient-per-month in the prophylaxis group were all-cause inpatient facility ($845), hemophilia-related inpatient facility ($694), all-cause ER facility ($167), and hemophilia treatment center (HTC) services ($7725). These cost-drivers were associated with 0.02, 0.01, 0.06, and 0.20 events of service per-patient-per-month within the prophylaxis group, respectively. Across these cost-drivers, prophylaxis patients using EHLs cost $46.40, $0, $99.06, and $51.81 per-patient-per-month across all-cause and hemophilia-related inpatient facility, ER facility, and HTC services, respectively. In comparison, patients on conventional therapies cost $932.17 (20-fold), $670.56, $174.60 (1.76-fold), and $8563.63 (165-fold), across the same cost-drivers, respectively.

Discussion/Conclusion: This claims-based analysis describes medical HRU in hemophilia A patients on prophylaxis therapy and indicates that key cost-drivers include all-cause and hemophilia-related inpatient facility, ER facility, and HTC services. Potential cost-saving

opportunities exist with the use of EHL therapies to reduce the burden of these cost-drivers of healthcare resource use.

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P135 | Periodontal health status and its relationship with the accessibility to health services in a hemophilia population of Tabasco, Mexico

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Introduction: Periodontal diseases go beyond inflammation caused by bacteria, they also comprise a multifactorial relationship between the aggressor and the host defenses. Hemophilia patients often neglect their oral hygiene due to the fear of bleeding at the time of brushing and with this increase the number of microorganisms and their own inflammatory responses. Oral care and oral health education in most developing countries are minimal, because they depend of accessibility to health systems. Purpose of the study: To determine the periodontal health status in a population with hemophilia and its relationship with accessibility to health services.

Methods: Observational, prospective and cross-sectional study carried out in the state of Tabasco with a sample of 133 patients with hemophilia aged 5-65 years. An interview was conducted using an *ad hoc* questionnaire to collect general and demographic data, as well as accessibility to health services. To evaluate the periodontal health status, Russell's periodontal index was used as a reference. In order to establish the association between the frequency of annual visits to the periodontal health services and the periodontal index, chi square was calculated.

Results: 45.9% had periodontal disease, 23.3% had mild gingivitis, 18% had generalized gingivitis, and 4.5% presented bagging gingivitis, in which there was already inflammation of the periodontal ligament and periodontal pockets, with loss of insertion alveolar but without tooth mobility. As for the place of residence, 34.6% lived in rural areas, 33.1% in suburban areas and 32.3% in urban areas. Chi square was calculated to obtain the association between the frequency of annual visits to the periodontal health services and the periodontal index, and it obtained a value of 20.46 with a $P < .001$, showing a statistically significant relation between both.

Discussion/Conclusion: The findings indicate that accessibility of oral health systems, area of residence, type of social security and occupation are some of the indicators that have been cited as predictors of the state of oral health and that individually or jointly can condition access to periodontal health services, decreasing their quality of life and increasing oral diseases.

Disclosure of Interest: None declared.

P136 | Incidence of inhibitor in a hemophilic population from the North of Spain

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Introduction: Inhibitor development is the major complication of therapy in developed world. Development of inhibitors is described in 36% and 5% of severe Hemophilia A and B patients respectively

Methods: We describe our inhibitor population among our hemophiliac patients, as we notice we have a higher incidence and prevalence than it is described previously. We have 54 patients diagnosed of hemophilia at the Hematology Department of the University Central Hospital of Asturias; 51 (95%) are HA (20 (37%) are severe); 3 (5%) are diagnosed of severe HB. We analyzed the variables correlated with development of inhibitor such as genetic mutation, age of diagnosis, number of exposures, type of treatment, symptoms, relapse, among others.

Results: In the period 1997- 2016, the overall incidence of inhibitor development in our severe hemophilia patient's population was 6 (26%); 4 (20%) patients having a severe HA and two (66%) patients having HB. The median of number of ED was 19 and one patient received continues infusion treatment of FVIII for intracranial hemorrhage in the diagnosis. The median age of the inhibitor detection was 11 months. The bleeding episodes included hemarthrosis, mucosal bleed, traumatic bleeding, hematuria and intracranial hemorrhage. A genetic study was performed in all of them: deletions and insertions were detected. Immunotolerance treatment was adopted in five patients (one was a transitory inhibitor); one patient with HB achieved immune tolerance, one patient with HA reached partial response, and two patients with HA and one patient with HB are refractory. In one HB patient, ITT had to be interrupted because a nephrotic syndrome development. In three refractory patients we used immunosuppressive treatment

Discussion/Conclusion: We find a higher incidence of inhibitor in our population than it is described. We have noticed a higher proportion of high risk mutations. We urgently need a better understanding of the mechanisms for inhibitor development and proper therapies to overcome it

Disclosure of Interest: None declared.

P137 | Experience in acquired coagulation factor inhibitors: rare entities

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Introduction: Acquired coagulation factor inhibitors (ACI) usually confer a serious hemostatic challenge, usually affecting elderly patients with autoimmune disorders and, less frequently, women in the immediate postpartum period, caused by auto-antibodies directed against specific domains of the coagulation factors molecule.

Methods: We have diagnosed four case of ACI in the last three years. First case it´s a 71-year-old man, with a simultaneous debut of diabetes mellitus and a dorsal hematoma; complementary studies demonstrated a FVIII inhibitor of 2 BU and FVIII levels: 23.6%; he received a first line treatment consistent of corticosteroids and Cyclosporine, and a second line with Cyclophosphamide and prednisone. The second case it's an 87-year-old woman with a history of rheumatoid arthritis, who debuted with a post-traumatic lower limb hematoma; complementary studies demonstrated a FVIII level of 0.8% and an inhibitor level of 4.74BU; bleeding was treated with rFVIIa and first line treatment was steroids, and a second line with Rituximab. The third case it`s a 7-month-old female baby with a front lump; complementary studies demonstrated a FIX:C of 9.7%, with poor FIX recovery (35%), although no inhibitor could be demonstrated, Kasper test was 0.8 (positive), and no mutations were detected, so she received treatment with corticosteroids with good response. The last case is a 78-year-old woman with herpes encephalitis who developed a lower limb hematoma, with a FXIII level of: 23% and a FXIII inhibitor of 1BU; she received a first line with corticosteroids and Cyclosporine, and a second line with Rituximab.

Results: The median age was 74 years, 75% the patient had a triggering disease, and received two line treatments. The main clinical symptom was muscle bleeding. The presence of other autoimmune or neoplastic diseases was ruled out in all cases, and the evolution was excellent as there were no more bleeding episodes and the inhibitor disappeared.

Discussion/Conclusion: ACI are uncommon and potentially fatal diseases that in 15% of cases are associated with autoimmune diseases. They require early treatment with by-pass (rFVIIa or CCPa) and immunosuppressant therapy, being basic the treatment of the associated disease. Our patients didn`t present thrombotic nor infectious events, and treatment tolerance was excellent.

Disclosure of Interest: None declared.

P138 | Patient personalized prophylactic factor replacement

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Introduction: In Turkey, prophylaxis (Px) for hemophilia A is reimbursed by healthcare payer to a max. of 4500 IU/week. This limit results in an almost fixed schedule of Px in adult patients consisting of FVIII doses of 1500 IU thrice/w or 2000 IU twice/w. At our centre patients with hemophilia A (PwH) with severe bleeding phenotype are prescribed to use a fixed Px schedule of 2000 IU twice/w. This study aims to investigate how the recommended fixed dose Px is taken by the PwH with regard to compliance, efficacy and real life application.

Methods: A total of 23 severe PwH aged 27-56 years receiving Px more than 3 years were included. All patients were on home therapy getting their prescription 3 monthly at a fixed dose of 2000 units twice a week. Patients' diaries were reviewed at 3 month intervals to obtain real-life data on the infusion frequency and dosing as well as on bleedings or unforeseen incidents.

Results: Patient characteristics are given in the Table. More than 1/3 of patients modified the fixed twice weekly regimen according to their needs. Five patients infused a lower dose at a higher frequency to adjust Px to the level of daily activities. Two patients were on once weekly schedule due to difficulties in venous access. They considered their Px to be sufficient although the median annual number of bleeds were considerably higher than other groups.

TABLE I Clinical characteristics of the patients

Factor activity level (%): 0.8 [0.1-1.1]
Median duration of prophylaxis (year): 7 [3-10]
ABR (median): 5 [0-19]
2000 units twice/week (n): 14
ABR on twice/week (median): 3 [0-11]
1000 U every other day (n): 5
ABR on every other day (median): 3 [0-6]
1500 U thrice/week (n): 2
ABR on thrice/week (median): 4 [2-6]
200 U once/week (n): 2
ABR on once/week (median): 13.5 [8-19]

Discussion/Conclusion: Compliance is crucial for a successful Px. Recent work showed that compliance decreases with increasing age. One size fits all principal is not applicable for Px given that even in clinical trials with fixed dose Px bleeds could not be prevented. Current evidence recommends personalizing Px according to the pharmacokinetic data and/or bleeding pattern. We showed that adult PwH, when they feel uncomfortable with the fixed dose Px, do modify their own schedule according to their needs in real life mainly based on the bleeding pattern, level of activity and/or venous access problems.

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P139 | Performance of the ISTH bleeding assessment tool in predicting the presence of inherited platelet function disorders

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Introduction: The ISTH bleeding assessment tool (ISTH-BAT) was developed to standardize the documentation of bleeding symptoms, to guide further laboratory investigation and to help diagnose patients with possible bleeding disorders. Previous studies have shown that the BAT score was low in healthy volunteers and elevated in participants with clinical evidence of a bleeding disorder, but very few studies have assessed the clinical utility of the ISTH-BAT in predicting the presence of a platelet defect. The objective of this study is to evaluate the performance of the ISTH-BAT bleeding score (BS) in predicting the presence of platelet defects in patients with an increased bleeding tendency and (suspected) inherited platelet function disorders (PFDs).

Methods: Patients with (suspected) PFDs were included in the Thrombocytopathy in the Netherlands (TiN) study, a nationwide cross-sectional study on PFDs. The ISTH-BAT was administered by a physician prior to platelet function testing consisting of light transmission aggregometry (LTA), platelet nucleotide content analysis and flow cytometry. In addition, genetic analysis was performed on a 89-gene NGS platform.

Results: In this interim analysis, a total of 143 patients were enrolled in the study, of whom 118 were female. Eighty-five patients (59%) had a platelet defect based on abnormal results on LTA, platelet nucleotide content, flow cytometry and/or genetic analysis. The ISTH-BAT score was not significantly different between patients with an objective platelet function defect (median 9; interquartile range 7-14) and those with normal results (median 11; interquartile range 7-13) ($P = .4$). The score was also not significantly different between men (median 8; interquartile range 5-13) and women (median 10; interquartile range 7-14) ($P = .06$). The ISTH-BAT score could not discriminate between patients with and without a platelet function defect on platelet function testing (area under the ROC curve = 0.459 [95% CI 0.365-0.552]).

Discussion/Conclusion: Although the ISTH-BAT is a useful tool for systematically documenting bleeding symptoms in patients with excessive bleeding, the BS obtained from the ISTH-BAT is unable to predict the presence of a platelet defect in patients with (suspected) platelet function disorders.

Disclosure of Interest: None declared.

P140 | Practice of circumcision in children with inherited bleeding disorders - experience from Saudi Arabia

M. Alsaleh[1,*]; Z. Habib[2]; A. Aljefri[1]; S. Jose[3]; L. Tuleimat[4]; H. Musallam[4]; M. Zulfiqar[1]; V. Mohammed[1]; N. Elsheikh[1]

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Introduction: Circumcision is one of the most common surgical procedure performed amongst male neonates. Apart from religious obligations, it is considered a vital ritual for a young adult to become a member of the society. It could pose serious hemorrhagic side effects amongst bleeders, which could be controlled with appropriate coagulation factor infusion, blood products, and antifibrinolytic agents; pre and post circumcision.

Methods: To analyze outcomes of circumcision amongst children with inherited bleeding disorders a retrospective review of pediatric patients (<14 years), in order to determine extent of complications at King Faisal Specialist Hospital and Research Centre, Riyadh was conducted. SPSS Version 20.0 was used for statistical analysis.

Results: A total of 35 patients with inherited bleeding disorders were identified, 49% (17) with Hemophilia, 31% (11) Glanzmann Thrombasthenia (GT), 14% (5) Von Willebrand disease and 6% (2) rare bleeding disorder, with a median age of 1 year and 4 months (3 months - 13.0 years) at the time of procedure. At our institution disease specific protocols with factor replacement therapy (FRT) before and after surgery in bleeders are proposed, it was observed that 80% (28) were circumcised in compliance with the protocol, while 20% (7) were not in compliance. An overall bleeding incidence of 14% (5/35) was observed, of which two (both GT) patients were circumcised on protocol while three (Hemophilia, 2; GT, 1) were not.

Discussion/Conclusion: Post-circumcision complication rate of 14% in our patients is comparable to published rates of 0.1 to 35%, in patients without bleeding disorder. In our experience circumcision for bleeders could be practiced under supervision of hematologist with adequate FRT, blood product support and local control by fibrin glue. However, parents and patients must be informed of bleeding risks despite taking adequate measures. National guidelines on use of hemostatic agents amongst bleeders for circumcision is warranted.

Disclosure of Interest: None declared.

P141 | Positive impact of social media on disease awareness and management in patients with inherited bleeding disorders: Saudi experience from a tertiary care hospital

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Introduction: Technology has changed individual social interactions, a published report ranks Saudi Arabia seventh globally for individual social media accounts. Social networking has evolved so has interactions between patients' and health care providers, with patients incorporating social media as part of their disease management. Pediatric Hematology/Oncology Department at King Faisal Specialist Hospital and Research Centre, Riyadh witnessed similar approach by families.

Methods: WhatsApp groups titled "Consult your Doctor" and "Female Glanzmann Thrombasthenia (GT) Support Group" were created by parent of a hemophilia patient and mother of a female GT patient exclusively for females, respectively. Hematologist, hematopathologist, dietitian, gynecologist dentist, in addition to nurse practitioner, clinical pharmacist, physiotherapist and social worker were added for comprehensive care. Patients and families started referring one another to respective groups.

Results: Hundred participants were added to "Consult your Doctor" group over 2 years, with most patients with Factor VIII deficiency. Average of 5 consults per day, involving trauma and factor replacement therapy. Concerns involving local control, oral bleeding, dental extraction were addressed too. Thirty participant were added to "Female GT Support Group" within a year involving discussions related to first time menstruation, heavy periods, mucus membrane bleeding, oral contraception and post-marital concerns. Women who bore children shared their experiences and information on risk of giving birth to an affected child. Non-medical concerns like, appointments, insurance, vacations etc. were addressed.

Discussion/Conclusion: Parents were psychologically relieved to learn they are not alone and shared their stories resulting in better understanding of disease spectrum i.e. mild to severe helping them remain calm avoiding immediate emergency room visits. Mothers were able to overcome social inhibitions and freely discuss challenges unique to females with GT .In our experience social media proved an effective support group model for disease awareness and management even in a conservative society.

Disclosure of Interest: None declared.

P142 | Evaluation of a standardized protocol for thrombin generation using the calibrated automated thrombogram: a Scandinavian study

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Introduction: The use of the thrombin generation method TGA-CAT has been hampered by large inter laboratory variability. Previous studies have shown that inter centre variability can be decreased by dividing all values with the result of a common reference plasma, co called normalization. In this study we investigated whether an elaborate standardization protocol and the use of dedicated reference plasmas for normalization could reduce the inter-laboratory variability.

Methods: Three different plasma types were tested: ("Hypo"-, "Normo"- and "Hypercoagulable" plasma). Frozen citrated (3.2%) plasma samples were distributed and analyzed by 6 Scandinavian centers. Three different commercial lyophilized reference plasmas were used for normalization. TGA-CAT was run according to the method described by Hemker et al. with the standardized reagents from Trombinoscope®. All analyses were run using 2 different concentrations of tissue factor (TF) in the initiating reagent: 1 pM and 5 pM.

Results: Four out of 6 centers had inter-assay CVs of 10% or lower for all parameters. The inter-centre CVs for TGA parameters ETP and Peak were 10% or below in "Normo"- and "Hyper" plasma. In "Hypo" plasma only Peak using TF 5 pM had a CV below 10%. We evaluated 3 different plasmas' ability to normalize data: HemosIL Calibration plasma, a normal plasma, as well as 2 so called dedicated normalization plasmas, Siemens Control Plasma P (dil. 1 + 5) for the "Hypo" samples and Affinity PS-DP for the "Hyper" samples. Normalization with normal plasma (HemosIL Calibration plasma) lowered CVs for all results except when analyzing "Hypo"- and "Hyper" plasma using TF 1 pM in the starting agent. Normalization with Affinity PS-DP decreased CV in all plasmas except when "Hyper" plasma was analyzed at TF 1 pM. Normalization with Siemens Control plasma P failed to improve CV in all plasmas.

Discussion/Conclusion: In this study the TGA-CAT assay gives as robust results as standard coagulation assays used in routine labs, with the exception of analyses of plasma samples with low coagulability ("Hypo") using TF 1 pM in the starting reagent. Normalization with a reference plasma with normal or increased coagulability decreases inter laboratory variability.

Disclosure of Interest: None declared.

P143 | Swedish national registry for bleeding disorders - first report

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Introduction: Hemophilia care in Sweden is centralized to 3 centers localized in Gothenburg, Malmö and Stockholm. All centers are certified as European Hemophilia Comprehensive Care Centers (EHCCs). Recently a web-based Swedish national registry has been established with funding from Swedish authorities.

Methods: One of the conclusions from the earlier reports from the Swedish agency for health technology assessment and assessment of social services (SBU) and the Dental and Pharmaceutical benefits agency (TLV) was that a national registry for hemophilia and other bleeding disorders was needed to be able to follow the long-term effects of the disease and treatment strategies. An application was submitted in 2012 to apply for funding from Sweden's municipalities and count councils (SKL). The registry was validated as an official national registry. A multi-professional steering committee is running the registry with representatives from all 3 hemophilia centers including physicians, nurses, physiotherapist and a patient representative. Support regarding legal aspects, IT-solutions, statistics and economy is provided by QRC Stockholm.

Results: By now, 780 patients with bleeding disorders are included in the Swedish national Registry and data regarding bleedings, treatment with factor concentrate, inhibitor status, mutations, viral infections such as hepatitis C and HIV are collected. Patient reported outcome measurements (PROM)- such as pain and quality of life - HJHS and target joints are followed continuously.

Discussion/Conclusion: The establishment of a Swedish National Registry enables us to perform national annual reports, have a close follow-up of our patients and perform clinical research. Currently are working on an on-line patient treatment application recording directly into the registry. Data from the registry will be an important tool for further evaluation of the treatment of hemophilia and how it affects the long-term consequences of the disease.

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P144 | Guardian™4: safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in previously untreated patients with hemophilia A

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Introduction: turoctocog alfa, a B-domain-truncated recombinant FVIII (rFVIII) developed by Novo Nordisk for the prevention and treatment of bleeding in people with hemophilia A, is being assessed in a multinational clinical trial program, guardian™. Here, we report data (cut-off 13 February 2017; 4.4 years) from guardian™4 (NCT01493778), a phase 3a, multi-national, non-randomized, open-label, safety and efficacy trial in pediatric previously untreated patients (PUPs; <6 years) with severe hemophilia A (FVIII level ≤1%).

Methods: The trial comprises 2 phases completed once ≥50 PUPs have ≥50 exposure days (ED; main phase) or 100 ED (extension phase) with turoctocog alfa, or developed inhibitors. Prophylaxis was recommended to initiate at 15–50 IU/kg once weekly, increasing to 20–50 IU/kg every second day or 20–60 IU/kg 2 or 3 times weekly at investigator's

discretion depending on the clinical situation. The primary endpoint was incidence of FVIII inhibitors (≥0.6 BU) during the main phase.

Results: At the cut-off date 59 PUPs were exposed to turoctocog alpha and included in the analyses. Most patients were White (72.9%) or Asian (20.3%) and non-Hispanic (91.5%). FVIII inhibitors developed in 24 of 56 (42.9%; 95% CI: 29.7; 56.8) patients completing the main phase and 15/24 were high-titer inhibitors (peak titer ≥5 BU); range 5.5–334.6 BU. High-risk mutations were predictors of inhibitor development ($P < 0.05$), accounting for the majority of total inhibitors in the main phase.

Patients on prophylaxis in the main and extension phases had a Poisson estimated annualized bleeding rate (ABR) of 4.23 bleeds/patient/yr (95% CI: 3.17; 5.64) and median (IQR) of 2.9 (5.6) bleeds/patient/yr. Poisson estimated spontaneous ABR was 0.72 bleeds/patient/yr (95% CI: 0.42; 1.22) and median (IQR) ABR was 0.0 (1.1) bleeds/patient/yr. Success rate in treatment of bleeds was 86.5%. The subset of 12 patients who completed the inhibitor cohort and continued in the extension phase reported a similar ABR: 4.28 bleeds/patient/yr (95% CI: 1.95; 9.38).

Discussion/Conclusion: The 42.9% incidence of inhibitor development in guardian™4 was within the range reported for rFVIII products in large studies (29–45%), eg SIPPET, albeit at the higher end. In depth analyses into further predictors of inhibitor development are currently ongoing.

Disclosure of Interest: M. Ozelo Grant/Research support from: Shire, Bayer, Biogen, CSL Behring and Novo Nordisk, Speaker Bureau of: Shire, Novo Nordisk, Pfizer and Grifols, R. Wu: None declared, M. Belhani: None declared, V. Lebedev: None declared, H. Yaish Consultant for: Shire, CSL and Bayer, Speaker Bureau of: Shire, L. Korsholm Employee of: Novo Nordisk A/S, I. Matytsina Employee of: Novo Nordisk A/S, T. Matsushita Consultant for: Novo Nordisk, Speaker Bureau of: Baxter, Bayer, CSL Behring, Novo Nordisk, and Pfizer.

P145 | Insight into the real-life of persons with hemophilia (PWH).impact of recently introduced prophylactic replacement

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Introduction: Joint disease is the hallmark of under-treated hemophilia. New improvement registered in our country in the time frame 2015-2017, justified our descriptive, non-interventional, cross-sectional study. Objectives. The aim was to assess the real status of musculo-skeletal system of PwH, comparing the results of PwH with and without prophylactic replacement.

Methods: The study was undertaken on 85 PwH, 39 children and 46 adults; secondary and tertiary prophylaxis was dedicated for PwH < 18 years with severe form of disease since 8-18 months. A multidisciplinary team performed a comprehensive evaluation of joint status (HJHS score, number of hemarthrosis and target joints, ABR and AJBR, HEAD US score) and of its impact on life quality (EQ 5D A and Y) and ICF condition.

Results: The joint parameters were significantly different in these 2 groups of patients ($P < 0.001$). Joint status of the majority of patients treated on demand was dramatic, (HJHS 56.5 ± 17.3, ABR 36.9 ± 13.9, AJBR 23.9 ± 8.6, target joint in 91.2% and disability and handicap in more than 50%); all these are pleading into the favor of the extension of short term prophylaxis in older ages, of a more intensive restorative physical therapy and of more strict discipline in adherence to therapy.

Discussion/Conclusion: The results concerning joint markers, quality of life and social insertion are aimed at having a key role for demonstrating the effectiveness/efficiency of the initiated prophylactic treatment in PwH < 18 years, bringing arguments into the favor of its extension in adulthood.

Disclosure of Interest: None declared.

P146 | Concomitant congenital factor vii deficiency and platelet disorders

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Introduction: Congenital factor FVII deficiency is a rare coagulation disorder that has a variable clinical picture – from spontaneous hematomas to massive intraoperative hemorrhages. Opposite to coagulation disorders, congenital platelet dysfunction presents with the microcirculatory type of bleeding. Combined disorders of both parts of hemostasis are even rarer (less than 1%) can demonstrate in the untypical clinical picture.

Methods: We diagnosed 4 members of 1 Caucasian family from Dagestan Republic with bleeding tendency age from 6 to 41 years using total blood count, clotting time tests, fibrinogen, light transmission aggregometry (LAT) with ristomycin, adenosine diphosphate (ADP), collagen, arachidonic acid, adrenaline, thrombodynamic assay, platelet morphology analysis and flow cytometry assay on active and non-active platelets.

Results: A girl age of 11 with the clinical phenotype of nosebleeds, ecchymoses, posttraumatic and spontaneous hematomas had a non-typical laboratory with prothrombin reduction to 31% and the decrease of platelet aggregation with ADP to 17% and collagen to 15%. The stationary clot growth rate in thrombodynamics was reduced to 10.4 mkm/min. Analysis of coagulation factors reviled isolated deficiency of FVII 6.1%. Flow cytometry assay discovered a decrease of

phosphatidylserine on activated platelets combined with deficiency of dense and alpha platelet granules. To exclude Scott syndrome genetic assay was performed – no mutation in gene TMEM16F was found.

A girl is from a cross-cousin marriage. After performing tests of parents we discovered that father had a normal value of FVII (65.5%) and a decrease of phosphatidylserine on activated platelets. Mother was diagnosed with slightly decreased values of FVII (48.7%) and the small reduction of alpha granules of activated platelets. Both parents had no clinical picture of hemorrhages.

Youngest brother (6 years) of the girl had a decreased level of FVII (43.4%) and deficiency of alpha and dense platelet granules. He was presented with the clinical picture of nose bleeds and posttraumatic ecchymoses.

Discussion/Conclusion: Concomitant disorders of coagulation and platelet hemostasis are higher in cross-cousin marriage than in general population and can be presented in untypical clinical phenotype.

Disclosure of Interest: None declared.

P147 | Efficacy and safety of RVIII-singlechain in surgical prophylaxis

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Introduction: rVIII-SingleChain (recombinant single chain Factor VIII [FVIII], AFSTYLA®) is a B-domain truncated construct with a covalent bond between the heavy and the light chains. As part of the AFFINITY development program for rVIII-SingleChain, surgical sub-studies were conducted to investigate the efficacy and safety of rVIII-SingleChain in severe hemophilia A patients undergoing surgery.

Methods: Studies in the AFFINITY program were approved by the relevant Ethics committee and national authorities and conducted according to ICH GCP and the Declaration of Helsinki. Surgery was defined as a procedure requiring general, spinal or regional anesthesia. rVIII-SingleChain was administered during the perioperative period, either as a bolus or as a continuous infusion. The investigator rated hemostatic efficacy on a 4-point scale; treatment success was defined as a hemostatic efficacy rating of either Excellent (hemostasis not clinically significant different from normal; blood loss ≤20% higher than predicted) or Good (hemostasis normal or mildly abnormal; estimated blood loss >20% but ≤30% than predicted).

Results: A total of 28 adult, adolescent or pediatric patients underwent 35 surgical procedures during the AFFINITY program. A total of 5 procedures were performed in 4 pediatric subjects (median age 9.5, range 5-11 years) after a bolus dose of rVIII-SingleChain. The median age was 31 (range 5–64) years. rVIII-SingleChain was administered as a bolus in 27 (77%) surgeries and as a continuous infusion in 8 surgeries (23%). The median pre/intraoperative consumption was 76 (range 40.45–150.0) IU/kg. The most commonly performed procedures were orthopedic surgery (17), circumcision (9) and dental extractions (3). Hemostatic efficacy was rated as Excellent (n = 32, 91%) or Good (n = 3, 9%) in all patients, and no serious or related adverse events were reported.

Discussion/Conclusion: rVIII-SingleChain is a safe and effective perioperative treatment as either bolus or continuous infusion to achieve and maintain hemostatic control in pediatric and adult hemophilia A patients undergoing surgery.

Disclosure of Interest: M. E. Mancuso Consultant for: Bayer Healthcare, CSL Behring, Novo Nordisk, Sobi/Biogen, Kedrion and Pfizer, Speaker Bureau of: Bayer Healthcare, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Sobi/Biogen, C. Male Grant/Research support from: CSL Behring, Consultant for: CSL Behring, Speaker Bureau of: Baxalta, Bayer Healthcare, Biotest, CSL Behring, Novo Nordisk, Pfizer, Roche, Sobi/Biogen, F. Abdul Karim: None declared, C. Djambas Khayat: None declared, J. Mahlangu Grant/Research support from: Baxalta, Bayer, Biogen, CSL Behring, Novo Nordisk and Roche, Consultant for: Amgen, Biotest, Baxalta, Bayer, Novo Nordisk and Roche, R. Baker Grant/Research support from: Biogen Idec, Boehringer Ingelheim, Bayer, Shire, Pfizer, Daiichi Sankyo, Portola Pharmaceuticals, Astellas, CSL Behring, Bristol-Myers Squibb and Alexion Pharmaceuticals, Consultant for: Amgen, Biogen Idec, Shire, Boehringer Ingelheim, Bayer, Alexion Pharmaceuticals, and Pfizer, J. Oldenburg Grant/Research support from: Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma and Pfizer, Consultant for: Baxter, Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum, Speaker Bureau of: Baxter, Bayer, Biogen Idec, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Swedish Orphan Biovitrum, J. Ong: None declared, S. P'ng: None declared, C. Leissinger Grant/Research support from: CSL Behring, Roche, Consultant for: Bayer, Biogen, CSL Behring, Kedrion, Novo Nordisk, Roche and Shire, A. Brainsky Employee of: CSL Behring, S. Lucas Employee of: CSL Behring, I. Pabinger Grant/Research support from: CSL Behring, Consultant for: CSL Behring, Speaker Bureau of: CSL Behring.

P148 | Direct acting antiviral drugs in patients with hemophilia and chronic hcv infection: a single center experience

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Introduction: Many patients with hemophilia (PwH) treated with plasma-derived concentrates acquired hepatitis C virus (HCV) infection. In HCV-infected PwH, liver-related morbidity and mortality are greater than in non-hemophilia subjects with chronic hepatitis C. Moreover, the progression to end-stage liver disease is accelerated in patients co-infected with HIV. Eradication of HCV is the only practical approach to halt progression of HCV-related liver disease toward cirrhosis and hepatocellular carcinoma that often complicate the clinical course of long-lasting chronic hepatitis C. Combined therapy with pegylated interferon (Peg-IFN) plus ribavirin (Rbv) has been the standard of care for HCV infected patients (with or without HIV) including PwH who have been often considered "difficult-to-treat" because of several bad predictors of response. The recent advent of direct acting antiviral (DAA) drugs has provided sustained virological response rates of 90% and above for many patient groups including the "hard-to-treat" ones, however scarce data are available on the safety and efficacy of DAA drugs in patients with bleeding disorders.

Methods: Patients with hemophilia and chronic hepatitis C of any age regularly followed-up at the Hemophilia Treatment Center of Milan were eligible for therapy with DAA drugs including those with compensated cirrhosis, HIV infection and/or previous failure to IFN-based antiviral therapy. Patients received DAA drugs with or without ribavirin for 12 or 24 weeks according to the current treatment guidelines. Sustained virological response was defined as persistent negative HCV-RNA at 12 weeks after treatment completion (SVR12).

Results: Eighty patients aged 27-84 years (median: 51) received DAA drugs between July 2012 and October 2017. The most prevalent HCV types were 1a (42, 53%) and 1b (22, 28%). Fourteen (18%) were HIV positive and 28 (35%) had cirrhosis. Forty-eight (60%) were non-responders or relapsers to previous interferon-based treatment. Ribavirin (800-1200 mg/day) was associated to DAA drugs in 48 patients (60%). At time of data analysis 70 patients (88%) had completed the 12-week post-treatment follow-up and SVR12 was achieved in 69 (99%). No patient had side effects related to DAA drugs.

Discussion/Conclusion: DAA drugs were safe and highly effective in PwH irrespective of HIV status, stage of liver disease and/or previous failure to IFN-based therapy.

Disclosure of Interest: None declared.

P149 | Inflammatory status in patients with severe hemophilia A and its relationship with 25-OH-vitamin D

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Introduction: Hemophilia A is a hemorrhagic genetic disorder resulting from a decrease in or absence of factor VIII or IX pro coagulant activity. Muscle and joint hemorrhages are characteristic of this entity. The inflammatory response plays a central role in the genesis and progression of hemophilic arthropathy. Optimal levels of 25-OH-Vitamin D (VitD) modulate, through its non-classical actions, the immune system in inflammatory processes. Aim: to evaluate concentrations of interleukins (IL) profile and VitD status in patients with severe hemophilia A with and without active inflammation

Methods: We studied 186 patients with severe hemophilia A (PWH A). They were divided into G1:n = 70, age=48 (19-94) presence of active inflammation considered as C reactive protein (CRP)>5, G2:n = 116 age=42 (13-78), without active inflammation CRP<5. In all serum PWH A, pre-infusion factor VIII, we measured CRP by immunoturbidimetry, VitD, parathormone (PTH) and IL profile (IL-2r; IL-6, IL-8, TNFα) by chemiluminescent method. Results are expressed as median and (range). Differences among groups were tested using Mann-Whitney test.

Results: Significant differences were observed among the 2 groups, G1 presented higher levels of IL compared to G2:IL-2r IU/mL 694 (314-2733) vs 445 (44-2579) $P < 0.001$; IL6 pg/mL 6.4 (2.0-485.0) vs 3.2 (2.0-96.2) $P < 0.001$; TNFα pg/mL 12.0 (4.1-866.0) vs 8.5 (4.0-178) $P < 0.05$. No differences were found between G1:IL8 pg/mL 16 (5-905) vs 15 (2-1208), and PTH G1 vs PTH G2. On the other hand G1 showed lower levels of VitD:5.7 (4.2-30.1) ng/mL compared to G2 18.4 (4.2-45.8) $P = 0.03$

Discussion/Conclusion: Although PWH A is associated with a chronic inflammation process explained by similar levels of IL-8 between G1 and G2, they presented different IL profile when undergoing an acute inflammation process. In agreement with the literature, there is an increase in IL accompanied by a decrease in VitD in G1, indicating that VitD insufficiency would be associated with an acute inflammatory process. It is not known whether this inflammation is a cause or a biomarker. The lack of difference in the PTH values between the 2 groups would allow associating VitD with its non-classical actions in these patients. Conclusion

Patients with severe hemophilia-A present a chronic inflammation which added to a worsened acute inflammatory state determined by IL, is associated with a decrease in Vit D.

Disclosure of Interest: None declared.

P150 | Does blood group 0 influence inhibitor development? Data from the pednet registry

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Introduction: In the context of the ongoing debate about the possible risk differences for inhibitor development among FVIII concentrates, some claim a lower immunogenicity of certain plasma-derived products containing von Willebrand factor (VWF). The lower-risk hypothesis is based on the idea that VWF has a modulatory role on FVIII endocytosis by antigen-presenting cells. Patients with blood group 0 have on average a 30-40% lower endogenous VWF concentration (vs non-O blood type patients). It has been postulated if the lower VWF in O blood type individuals might increase their risk of inhibitor development.

Objective. To investigate whether patients with blood group 0 have a higher risk of inhibitor development than patients with other blood groups.

Methods: All patients with severe hemophilia A born between 2000 and 2016 and followed in one of the participating centers of the PedNet study group were included in this analysis. Inhibitors were considered present when at least 2 positive samples were present. High-titer inhibitors were defined as any inhibitor titer >5 BU/ml.

Results: Blood groups were available for 642 of 973 patients; 253 were blood group A, 85 were blood group B, 275 were blood group 0 and 29 were blood group AB. More than 98% of these patients were followed until 50 exposure days. The inhibitor incidence for the various blood groups varied between 30.5% and 33.9%, 95% CI for Blood group O was 27.2-38.2%; these differences were not significantly different .

Discussion/Conclusion: Blood group 0 patients have the same inhibitor risk as patients with other blood groups. Our findings do not support an effect of endogenous levels of VWF on inhibitor development.

Disclosure of Interest: None declared.

P151 | Absence of thrombotic complications with the use of bypassing agents in young hemophilia patients with inhibitor presence

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Introduction: Inhibitor development is the most challenging complication of hemophilia. In inhibitor patients the use of bypassing agents is required in order to induce clot formation. Two bypassing agents, activated prothrombin complex (FEIBA) and recombinant activated factor VIIa (Novoseven), are currently used and both have been shown to be efficacious in controlling bleeds in the majority of cases. A safety concern regarding thrombotic events remains with the use of these agents - although such events seem to occur in the presence of additional risk factors.

Methods: This is a single center retrospective report covering the last 10 year period. Files of 9 inhibitor cases were retrospectively studied and relevant data were reported: age, inhibitor titers and concentrates used - including type of agent, daily dose, frequency of administration, exclusive or sequential administration, yearly needs of each agent per patient, as well as total factor consumption for the given 10-year period. Thrombosis occurrence during the study period was reported.

Results: At the end of study period mean patient age was 16.7 years (7-24 years). Out of 9 patients 3 were in remission, presenting inhibitor titers <0.6 BU, while 6 patients had an active inhibitor - out of them 4 were on ITI (50-100 U/kg/dose, 3 times a week – every day), 1/6 receiving on demand treatment and 1/6 receiving prophylaxis with Feiba. Out of 9 patients 3 had received only Novoseven and 6 either factor at some time point - 4/6 requiring sequential therapy in order to treat heavy bleeds (either peri-operatively or outside the surgery setting). The regimens used were 90 μg/kg/dose, every 2-12 hours for Novoseven, 50-100 U/kg/dose every 8-12 hours for FEIBA (max 200 U/kg/day). In total, during the 10 year period 15 267 000 U of Feiba and 721 800 000 U of Novoseven were administered. Mean yearly factor use per patient was 332.756 U for FEIBA (240.600-469.000 U/patient/yr) and 19.366.700 U for Novoseven (6.616.600 – 46.950.000 U/patient/yr). During the 10 year use of the 2 factors no thrombotic event was reported, even in patients in increased risk - such as high dosage use or prolonged immobility following surgery.

Discussion/Conclusion: Both bypassing agents demonstrated a completely safe profile regarding thrombotic risk when used in children, adolescents and young adults with congenital hemophilia and inhibitor presence.

Disclosure of Interest: None declared.

P152 | F9 genotype and PK hemophilia B international study (GEPKHIS)

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Introduction: Factor IX (FIX) pharmacokinetics can be hypothetically modeled by 3 compartments (1-central plasma; 2-subendothelial matrix; 3-extravascular fluids) which are in equilibrium. Flows back from extravascular to plasma compartment could contribute to extended FIX half-life.. The residual FIX levels, activity and protein, including dysfunctional and/or truncated molecules, could help to interpreting the outcomes of PK.

The correlation between outcomes of a single dose PK of FIX (Nonacog alfa) and *F9* genotype of hemophilia B (HB) patients, which dictates the residual levels of normal and altered FIX molecules, has been never deeply investigated.

Methods: Study design: 1-Single dose PK of Nonacog alfa and Non-Compartment analysis, 2 and 3 compartment analysis; 2-Recombinant expression (rFIX) of patients' mutations; 3-Effect of covariates (mutations) on population PK. Severe or moderately severe HB patients (FIX < 3 IU/dL) were enrolled. In 15 HB patients, a single dose of Nonacog alfa, 50 IU/kg, has been infused and blood samples collected at 1 hour ± 15 minute, 8 ± 1 hour, 24 ± 1 hour, 48 ± 1 hour, 72 ± 1 hour, 96 ± 1 hour.

Expression studies were performed by transfection of HEK293 cells with mutagenized vectors bearing the *F9* mutations. Protein levels in medium were evaluated by ELISA and Western blotting with anti-human FIX polyclonal antibodies. FIX:C of rFIX variants was evaluated by One Stage clotting assay.

Results: Preliminary results of PK partially confirmed the variable genotype/pharmacokinetic relationships observed in a small cohort of hemophilia B patients (Morfini 2016, Haemophilia; 22:537-42).

Expression of 14 nonsense rFIX variants allowed to evaluate truncated molecules for 50% of stop codons. For the p.240X (TGA and TAG stop codons in patients) we detected levels of truncated FIX molecules similar to wild type rFIX. Among the 8 expressed missense variants, the p.Phe383Leu produced in medium 25% of FIX:Ag with undetectable activity.

Discussion/Conclusion: The appreciable secretion of full length variants and truncated molecules, even in the presence of FIX.C < 1%, would permit flow from plasma to the extravascular compartments of abnormal FIX molecules that could compete for collagen binding with infused rFIX, thus increasing its bioavailability. Expression of the patient's mutation should be further investigated and taken into account to predict the efficacy and cost/effectiveness of individual replacement therapy of HB patients.

Disclosure of Interest: None declared.

P153 | Assessment of over protective parenting attitudes and emotional status among ill children with chronic or serious hematologic disease

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Introduction: Excessive protective parental attitudes that are reported to cause various behavioral or psychopathological problems when the child has a serious or chronic illness are more common than the normal population. For this reason, the purpose of this study is to examine the overprotective parental attitudes of mothers of children with some serious or chronic illness and to examine the relationship between mothers' overbearing parental attitudes and mood.

Methods: Seventy-four children whom were between 6 and 16 years old participated in current study. Fifty-two children were in the study group (thalassemia major, hemophilia and leukemia patients) and 22 children in control group. Brief Symptom Inventory and Parental Attitude Research Instrument (PARI) were used to collect data.

Results: According to the current study over protection parenting styles increased among study group and over protection were positively correlated with anxiety. Although the most of the hemophilic patients are under prophylaxis with factors, these patients mothers' anxiety and over protection score did not differ other patients mothers'.

Discussion/Conclusion: In hemophilic patients, use of factor prophylaxis does not decrease mothers' anxiety. This result may be due to both the risk of bleeding and the blaming of the mother for her genetic transmission. Over protective parenting styles can cause some of psychopathology and developmental deficiency in the children's future personal life. Children diagnosed chronic or serious illness and their family should evaluate psychologicaly.

Disclosure of Interest: None declared.

P154 | Hemophiliacs' management in an emergency department: A 7-years survey to identify areas for safety and quality improvement

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Introduction: The use of emergency service is a common situation during the life of a hemophiliac patient. Still, it remains a challenging situation for the emergency clinicians who are unfamiliar with inherited bleeding disorders. A key issue for optimal care is to identify hemophilia early. The purpose of this study was to analyze the visits of hemophiliac children and adults in an Emergency room (ER) in order to identify the factors influencing the overall stay.

Methods: The descriptive survey (January 2010- December 2016) took place in a French academic hospital with a comprehensive care in the Hemophilia Treatment Center (HTC). The participants were 34 children (average age of 11.2 years) and 43 adults (42.3 years) with respectively 295 visits (70.1%) in the pediatric ER and 126 visits (29.9%) in the adult ER. Data collection included information about 1- hemophilia: type and severity, inhibitor status, current treatment (prophylaxis vs on demand), the validation of a therapeutic educational program (TEP), 2- reason for the consultation and management before and during the ER visit.

Results: The reason for consultation was quite different between children and adults, particularly in terms of head injury. The rapidity of care was significantly shorter in children than in adults (107.5 vs 234.4 minute, $P < 0.0001$). The ED stay was significantly longer

when a laboratory or an imaging examination was ordered (201.7 vs 83.4 minute, $P < 0.0001$). The length of stay in the ER was slightly shorter when the patient was sent by the referee hematologist (110.2 vs 150.2 minute, $P = 0.03$) and when an early substitution (before ER admission) was done (120.4 vs 151.0 minute, $P = 0.04$).

Discussion/Conclusion: The early identification of a hemophiliac patient in ER is a key point for optimal care. The usefulness of biology and imaging has to be assessed in order to avoid time-consuming examination without any loss of security. In this regard, established procedures and recommendations are mandatory. Multidisciplinary training programs should allow improving the quality of care.

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P155 | London 2020: understanding the current and future shape of London hemophilia services and pathways – A clinical perspective

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Introduction: The UK's National Health Service has a reputation for high quality hemophilia services and patient pathways. These services face opportunities and challenges from the growing range of hemophilia treatment options; greater engagement of patients in self-management; and the continuing goal of clinicians to improve clinical practice while the NHS is tasked with delivering efficiency savings. Around one-third of UK hemophilia patients are treated in London. We set out to better understand the current and future shape of London services and pathways.

Methods: We undertook a series of qualitative interviews with clinicians from across multidisciplinary teams in London hemophilia centers and conducted a thematic analysis of these interviews.

Results: There is much that works well and impacts positively on the quality of life of people with hemophilia. For example, the excellent care provided through established formal pathways that enable patients from 1 hospital to access specialist services in others, most notably with respect to dental care. Informal pathways are being developed (e.g., for radiosynovectomy) that will further enhance the quality of care provided. The positive outcomes resulting from intensive treatment, effective MDT working, and the high levels and range of experience as well as access to clinical trials were further themes highlighted by interviewees.

Looking to the future, recurring themes included the need to share experience of new treatments (such as, dosing strategies, the role of laboratories) and developing knowledge and understanding among patients and families/carers, particularly around access to new therapies. The importance of MDT involvement, the potential for greater and different nurse roles and the need for more physiotherapy and psychosocial support were also raised. Questions were put forward about the balance of outreach provision closer to home alongside evolving hospital provision to meet individual patient needs.

Discussion/Conclusion: Working collaboratively in responding proactively to these changes was recognized as a central theme, as was the challenge of creating opportunities to do so while maintaining day-to-day delivery of care.

Disclosure of Interest: None declared.

P156 | Joint outcome in 4 years follow-up in children with hemophilia treated with early prophylaxis

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Introduction: The methods to early recognize joint disease are Hemophilia Joint Score (HJHS) and Hemophilia Early Arthropathy Detection with UltraSounds (HEAD-US). However, especially in children the interphysiotherapist and radiologist discrepancies may hamper the conclusion of these scores. The recommended frequency of these evaluations is not confirmed.

Methods: We evaluated 17 children with severe HA and HB who were more than 4 years old in 2013 – 2014 and again in 2016-2017 along with 9 new patients treated in our centre as a part of the clinical review. All the children had received primary prophylaxis. Patients with present or a history of inhibitors were included. HJSH were done by the same physiotherapists and the HEAD-US by the same experienced radiologist in all time-points. The ultrasound examination included the elbows, knees and ankles.

Results: The first part of the study included 17 boys with severe HA (n = 12) or HB (n = 5). Median age was 11.5 (range 5-17) years. In the second part of the study, 15/17 of these boys were re-evaluated and 9 more. Six patients had a history of inhibitors and immune tolerance treatment (ITI), 2 of them had an on-going treatment during the follow-up. The children with severe HA had prophylaxis with 2-4 injections per week (20-40 IU/kg/d), and the children with severe HB had prophylactic treatment with 1-2 injections per week (50 IU/kg/d). None of the children had HJHS > 0 during the first time-point, and 3/17 patients HJSH available 4 years later had HJHS > 0 (5, 13 and 17). HEAD-US showed no signs of abnormalities in synovia in any of the children during the first time-point, and 4 years later 1 patient showed minimal changes in ankle joints both sides (synovial) and 1 patient with suprapatellar synovitis. Both of the patients do actively sports, and had no severe symptoms related to ankles or knees. At the time of the later time-point 2/26 had ≥ 1 annual joint bleed rate.

Discussion/Conclusion: A low joint bleeding frequency and well preserved joint status evaluated by experienced physiotherapist

and radiologist in the 4-years follow-up was seen. We estimate the need of routinely follow-up with HEAD-US may be 3-4 years in the subjects without special clinical problems for early recognition of joint damage. These check-ups may also motivate the young people for continuing the regular prophylaxis and early treatment of bleeds.

Disclosure of Interest: None declared.

P157 | Coexistence of glanzmann's thrombasthenia and maple syrup urine disease (MSUD): Implications for hemostatic management

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Introduction: In Oman, autosomal recessive disorders are commoner than western communities due to the high prevalence of inter-tribal marriage. Some patients might have more than one autosomal recessive genetic disorder, owing to complex consanguinity.

Methods: Case report and retrospective data analysis of platelet function disorders in Pediatric Hematology Unit, Sultan Qaboos University Hospital, Muscat, Oman from January 2006 till August 2017.

Results: We report a 4 year-old girl who is a known case of MSUD. Her parents are double first cousins (from both maternal and paternal sides). At the age of 3 months, she required Gastrostomy tube (G-tube) insertion. Preoperatively, full blood count and coagulation screen were perfectly normal. Unfortunately, she developed profuse bleeding at the site of G-tube insertion and massive hematemesis. The patient received multiple blood products, but bleeding persisted. As an emergency measure, recombinant activated factor VII (rFVIIa) was given and bleeding stopped. Platelet aggregation studies revealed defective aggregation with ADP, collagen and epinephrine which is consistent with Glanzmann's thrombasthenia. The diagnosis was confirmed by platelet flow cytometry which showed no activity with CD41 and CD61, indicating absent GpIIb/IIIa complex.

The patient experienced a severe bleeding phenotype, which is further complicated by multiple coexisting factors; including recurrent episodes of metabolic crises negatively impacting platelet functions, development of platelet refractoriness, and recurrent invasive procedures such as G-tube and central line insertion. Currently, the bleeding episodes are managed by rFVIIa at a dose of 120-180 μg/kg/dose.

Excluding von Willebrand disease, we have 41 cases of confirmed or suspected platelet function disorders, including 17 cases with Glanzmann's thrombasthenia, 8 cases with Bernard-Soulier syndrome, 5 cases with May–Hegglin anomaly and 11 cases of suspected, yet unconfirmed platelet storage pool deficiency.

Discussion/Conclusion: In conclusion, children with platelet function disorders still have plenty of unmet needs, ranging from deficient accurate diagnostic facilities to the lack of agreed-upon consensus management guidelines. The coexistence of another hereditary disorder may result in mutual management difficulties of both diseases. Proper registry is needed to establish optimum care of such rare disorders.

Disclosure of Interest: None declared.

P158 | Platelet's disorder in a case of chronic lymphocytic leukemia (LLC)

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Introduction: A 65-years-old white man affected by LLC was hospitalized at Humanitas Research Hospital for recurrent intracranial hemorrhages (3 events). He was investigated for hemorrhagic diathesis and was diagnosed δ-storage pool disease. He started therapy with bendamustine 90 mg/m^2 (3 cycles) and rituximab 375 mg/m^2/28 days (6 cycles) for the hematological malignancy and he was also treated with antifibrinolytic tranexamic acid (1 g/daily) to prevent other bleedings. After the 5th cycle of the oncologic therapy the patient was revaluated.

Methods: We first screened blood clotting assays, von Willebrand (VW) antigen and activity, secondly platelet's aggregation to different agonists by optical aggregometry. Surface platelet's antigens (GpIbα, GpIIb, p-selectin and pac1) was measured by flow cytometry in resting and activated platelets using ADP and collagen. Delta-granules were studied by uptake and release of mepacrine by flow cytometry. Aggregometric and flow cytometric mixing experiments were also performed by adding plasma and serum of the patient to platelet's rich plasma of an healthy control (PRP-H)

Results: Before starting therapy, coagulation screening assays, VW-antigen and activity were normal; platelet aggregation to adp 10 μmol/L, trap 10 μmol/L and epinephrine 10 μmol/L were reduced (56%, 15%, 23% vs 70%, respectively), collagen showed mild decrease (62 vs 70%), ristocetin and arachidonic acid showed normal function before and during the therapy. Surface antigen GpIbα, GpIIb and α-granules contents were normal, a decreasing in δ-granules contents was observed (45% vs 70%), suggesting a diagnosis of δ-storage pool disease. Mixing test, performed during therapy, seems exclude an autoimmune mechanism. The aggregometric and flow cytometric assays performed after the Vth cycle of rituximab, documented an improvement of platelets response to trap (67%), epinephrine (61%) and δ granule's contents (60%)

Discussion/Conclusion: Our analysis confirmed the clinical suspicion of a platelets disorder, as δ-storage pool, related to LLC in a patient with several spontaneous cerebral hemorrhages. We documented an improvement in platelet function associated to an apparently clinical resolution of bleeding diathesis, subsequent to the treatment of the hematological malignancy. We intend to confirm these data at the end of treatment and after a longer follow-up.

Disclosure of Interest: None declared.

P159 | The experience of switching factors for treatment of severe hemophilia A patients

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Introduction: Hemophilia A (HA) is an X-linked hereditary disorder caused by deficient levels of the coagulation protein factor VIII (FVIII). The most challenging complication of replacement therapy in (HA) is the occurrence of alloantibodies against infused factor FVIII. The goal is to developed technological strategies to improve hemostatic efficacy and safety of the replacement factor. In this line, a new recombinant FVIII, BAY 81-8973 (octocog alfa; "Kovaltry®", Bayer) has recently been introduced for treatment of these patients. "Kovaltry®" is an unmodified, full-length, recombinant FVIII concentrate with the same amino acid sequence as "Kogenate FS®" (Bayer), but produced without human- or animal-derived raw materials from purification or formulation processes, inclusion of a higher degree of sialic acid capping of N-terminal glycans, coexpression of the human chaperone protein heat shock protein 70, and a 20-nm nanofiltration step to remove small non-enveloped viruses and potential protein aggregates. On this basis we considered beneficial for our patients changing "Kogenate FS®" therapy for "Kovaltry®".

We aimed to determine if switching from "Kogenate FS®" to "Kovaltry®" increases the risk of bleeding or FVIII consumption in severe HA (SHA) patients.

Methods: Sixty-two adult and pediatric patients with SHA without inhibitors, treated with "Kogenate FS®" either on on-demand treatment (n = 13) or on prophylaxis regimen (n = 49), were recruited. The trend of prophylaxis with "Kovaltry®" was evaluated by determining mean injection frequency (per week), mean dose of each injection (IU/kg), mean total dose injected/week (IU), baseline and post-infusion levels of FVIII and annual bleeding rate (ABR). Same data for "Kogenate FS®" were collected retrospectively from clinical histories of patients.

Plasma FVIII:C was measured by chromogenic assay at baseline and post-infusion .

Results: Switching from "Kogenate FS" to "Kovaltry" caused no changes in all parameters evaluated, except in 2 patients. Increment in mean total dose observed in these patients was due to an increase in physical activity (patient 2) and to weight gain (patient 8).

Discussion/Conclusion: We conclude that changing SHA treatment from "Kogenate FS®" to "Kovaltry®" can be performed easily and did not pose any risk to the patient.

Disclosure of Interest: M. Álvarez Román Speaker Bureau of: Pfizer, Shire, Novartis, Novo Nordisk, P. Acuña: None declared, N. Butta Speaker Bureau of: Pfizer, Novartis, Novo Nordisk, M. Martín Salces Speaker Bureau of: Pfizer, Shire, Novartis, Novo Nordisk, M. Rivas Pollmar Speaker Bureau of: Pfizer, Novartis, Novo Nordisk, I. Fernandez Bello Speaker Bureau of: Pfizer, Novartis, Novo Nordisk, V. Jiménez Yuste Speaker Bureau of: Pfizer, Shire, Novartis, Novo Nordisk.

P160 | Successful management of ovarian cyst rupture in a patient with factor V deficiency: a case presentation

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Introduction: Factor V (FV) deficiency is a rare with autosomal recessive inheritance encountered at a rate of 1:1000000. It is more commonly observed as bleeding under the skin and mucosal bleedings. In the present time, the only treatment approach is administration of the Fresh Frozen Plasma (FFP). Dosage and treatment type depend on the bleeding site, factor level and plasma half-life of FV. There is paucity of data regarding outcome of ovarian cyst rupture in congenital FV deficient patients.

Methods: We report a 14-year-old female with congenital Factor V deficiency who developed ovarian cyst rupture successfully managed by FFP.

Results: A 14-year-old female with FV deficiency admitted to pediatric hematology unit with acute onset of abdominal pain. The physical examination of the patient without a previous history of trauma showed a pale appearance of skin and diffuse abdominal tenderness. Laboratory studies revealed, Hemoglobin 6.25 g/dl, elevated activated partial thromboplastin time (149 seconds), prolonged prothrombin time (57.6 seconds), INR: 4.8, FV level was 1.8%. Abdominal and pelvic ultrasound (USG) revealed a cystic formation in size of 87 × 55 mm in the right adnexal area which lost its distortion (ovarian cyst rupture). FFP 15 ml per kilogram of body weight was administered immediately. She also received I/V fluids, antibiotics and packed red cells transfusion. The complaint of abdominal pain is over in the 3rd admission day who received FFP. The control USG encountered a cystic lesion with an intense content in the right ovary measured in size of 5 × 3 cm. The cyst was evaluated to have a lobulated contour without tension. The therapy of the patient was completed in 7 days. The patient was discharged on prophylactic FFP therapy. The follow-up process, FFP prophylaxis and oral contraceptive treatment of the patient were currently continued. The patient had no complication about 6 months.

Discussion/Conclusion: Functional ovarian cysts are very commonly found in the perimenarcheal and perimenopausal periods. Surgical intervention should be considered for the cysts sized over 5 cm and ovarian cysts which lead to acute abdomen. Surgical intervention is the only method if no improvement was encountered in the repeated USG. The appropriate therapy provided a reduction in the diameter of the cyst in our patient and she was treated successfully with administration of FFP without need for surgical intervention.

Disclosure of Interest: None declared.

P161 | The improvement of quality of life of hemophilia and von Willebrand disease in Russian federation

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Introduction: FVIII/FIX consumption in Russia is steadily increasing during the last 10 years. Today the supply with FVIII is 6 IU/capita. It is enough for adequate replacement prophylactic treatment in hemophilia patients.

Methods: Quality of Life (QoL) survey was held in Russian patients with hemophilia and wVD. The questions addressed in the survey covered the period from 2007 until 2017. The survey was designed and conducted by the National Research Center for Hematology, Russian Hemophilia Patients Society, and Pharmacoeconomic Research Society. The Euroqol EQ-5D and Visual analog scale (VAS) questionnaires were also used in the survey.

Results: The average age of patients with Hemophilia in Russia was 37.5 years that is equal to the general population (38 years according to Data of All-Russian population census, 2010). Home treatment increased 1.6-fold. Prophylaxis increased 1.5-fold. The share of patients with ABR ≤1 increased 1.9-fold. The percentage of patients not calling emergency ambulance increased by 18.7%. The share of patients with higher education increased by 13.5%. The share of patients having permanent job increased 2-fold. 80% of patients with hemophilia do not feel themselves lonely.

Discussion/Conclusion: Due to the increase of factor concentrate supply, the possibility of using prophylaxis and home treatment since 2007 the QoL of hemophilia and vWD patient have significantly improved. These changes are well illustrated in long-term observation of patients. It is essential to conduct the analysis of QoL for the study of the efficacy of treatment.

Disclosure of Interest: None declared.

P162 | Evaluation of balance in children with hemophilic arthropathy

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Introduction: Arthropathy, the most common and severe complication in patients with hemophilia (PWH), causes joint deformity, shape-dysfunction and loss of proprioception. Disturbance of balance caused by arthropathy results in further bleeding in joints due to accidents. In this study, we aimed to investigate deterioration of the balance, and the risk of falling in PWH and compared our findings with those in control group (CG).

Methods: 34 hemophilic patients [27 hemophilia A (3 with inhibitors), 7 hemophilia B, 33 with severe, 1 with moderate disease] whose target joints were knee or ankle included in the study. All the patients were on prophylaxis. They are evaluated using WFH Physical Examination Score [Gilbert score (GS)], pediatric Functional Reach Test (FRT) and Time up and go Test (TUG) in order to show dynamic and functional balance, and Pediatric Berg Balance Scale to show risk of falling. The results were compared to those in CG (34 males) who stratified according to age.

Results: There was no difference in 2 groups in terms of age (15.6 ± 3.3 years in PWH and 15.7 ± 3.3 years in CG). Knee was target joint in 27 (79.4%) and ankle was target joint in 7 (20.6%) PWH. Each patient had only one target joint. According to GS, arthropathy was slight in 11, moderate in 16, and severe in 7 PWH. There was a trend toward worse results in patients with severe arthropathy for all 3 tests. Comparison of test results between 2 groups was similar for TUG and FRT, however, Berg score which shows impaired balance was significantly low in PWH.

Discussion/Conclusion: Our study revealed PWH have impaired balance due to arthropathy in lower extremity. Therefore, they are more vulnerable to falling due to loss of balance. Within PWH, patients who had severe arthropathy are more prone to danger of falling compared to the other patients with arthropathy. These results strongly support primary prophylaxis in PWH in order to prevent joint damage and disturbed balance.

Disclosure of Interest: None declared.

P163 | Audit of bleeding complications following invasive procedures and minor surgeries in patients with bleeding disorders: considering a rationale for same day discharge

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Introduction: Minor, invasive procedures are increasingly a routine part of standard and preventative medical care. There is no established standard of care regarding admission of patients with bleeding disorders (PWBD) following such procedures. In the National Coagulation Centre (NCC) at St James's Hospital (SJH), currently all PWBD are admitted for observation following minor invasive procedures, except endoscopy without biopsy and selected minor procedures. We reviewed bleeding complications after minor, invasive procedures to define a cohort who may be suitable for same-day discharge.

Methods: We performed a retrospective review of procedure reports and electronic clinical notes for all PWBD with planned admissions of 1 day following invasive, minor procedures throughout 2016. Data collected included procedure type, patient demographics, bleeding disorder, length of inpatient stay, and timing and severity of bleeding

complications. Proposed criteria for same-day discharge were also evaluated, i.e. patients who fulfilled all the following criteria: mild bleeding disorder, procedures with low risk of bleeding and no immediate bleeding complications.

Results: In total, 96 PWBD underwent a minor invasive procedure, of whom 30 were discharged on the same day and 66 were admitted for at least 1 day. The most common diagnosis in those admitted was Factor VIII deficiency (n = 12). Post-procedure bleeds occurred in 13 patients, 12 of whom had been admitted (clinically relevant non-major bleed [n = 11] and minor [n = 2]). Colonoscopy was the procedure most commonly associated with bleeding (n = 4). More bleeds occurred in Factor VIII deficiency (n = 5) than any other disorder. Based on the proposed criteria, 24 additional patients would be suitable for same-day discharge and all significant bleeding complications occurred in patients who would not be eligible for discharge.

Discussion/Conclusion: 34.8% of PWBD admitted following minor, invasive procedures could potentially have been safely discharged. 91.6% of admitted patients with bleeding complications were classified as high-risk based on our proposed criteria, and excluded from same-day discharge. We are implementing a new admission policy for PWBD attending for invasive procedures based on the above criteria. Potential benefits include better resource utilization and improved quality of life for PWBD.

Disclosure of Interest: None declared.

P164 | Mutation in factor VIII and inhibitor production in hemophilia A

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Introduction: Hemophilia A is an X-linked recessive disorder (XLR) caused by factor VIII deficiency (FVIII). Male patients have clinical symptoms such as joint bleeding and bruising. This study aimed to measure possible mutations in factor VIII and inhibitor production in hemophilia A patients.

Methods: In this cross-sectional study, 20 cases of hemophilia A, registered in Hematologic and Oncologic Research Center of our academic Hospital in Gorgan during the year 2013 were studied. They were divided into 3 groups based on the inhibitor level recorded in their medical files: 1) a group with an inhibitor level less than 0.5 BU/ml, 2) levels of 0.5-5 BU/ml and 3) higher than 5 BU/ml.

Ten ml of blood was taken from all cases and transferred to EDTA-containing tubes. DNA samples were extracted from blood samples. Introns 18 of hemophilia A gene was amplified with the aid of a PCR-assisted primer. Ten microliters of the PCR product were cut by BCLI Enzyme, using the RFLP Method the results of DNA digestion were analyzed in 3 groups. Finally, the association of these polymorphisms with the inhibitor level was analyzed.

Results: Of the 20 patients with hemophilia, 11 (55%) patients had severe inhibitors' production, 6 (30%) moderate and 3 (15%) had mild inhibitor levels.

Regards to the blood group, 9 (45%) of these patients were O+, 5 (35%) was B+ and 6 (30%) were A + . The normal range of factor VIII level is between 15-50 AU, and all patients were under 50 AU. The age range of patients was between 1 and 36 years, and 3 patients were in the age range of 0-10 years.

The intensity of the BCL1 band was with bp142 band strength in 11 cases ($P = 0.312$) and 9 cases with band strength bp99 ($P = 0.301$). There was no significant relationship between age and level of inhibitor production and also between blood group and factor VIII ($P < 0.05$). There was no significant relationship between age and factor VIII. There was no significant relationship between age and expression of 142 bp ($P < 0.05$), and there was no significant relationship between the blood group and the level of inhibitor and factor VIII, but there was a significant relationship between blood group and the introns 18 binding region ($P < 0.05$).

Discussion/Conclusion: Present data showed that intron 18 gene regions can be identified as a marker in genetic evaluation of hemophilia A in the studied population in Golestan province.

Disclosure of Interest: None declared.

P165 | Efficacy on pain of a single injection of hyaluronic acid in hemophilic arthropathy of the ankle: a prospective study

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Introduction: Hemophilic arthropathy (HA) of the ankle is the most common source of pain in hemophilic patients. Intra-articular injections of hyaluronic acid (HyA) have shown encouraging outcomes in HA, but with limited data and heterogeneous protocols. Objective: to investigate the efficacy on pain of a single intra-articular injection of HyA in the HA of the ankle.

Methods: In this prospective, monocenter, non-controlled study, adult patients with painful HA of the ankle were included. All received a single ultrasound-guided intra-articular injection of HyA (HYALGAN® 20 mg/2 ml), under guidance of ultrasonography. Patient-reported pain on Visual Analogue Scale (VAS), American Orthopaedics Foot and Ankle Society (AOFAS), World Federation of Haemophilia (WFH) and Pettersson scores were assessed before and at regular intervals following the injection. Primary endpoint was pain variation on VAS 3 months after the injection (M3).

Results: Of the 14 patients (16 ankles) included, 11 had a severe factor deficiency and 9 were under prophylaxis, for 5.9 years in average. At baseline, mean Pettersson score was 5 ± 2.8. Median VAS score significantly decreased from 57[24-86]mm to 30[0-68]mm at M3 (P = 0.004). 78% of the injections were followed by any decrease in VAS and 56.3% by a clinically significant pain relief (^{3}20 mm) at M3, sustainable at M6. Mean AOFAS and WFH scores improved. No adverse effect was recorded.

Discussion/Conclusion: As previously suggested, viscosupplementation seems to be an efficient and safe therapeutic strategy in the HA of the ankle, even with a single injection. Further and larger studies are required to confirm those data and identify determinants of response.

Disclosure of Interest: None declared.

P166 | Previously untreated patients with hemophilia: a single center experience

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Introduction: Primary prophylaxis with coagulation factor concentrates has become the standard of care for children with hemophilia. Development of neutralizing inhibitory antibodies to FVIII and FIX is the most challenging treatment-related complication of hemophilia. We documented the patients from January 2014 to September 2017 and evaluated previously untreated patients (PUP).

Methods: We report a retrospective case series of 45 PUP between 2005-2017 at Cerrahpasa Medical Faculty Pediatric Hematology Outpatient Clinic which consists of 26 severe hemophilia A (HA), 6 moderate-mild HA and 13 moderate-mild hemophilia B (HB) patients.

Results: Twenty four of the 26 severe HA and 1 of the 6 moderate-mild HA patients were under primary prophylaxis. Four of the 25 patients whom were getting primary prophylaxis, were treated with plasma derived factors (beriate, octanate) and the other 21 patients were treated with recombinant factors (refacto, advate). Two of the severe HA patients who were under primary prophylaxis with plasma factors developed inhibitors to FVIII and both were negative after immune tolerance induction (ITI) in 3 months. Three of the severe HA patients who were under primary prophylaxis with recombinant factors developed inhibitors to FVIII. Two of their inhibitors were negative after immune tolerance induction (ITI), whereas the third patient still has inhibitors. Although after SIPPET study it is recommended to begin primary prophylaxis with plasma derived factors, our experience revealed that both the type of the factor concentration and genetical factors are crucial for inhibitors.

Discussion/Conclusion: Hemophilia is a serious congenital bleeding disorder that requires early diagnosis, intensive family and patient education, and regular comprehensive care to prevent life-threatening complications and potentially lifelong disability.

Disclosure of Interest: None declared.

P167 | Treatment of bleeding in a glanzmann thrombasthenia case with recombinant FVIIA complicated with acute renal failure

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Introduction: Glanzman thrombasthenia (GT) is a rare, autosomal recessive disorder. It is caused by the qualitative or quantitative abnormalities of GPIIb/IIIa platelet surface receptors. Spontaneous mucocutaneous bleeding is common. We report a patient who presented with hematuria and severe gastrointestinal bleeding and was treated with recombinant factor VIIa (rFVIIa). His hemostatic treatment was complicated by acute renal failure.

Methods: xxx.

Results: Case: A 4.5-year-old, GT male patient from consanguineous parents presented with macroscopic hematuria and bloody vomiting. Vital signs were stable. Platelets were transfused however bleeding continued. Upper gastrointestinal endoscopy was performed and erythrocytes were transfused due to anemia. Endoscopy revealed a hematoma in the posterior pharynx and extensive active bleeding foci in the stomach. The patient was started on proton pump inhibitors. One dose of 90 mcg/kg rFVIIa was administered because bleeding could not be controlled despite thrombocyte transfusion. After rFVIAA bleeding continued from GIS tract and the patient's urine output gradually decreased. A CT scan was performed. Left kidney size was increased, left ureter was dilated and an hematoma was seen in the left ureter orifice of the bladder. The patient developed fever and antibiotics were started. Creatinine increased from 0.6 mg/dL to 4.9 mg/dL and there was no urine output. The patient was transferred to intensive care unit (ICU) with diagnosis of acute renal failure. He was intubated and was put on hemodialysis. rFVIIa was administered one more time to the patient who still had bleeding in the ICU and the bleeding stopped. *Serratia plymuthica* was cultured in urine. He is on follow-up in out-patient clinic with no bleeding and normal kidney functions.

Discussion/Conclusion: The mainstay of treatment of bleeding in GT is local precautions, antifibrinolytic therapy and, if necessary, platelet transfusion. However, successful use of rFVIIa has been reported in alloimmune patients who have not been able to control hemorrhage despite platelet transfusion. Hemostatic therapies should be used cautiously in patient with urinary bleeding due to risk of clot formation and acute renal failure.

Disclosure of Interest: None declared.

P168 | Study design for veriti-8 study: a global, multicenter, open-label, interventional study evaluating rFVIIIFc for initial iti therapy

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Introduction: Inhibitor development is one of the most serious complications of treatment in hemophilia A, with the highest risk occurring within 20 to 50 exposure days. Immune tolerance induction (ITI) is considered the standard of care for inhibitor eradication, an essential step to restore patients' responsiveness to FVIII. Currently, the outcomes of ITI using extended half-life products, including recombinant factor VIII Fc fusion protein (rFVIIIFc), are limited to case reports, with no specific treatment recommendations. Fc-containing fusion proteins, like rFVIIIFc, are thought to have immunomodulatory properties associated with the upregulation of regulatory T cells and the promotion of FVIII-specific T-cell tolerance. Recent case series of 3 patients with inhibitors using rFVIIIFc in ITI showed faster time to tolerization (17 weeks, 18 weeks, and 17 months) as concluded by the author. A prospective study (NCT03093480) to evaluate the time to tolerization using rFVIIIFc for ITI in patients with inhibitors is under way.

Methods: A prospective, open-label, single-arm, interventional, multicenter study will be conducted in ~30 subjects of any age with severe hemophilia A who were diagnosed with high-titer inhibitors (≥5 BU/mL). The study consists of: screening period (2–4 weeks), ITI period (up to 48 weeks), tapering period (minimum of 16 weeks, to achieve prophylactic dosing), and follow-up period (32 weeks). During the ITI period, rFVIIIFc will be administered at 200 IU/kg/day (once-daily or divided daily doses), aiming to achieve faster tolerization and fewer bleeding episodes. The primary endpoint is the time to tolerization with rFVIIIFc. Eradication of inhibitors (ie, ITI success) is defined by: negative inhibitor titer (<0.6 BU/mL by Nijmegen-modified Bethesda assay) at 2 consecutive visits, incremental recovery >1.3 IU/dL per IU/kg (ie 66% of the expected IR) at 2 consecutive visits, and an rFVIIIFc half-life of ≥7 hours.

Results: The study is enrolling. Results will be presented after completion of the study.

Discussion/Conclusion: This study will examine the time to tolerization in subjects receiving rFVIIIFc for initial ITI who have severe hemophilia A and high-titer inhibitors. Decreased ITI treatment time leading to restoration of FVIII efficacy may lead to better outcomes on patient morbidity, joint arthropathy, quality of life, and decreased factor consumption for ITI treatment.

Disclosure of Interest: L. Malec Grant/Research support from: Bayer, Biotest, Pfizer, Shire and Sobi, Consultant for: Bayer, Biotest, CSL CSL Behring, Grifols, Janssen, MSD, Novo Nordisk, Pfizer, Roche, Shire and Sobi, Speaker Bureau of: Bayer, Biotest, CSL CSL Behring, Grifols, Janssen, MSD, Novo Nordisk, Pfizer, Roche, Shire and Sobi, R. Kulkarni: None declared, R. Sidonio: None declared, M. Wang: None declared, N. Rodriguez: None declared, S. Lethagen Shareholder of: Sobi, Employee of: Sobi, E. Tsao Employee of: Bioverativ, D. Glazebrook Employee of: Bioverativ, N. Jain Employee of: Bioverativ. This research is funded by Sobi and Bioverativ.

P169 | An unusual coexistence of high titer inhibitor development and gastrointestinal stromal tumor in a patient with severe hemophilia: case report

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Introduction: The development of inhibitors in severe hemophiliacs complicates the course of disease and management.

Methods: We herein reported an unusual case of newly developed high titer inhibitor in a severe Hemophilia A patient who was admitted with upper gastrointestinal system (GIS) bleeding and further diagnosed as gastrointestinal stromal tumor (GIST).

Results: 37-year-old man, with known hemophilia A, was admitted to emergency service with upper GIS bleeding. His factor VIII level was at 0.25% and had no inhibitor at last visit in outpatient clinic about 3 months ago. His hemoglobin level was 4.9 g/dl (ref. 13.5–18 g/dL), platelet count was 272 × 10^9/L (ref. 151–304 × 10^9/L). The partial thromboplastin time (aPTT) was 120 seconds (ref. 24-36 sn). We immediately started factor VIII replacement (50 u/kg as beginning dosage, 25 u/kg twice a day as maintenance dosage). Upper GIS endoscopic examination detected a 4 cm polypoid lesion with an ulceration on anterior surface of stomach corpus. Surgical excision of polip was recommended but aPTT prolongation was not improved despite replacement of factor VIII. A mixing test failed to correct aPTT prolongation. The inhibitor level resulted as 17 Bethesda Unit. We started recombinant activated coagulation factor VII (rFVIIa) –NovoSeven® (Novo Nordisk A/S, Bagsvaerd, Denmark) with a dosage of 90 mcg/kg in every 2 hours on 8th day of admission. Emergent subtotal gastrectomy was performed successfully without severe bleeding under treatment of rFVIIa. Postoperatively his GIS bleeding was stopped and his aPTT level decreased to normal range on day 18 of rFVIIa treatment. Result of subtotal gastrectomy pathology was later reported as GIST grade 2. During ongoing treatment of rFVIIa, acute right femoral vein thrombosis occurred on the day 35 of rFVIIa treatment and we had to stop treatment. No further bleeding episodes developed later in clinical follow-up.

Discussion/Conclusion: To our knowledge, this constitutes the first reported case of GIST associated with inhibitor development in a hemophilia A patient. We also reported a successful bleeding control

with rFVIIa during surgery in a severe Hemophilia A patient with high titer inhibitor. Else, the occurrence of thrombosis during treatment shows that factor preparations should be used with caution.

Disclosure of Interest: None declared.

P170 | Effective protection for >5 years with bay 94-9027 prophylaxis: interim results from the protect VIII extension trial

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Introduction: BAY 94-9027 is a B-domain–deleted prolonged–half-life recombinant factor VIII site-specifically conjugated with a single (dual 30-kDa branched) 60-kDa polyethylene glycol molecule. In the PROTECT VIII phase 2/3 trial, BAY 94-9027 provided effective bleed protection with twice-weekly, every-5th-day, and every-7th-day prophylaxis for 36 weeks. Herein, we report interim efficacy data from the PROTECT VIII extension study in patients using BAY 94-9027 prophylaxis for up to 5.2 years.

Methods: In the PROTECT VIII trial, previously treated males aged 12-65 years with severe hemophilia A received BAY 94-9027 for 36 weeks on demand or for prophylaxis either twice weekly (30–40 IU/kg), every 5 days (45–60 IU/kg), or every 7 days (60 IU/kg). Patients could continue in the extension study using the same or a different regimen. Bleeds were recorded in electronic patient diaries, and annualized bleeding rates (ABRs) were calculated.

Results: Of 134 patients enrolled in PROTECT VIII, 121 patients aged 15-67 years at time of analysis (median age, 39 years) continued in the extension with either on-demand treatment (n = 14) or prophylaxis (n = 107). At data cutoff (August 2017), patients had spent a median of 1420 (range, 297–1903) days in the study since enrollment, with a median of 223 (range, 23–563) exposure days. Prophylaxis patients in the extension were treated either twice weekly (n = 23), every 5 days (n = 34), every 7 days (n = 23), or switched frequency during the extension (n = 27). Median (quartile [Q] 1; Q3) ABR for total bleeds was 33.7 (20.3; 36.6) for on-demand patients. For prophylaxis patients, median (Q1; Q3) ABR was 1.6 (0.3; 4.6) for total bleeds and 0.9 (0; 3.4) for joint bleeds. For total bleeds, median (Q1; Q3) ABR was similar for patients using prophylaxis twice weekly (1.8 [0.8; 3.6]), every 5 days (1.3 [0; 4.6]), and every 7 days (0.7 [0; 1.6]). Thus, ABR was further reduced compared with the main study in patients who remained in their treatment arm, including every-7th-day patients (median [Q1; Q3] main study ABR, 0.96 [0; 4.3]). No safety issues were identified.

Discussion/Conclusion: Good bleeding control was maintained with BAY 94-9027 prophylaxis with extended intervals of every 5th day and every 7th day throughout the PROTECT VIII extension study for >5 years.

Disclosure of Interest: G. Thomson: None declared, P. A. Holme Grant/Research support from: Bayer, Consultant for: Bayer, M. Wang Employee of: Bayer, M. Maas Enriquez Employee of: Bayer.

P171 | Concizumab population pharmacokinetic model in healthy volunteers and in patients with hemophilia A/B: applicability to phase 2 concizumab trial design

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Introduction: A population pharmacokinetic (PK) model developed to guide the concizumab clinical development program is described. The model was constructed based on available intravenous (iv) and subcutaneous (sc) human data for concizumab doses >50 μg/kg and up to 9 mg/kg.

Methods: The PK model was developed by first describing mean iv data (disposition), then including mean sc data for a description of the absorption, and finally including all data in order to describe between-subject and within-subject variability. The data supported a 2-compartment model with a linear and a substantial non-linear clearance component and a parallel absorption model, with classical disposition parameters similar to those of other monoclonal antibodies. The non-linear clearance was high, leading to ~100-fold higher total clearance for low concentrations. Single-dose data were used to identify both a fast and a slow absorption component in the model, where the amount absorbed via the fast absorption component appeared to be higher for high dose levels. The total bioavailability was estimated to be between 0.4 and 0.8 for 0–250 and 3000 mg/kg, respectively. Two independent variability parameters were included; one for fast absorption rate (Ka_{fast}) and one for CL/MM clearance (CL and V_m). PK data from explorer™3 were used first for external model validation and, subsequently, in combination with data from other concizumab clinical trials to provide updated model parameter values.

Results: A tight fit was observed between the model-predicted and the observed PK data in concizumab clinical trials for individual patient predictions for concizumab concentrations and the population predictions of the geometric mean, regardless of administration route and dose regimen. Once-daily (QD) dosing was predicted to minimize within-subject PK variability observed with dosing once every 4 days (Q4D) in explorer™3; the peak-to-trough ratio for Q4D dosing was estimated to be 2- to 3-fold larger compared with QD dosing, depending on the dose. Individual dose escalation of concizumab is expected to mitigate between-subject PK variability.

Discussion/Conclusion: A once-daily, efficacy-based, individual, dose-escalation regimen (0.15, 0.2 and 0.25 mg/kg) has been selected for the concizumab phase 2 clinical development program.

Disclosure of Interest: P. Anderson Employee of: Novo Nordisk, A/S, U. Friedrich Employee of: Novo Nordisk, A/S, R. Overgaard Employee of: Novo Nordisk, A/S.

P172 | Evaluation of a chromogenic assay for factor VIII

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Introduction: Today, factor VIII (FVIII) is usually evaluated using aPTT-based 1-stage clotting assays (OSA). Interest for its measurement using chromogenic assays was raised after the publication of discrepant test results that could lead to misdiagnose as normal some mild/moderate hemophiliacs A by using OSA, and more recently by the availability of long-acting products for the treatment of hemophilia A that could behave differently from plasma-derived or traditional recombinant FVIII in clotting assays.

Methods: The aim of the present multicenter study involving 7 laboratories was to evaluate the performances of a chromogenic assay for FVIII (Biophen FVIII:C, Hyphen Biomed) automated on different coagulation analyzers i.e. ACL TOP (IL, n = 2), BCS XP (Siemens, n = 2), CS-5100 (Siemens, n = 1) and STAR (Stago, n = 2). It used 2 calibration curves, one for FVIII levels between 20 and 160 IU/dL (high calibration curve) and one for levels between <1 and 25 IU/dL (low calibration curve). In addition, test results obtained in various clinical materials using that chromogenic assay were compared to those obtained using OSA performed with different aPTT reagents i.e. HemosIL SynthASil, Actin FS and STA-CK Prest 5 automated on the same analyzers.

Results: The within-run precision, expressed as the coefficient of variation (CV%, n = 20), and the between-run precision (n = 6-24) were evaluated on the different analyzers using normal and pathological lyophilized plasmas (Hyphen). Obtained within-run CV% was below 4.3% when evaluated using the high calibration curve and below 5.3% using the low calibration curve. The between-run CV% was below 6.4% and 14.6% respectively. FVIII test results obtained using the Biophen FVIII:C reagent in the plasma of patients with different disease states (n = 80-116, different in each center) were well correlated with those obtained using the OSA performed on the same analyzer (r between 0.949 and 0.995). Bias calculated according to Bland-Altman was below 4.5 IU/dL, except on 1 center (14.5 IU/dL). Discordant test results were demonstrated in 2 mild hemophiliacs A, in 2 patients with lupus anticoagulant, and in 2 patients treated with rivaroxaban. These data were not included in the above-mentioned calculation.

Discussion/Conclusion: In conclusion, these results suggest that the Biophen FVIII:C reagents allows an accurate measurement of FVIII and would be suitable to evaluate FVIII in the plasma of patients, either hemophiliacs or not.

Disclosure of Interest: None declared.

P173 | Evaluation of a chromogenic assay for factor IX

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Introduction: Today, factor IX (FIX) is usually evaluated using aPTT-based 1-stage clotting assays (OSA). Interest for its measurement using chromogenic assays was recently raised by the availability of long-acting products for the treatment of hemophilia B that could behave differently from plasma-derived or traditional recombinant FIX in clotting assays.

Methods: The aim of the present multicenter study involving 7 laboratories was to evaluate the performances of a chromogenic assay for FIX (Biophen FIX, Hyphen Biomed) automated on different coagulation analyzers i.e. ACL TOP (IL, n = 2), BCS XP (Siemens, n = 2), CS-5100 (Siemens, n = 1) and STAR (Stago, n = 2). It used 2 calibration curves, one for FIX levels between 20 and 180 IU/dL (high calibration curve) and one for levels between 0.8 and 25 IU/dL (low calibration curve). In addition, test results obtained in various clinical materials using that chromogenic assay were compared to those obtained using OSA performed with different aPTT reagents i.e. HemosIL SynthASil, Actin FSL and STA CK-Prest 5 automated on the same analyzers.

Results: The within-run precision, expressed as the coefficient of variation (CV%, n = 20), and the between-run precision (n = 6-24) were evaluated using lyophilized plasmas (Hyphen) both in the normal and pathological ranges of concentrations. Obtained within-run CV% was below 8.3% when evaluated using the high calibration curve and below 14.3% using the low calibration curve. The between-run CV% was respectively below 15.0% and 16.1%. FIX test results obtained using the Biophen FIX reagent in the plasma of patients with different disease states (n = 80-111, different in each center) were well correlated with those obtained using the OSA performed on the same analyzer (r between 0.948 and 0.995), except in 2 centers (r = 0.870 and 0.891. Bias calculated according to Bland-Altman was below 10 IU/dL, except on 1 center (14.3 IU/dL). Discordant test results were demonstrated in 5 hemophiliacs B treated with albutrepenonacog alfa (Idelvion®), a long acting product, in 2 patients with lupus anticoagulant, and in 7 patients treated with rivaroxaban. These data were not included in the above-mentioned calculation.

Discussion/Conclusion: In conclusion, these results suggest that the performances of the Biophen FIX reagent could be variable depending

on the analyzer and that additional investigation would be needed before making recommendations concerning its use in routine testing.

Disclosure of Interest: None declared.

P174 | Epidemiologic profile of hemophilia patients from the Amazon, Brazil

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Introduction: The studies of epidemiologic profiles are important for the establishment of individualized health care plans. Thus, the objective of the study was to establish the epidemiologic profile of hemophilic patients from a State in the Amazon (Pará), and compare this to the national standard.

Methods: The information that was used is from the National System of Coagulopathies date base, between the years of 2009 to 2015.

Results: In Pará there are 383 carriers of hemophilia A (hemoA) and 88 carriers of hemophilia B (hemoB) with the coefficient of prevalence of 0.9 for hemoA and 0.7 for hemoB, while in Brazil as a whole these coefficients are 1.0 and 0.7, in the same order. The mild form (avg = 46.9%) was the most prevalent form within the analyzed years, followed by the severe form (avg = 22.16%) and the moderate form (avg = 18.78%) in hemoA. The same results occurred with hemoB (mild = 42.27; severe = 25.91; moderate = 25.18). The National severity profile follows as severe (37.04%), mild (25.15%) and moderate (24.01%) in regards to hemoA and moderate (33.06%), severe (30.60%) and mild (22.54%) in regards to hemoB. The occurrence of inhibitors was 5.98% in Brazil and 2.39% in Pará for hemoA and 1.33% in Brazil and 0% in Pará for hemoB. In replacement concentrates evaluations of factor VIII, secondary prophylaxis is most common for hemoA in Pará, followed by home therapy (11.95%) and outpatient treatment (9.21%). Whereas in Brazil secondary prophylaxis (52.13%) was the most used, followed by home therapy (22.88%) and immunotolerance. For factor IX the categories follow as secondary prophylaxis (51.30%), home therapy (22.9%) and outpatient treatment (16.5%) in Brazil and secondary prophylaxis (47.65%), outpatient treatment (17.84%) and home therapy (11.40%) in Pará. When we evaluate the consumption per capita, consumption in Brazil was 3.21 IU/person, while in Pará it was 1.84 IU/person.

Discussion/Conclusion: This confirms a difference in the severity profile in Pará in relation to the national standard, with the predominance of mild hemophilia in almost half of the patients. This finding could also justify the low incidence rate of inhibitors in the hemophilic population of the State. The median consumption rate of FVIII and FIX per person in Pará are lower than the rest of the country because of the severity profile, but also because of the size of the State and the difficulty for the patients to reach the Treatment Centers.

Disclosure of Interest: None declared.

P175 | Bleeding events and safety outcomes in persons with hemophilia A (PWHA) without inhibitors: non-interventional study (NIS) from a real-world setting

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Introduction: PwHA have high disease burden, requiring frequent IV infusions of factor replacement. A global NIS (NCT02476942) prospectively assessed real-world data (RWD) on bleed rates and treatment approaches in PwHA to support clinical development of emicizumab, a subcutaneously administered, bispecific monoclonal antibody for bleed prevention. After the NIS, participants (pts) could enter a phase 3 emicizumab study. We describe bleed and safety outcomes in PwHA without (wo) inhibitors on FVIII therapy per routine clinical practice (NIS Cohort C).

Methods: Inclusion criteria: ≥12 y.o., severe HA (FVIII activity <1%), no FVIII inhibitors, ≥6 mo. of episodic or prophylactic FVIII; for episodic regimen, pts had ≥5 bleeds in 6 mo. prior to study (no requirement for prophylaxis [Px]).

Results: This cohort (data cutoff 31 Mar 2017) had 94 PwHA wo inhibitors on episodic (n = 45) or prophylactic (n = 49) FVIII regimens from 10 countries; median (range) age, 34 (12–76) y.o. Median (range) observation time, 30 (12–48) week. Most bleeds were treated (82%). Annualized bleeding rates (ABRs [95% CI]; negative binomial regression) for treated bleeds, 36.1 (30.8–42.3) (episodic) and 5.0 (3.3–7.5) (Px); corresponding ABRs (95% CI) for all bleeds, 43.1 (36.5–50.9) and 6.2 (4.2–9.2). Calculated median ABRs (IQR), 31.1 (19.8–51.6) (episodic) and 1.9 (0–8.22) (Px) for treated bleeds; corresponding median ABRs (IQR) for all bleeds, 35.3 (21.7–62.9) (episodic) and 2.7 (0–9.4) (Px). Most pts received standard half-life FVIII (83/94 [88%]). Pts on Px had a median (IQR) 2.9 (2.1–3.1) doses per week, and most had break-through bleeds (31/49 [63.2%] pts, treated bleeds; 33/49 [67.3%] pts, all bleeds). Most common adverse events (AEs) were viral upper respiratory infection and arthralgia. Incidence of SAEs was low, 5 (including hemarthrosis, GI polyp bleed) in 3/49 (6.1%) pts on Px and none on episodic regimen.

Discussion/Conclusion: In this real-world setting, FVIII Px effectively controlled bleeding in PwHA wo inhibitors and ABRs were comparable to those from clinical trials. However, Px in this NIS was associated with high infusion burden and a large proportion of pts had break-through bleeds. A high proportion of bleeds were treated, in contrast to previous RWD from this NIS in PwHA with inhibitors. These data

suggest an unmet need for improved treatment options for PwHA wo inhibitors.

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P176 | Switch to extended half-life recombinant factor VIII FC in severe hemophilia A patients under prophylaxis. Experience in one centre

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Introduction: Prophylactic treatment in hemophilia is effective in avoiding or minimizing the arthropathy. The use of extended half-life (EHL) recombinant factor FVIII (rFVIII) reduce monthly doses and the number of infusions, without increasing bleeding events or lowering FVIII trough levels. In our country, the first EHL rFVIII was commercialized in Oct-16: efmoroctocog alfa (Elocta®), a human rFVIII Fc (rFVIIIFc) fusion protein. It was approved at the same price as conventional rFVIII. We evaluate the switch to this factor at a Haemophilia Center.

Methods: Six severe hemophilia A patients on prophylaxis were switched from conventional rFVIII to EHL rFVIIIFc. Median age was 14 years (5-24). Prophylaxis was initiated at 2.75 years of age (1.4-7). All patients had a ABR rate of 0.5 (0-2). The joint balance was normal in all patients, except a discrete elbow flexion of 15º in one of them. Mean follow-up period was 6.8 months (3-10). Efficacy and potential adverse events were evaluated through clinical endpoints (bleeding events, weekly doses, impact on quality of life). The impact of rFVIIIFc on cost was also evaluated.

Results: Using rFVIIIFc allowed decreasing by 34% the number of injections (63-42 injections/month) and by 31% the amount of IU administered (115 000-80 000 IU/month). In 4 out of 6 patients, reducing 1 injection/week was achieved, maintaining the same dose. One patient reduced 1 injection/week, minimally increasing the dose/injection. All patients interviewed agreed that this change had significantly increased their quality of life. The youngest patient kept both the number of injections and dose, in order to obtain a longer period above 1%. Only 1 patient experienced an adverse event during the follow-up period (right ankle sprain). Neither breakthrough bleeds nor inhibitor development were observed. Considering the mean cost per IU of conventional rFVIII at our hospital (0.547€) vs rFVIIIFc (0.620€), monthly spending was reduced by 12665€.

Discussion/Conclusion: In our experience the switch to rFVIIIFc has allowed to:

- Significantly reduce the number of injections and the IU consumption, meaning an important cost saving of prophylaxis, without increasing the number of bleeding events.
- Achieve an individualized prophylaxis based on bleeding phenotype and lifestyle of each patient, which positively affects both quality of life and treatment adherence.

Disclosure of Interest: None declared.

P177 | Annual bleeding rate and bleeding-related costs in hemophilia A and B in real-life clinical practice: A 4-year follow-up study in Finland

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Introduction: The majority of direct healthcare costs for hemophilia treatment derive from factor-replacement therapy. Complications, such as breakthrough bleeds, further increase the costs. We characterized annual bleeding rate (ABR) and related costs among Finnish adult non-inhibitor patients with hemophilia A (HA) and B (HB), in a real-life clinical setting.

Methods: This was a nationwide, retrospective, multicenter chart review study on patients having all hemophilia severities. Detailed clinical data were collected (by HV) from patient charts generated over a period of 4 years (2012–2016). The cohort included all adult patients who had at least 1 contact with 1 of the 5 Finnish University Hospitals during the follow-up period.

Results: We included a total of 170 patients aged 18–89 years; 77% (n = 131) HA and 23% (n = 39) HB patients. In total, 56% (n = 74) of HA patients received prophylaxis, however the corresponding proportion for severe HA was 85% (n = 61). The corresponding proportions were 31% (n = 12) for all HB and 75% (n = 6) for severe HB. Of prophylactically treated (PRO) patients, 73% (n = 54) of HA and 58% (n = 7) of HB experienced bleeds during the 4-year follow-up. Six PRO HA patients had over 10 annual bleeding episodes. The median ABR for the PRO HA patients was 1.5 [range: 0.20–25.5], and for HB the ABR was 0.5 [0.2–8.0]. The total annual medication costs for PRO patients were 139 491 €/yr/patient for HA and 138 984 €/yr/patient for HB. The mean ABR-related medication costs for PRO patients were 6284 €/yr/patient for HA, and 6731 €/yr/patient for HB. Bleeding episodes increased these costs by 4.7% in HA and 5.1% in HB.

Discussion/Conclusion: Our study showed that the median ABR is within recommendations. However, over 100-fold ABR range highlights the importance for further analysis on the use of factor-replacement therapy and the management of hemophilia.

Disclosure of Interest: H. Ventola Employee of: MedEngine Oy, J. Jokelainen Employee of: MedEngine Oy, T. Ylisaukko-oja Shareholder of: MedEngine Oy, Employee of: MedEngine Oy, M. Linna: None declared, A. Lepäntalo: None declared, R. Lassila: None declared.

P178 | The advance study: a longitudinal study of age-related comorbidities in people with hemophilia: interim results

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Introduction: The ADVANCE Group, a collaboration of 22 European hemophilia centers representing 6500 PWH, will collect prospective data on the incidence and management of CVD in older PWH and compare the observed fatal and non-fatal CVD events against expected numbers based on CVD risk prediction scores [SCORE & Q-RISK2] at baseline. A total of 800 patients from approximately 20 European centers will be recruited and followed up annually.

Methods: This prospective, non-interventional, multi-center, observational study will collect data from patients with mild (5-40%), moderate (1-5%) and severe (<1%) hemophilia A and B under routine treatment, and monitor disease status and comorbidities in the recruited age cohorts annually over several years (initially 4 years; extended to up to 10 years). The primary research focus is the development of cardiovascular comorbidities and their management in the aging hemophilia patient. Secondary outcomes will include other co-morbidities, social status, hemophilia status and its treatment.

Results: The first interim analysis on disease characteristics and management of comorbidities in different age-cohorts has been performed. Baseline data is available for 595 patients. Of the 595, 81% have hemophilia A (30% mild, 10% moderate, 55% severe) and 14% have hemophilia B. Less than 40% of patients were treated prophylactically compared with 56% receiving on-demand treatment. Six patients reported with an acute coronary syndrome and although 30% had a history of hypertension, 36% of patients had current hypertension (87% of which were treated). Out of the 15% of patients who are HIV positive, approximately 60% are aged 40-49 and most have severe HA. One-third of patients have never been infected with hepatitis C (HCV) or have had natural clearance of HCV; HCV is more common in patients with severe hemophilia, and the prevalence reduces with increasing age. Of the 22% of patients with chronic liver disease, 93% had hepatitis. Of the 37% of patients with a history of hematuria, 28% required hospital admission.

Discussion/Conclusion: The interim analysis highlights the increasing importance of data collection in this population. Recruitment for the study is on target to achieve ~5000 follow-up years from 800 participants. The final analysis should enable the development of guidelines specific to the management of older PWH and comorbidities.

Disclosure of Interest: None declared.

P179 | Real-world bleeding frequency in inhibitor patients on prophylaxis with apcc: data read-out of the "feiba global outcomes study (FEIBA GO)"

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Introduction: The "FEIBA GO" study was designed to capture long-term outcomes on effectiveness, safety, and quality of life in patients with hemophilia and inhibitors treated with FEIBA (activated prothrombin complex concentrates [APCC]) in routine clinical practice. The primary objective is to describe the hemostatic effectiveness of APCC in different settings such as prophylaxis and on demand, including patients on immune-tolerance induction. Secondary objectives include joint functionality outcomes, safety, health-related quality of life (HRQoL), daily activity level, acute and chronic pain associated with hemophilia, and healthcare resources used.

Methods: This is a prospective, non-interventional, observational, multicenter, cohort study in ~100 patients with hemophilia A or B and high-responding inhibitors treated with APCC prior to the decision to enroll in the study. Treatment regimens are at the discretion of the

attending physicians according to routine clinical practice, either in prophylaxis or on demand, including immune-tolerance induction. The observation period per patient is planned to be 4 years.

Results: A data read-out was carried out on May 18, 2017 on 41 patients with severe hemophilia A and inhibitors from 14 hemophilia centers in 10 countries: median age 17 year (range, 3–71). At screening, 28 were on prophylaxis, and for 38 patients for whom first FVIII inhibitor detection was available, median titer was 13.5 BU (range, 1–2410). Of 28 patients on prophylaxis analyzed in the data read-out, 10.5% had an annualized bleeding rate (ABR) of 0, 26.3% an ABR of ≤2, and 36.8% an ABR of ≤3. Median ABR was 4.1 (range, 0–50). For annualized joint bleeding rate (AJBR), 31.6%, 36.9%, and 47.4% had values of 0, ≤2, and ≤3, respectively. Median AJBR was 2.3 (range, 0–17).

Discussion/Conclusion: These preliminary findings demonstrate prevention of joint bleeding with APCC prophylaxis comparable to that in patients without inhibitors on replacement prophylaxis. This study will further augment the knowledge of long-term prophylaxis in the real-world setting by assessing effectiveness, HRQoL, and safety of APCC. It is anticipated that this study will capture important outcome data across and beyond the European Union on hemophilia A and B patients with high-responding inhibitors under a variety of prescribing regimens in routine clinical practice.

Disclosure of Interest: C. Escuriola Ettingshausen Grant/Research support from: Baxalta, Shire, Bayer, Biotest, CSL Behring, Grifols, Octapharma, and Novo Nordisk, Consultant for: Baxalta, Shire, Bayer, Biotest, CSL Behring, Grifols, Octapharma, and Novo Nordisk, Paid Instructor at: Baxalta, Shire, Bayer, Biotest, CSL Behring, Grifols, Octapharma, and Novo Nordisk, J. Windyga Grant/Research support from: Bayer, CSL Behring, Baxalta, Biogen, Novo Nordisk, Octapharma, Pfizer, Roche, and Shire, Paid Instructor at: Bayer, CSL Behring, Baxalta, Biogen, Novo Nordisk, Octapharma, Pfizer, Roche, and Shire, P. Holme Grant/Research support from: Bayer, Baxalta (now part of Shire), Octapharma, Pfizer, Sobi, Paid Instructor at: Bayer, Baxalta (now part of Shire), Biogen Idec, Novo Nordisk, CSL, Grifols, Pfizer, Sobi, C. Hermans Consultant for: Shire and Novo Nordisk, C. Negrier Grant/Research support from: Alnylam, Baxalta/Shire, Bayer, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, SOBI/Biogen, Consultant for: Alnylam, Baxalta/Shire, Bayer, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, SOBI/Biogen, Paid Instructor at: Alnylam, Baxalta/Shire, Bayer, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, SOBI/Biogen, A. Cid Paid Instructor at: Shire and Novo Nordisk, S. Rangarajan Grant/Research support from: Shire, Grifols, Pfizer, Novo Nordisk, Biomarin, LFB, and Alnylam, Paid Instructor at: Roche, A. Rocino Consultant for: Baxalta, Bayer, CSL Behring, Kedrion, Novo Nordisk, Pfizer, Shire, and Sobi, Paid Instructor at: Baxalta, CSL Behring, Novo Nordisk, Pfizer, and Shire, A. Gringeri Employee of: Shire, R. Crea Employee of: Shire.

P180 | Tolerability/safety of feiba reconstituted in regular or 50% reduced volume and faster infusion rates: Rationale and study design in patients with hemophilia A or B with inhibitors

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Introduction: Treatment of hemophilia is complicated by the development of FVIII or FIX neutralizing antibodies in ~30% and ~2–5% of patients with severe hemophilia A (HA) and hemophilia B (HB), respectively, which precludes the efficacious use of replacement therapy. The bypassing agents, FEIBA (activated prothrombin complex concentrates [APCC]) and recombinant FVIIa, are used in these patients. However, the time required for administration of APCC reconstituted at standard volume and at the recommended rate (2 U/kg/min) may burden patients and clinicians. The mean infusion rate during routine clinical practice in the "FEIBA PASS" study was 3.7 U/kg/min (range, 0.9–23.5). Even with a maximum rate being 12 times higher than that recommended in the SmPC of APCC (2 U/kg/min), a manual analysis of safety data did not disclose any adverse events associated with a higher infusion rate.

Methods: Based on these results, and with the goal of reducing the burden of infusion, the "FEIBA STAR" study was designed to evaluate the tolerability and safety of infusing a 50% reduced volume at standard (2 U/kg/min) and increased (4 and 10 U/kg/min) infusion rates compared with regular volume at the standard infusion rate. Adverse events, thromboembolic events, hypersensitivity reactions, infusion-related reactions, vital signs, and laboratory parameters will be monitored. Patient treatment preference and pre- and post-infusion FII levels will also be evaluated.

Results: This is a 2-part, prospective, open-label, multicenter trial in patients with HA or HB with inhibitor titers ≥0.6 BU requiring bypassing agents. In the 2-way cross-over design of Part 1, patients will be randomized 1:1 to receive, at the standard infusion rate (2 U/kg/min), 3 infusions of APCC reconstituted in 50% reduced volume followed by 3 infusions of APCC reconstituted at regular volume, or vice versa. In Part 2, evaluable patients (receiving 4 of 6 doses in Part 1) will sequentially receive 3 infusions of APCC reconstituted in 50% reduced volume at 4 U/kg/min followed by 3 infusions of APCC reconstituted in 50% reduced volume at 10 U/kg/min. All infusions will be given at 48-hour intervals.

Discussion/Conclusion: This study will provide real-world evidence on the tolerability and safety of using higher infusion rates of APCC, which has the potential to reduce the burden of infusion.

Disclosure of Interest: T. Ali Employee of: Shire, R. Crea Employee of: Shire, K. Wanek Employee of: Shire, V. Cano Employee of: Shire.

P181 | Real world use of B-domain–deleted, porcine-sequence factor VIII (RPFVIII) in patients with acquired hemophilia A (AHA): post-marketing safety (PMS) studies in European Union (EU) and in the United States (US)

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Introduction: OBIZUR is a B-domain–deleted, porcine-sequence factor VIII with low cross-reactivity to anti-human–FVIII antibodies for the treatment of AHA. Each PMS study will assess the safety, utilization, and effectiveness of rpFVIII in the treatment of bleeding episodes in clinical practice.

Methods: There are 2 multicenter, prospective, noncontrolled, open-label, single cohort, non-interventional studies being conducted in the EU and US. Patients above 18 years of age with AHA are enrolled once, per routine clinical practice, and treated with rpFVIII for bleeding episodes. Patients' demographics, clinical characteristics, comorbidities and other medical history, characteristics of bleeding episodes prompting treatment with rpFVIII, indication for treatment, rpFVIII treatment details, bleeding control, concomitant medications, inhibitor levels (anti-hFVIII and anti-pFVIII), prior treatments with rpFVIII, and AEs/serious AEs (SAEs) will be collected at baseline, as available in the medical records, and as available from routine follow-up visits for up to 180 days after the last administration of rpFVIII.

Results: The EU study started at the end of 2016, is ongoing in Austria, Germany and Italy and currently 2 subjects have been enrolled but data are limited at the moment. There are 12 active sites in the US with 28 subjects enrolled. In the evaluable patients, 14 bleeding episodes were resolved (11 subjects) and 4 were not resolved (3 patients). The loading dose administered to patients ranged from 50 to 300 U/kg, which in general differs from the initial dose of 200 U/kg recommended in the label. Overall median number of infusions is 13.3 (min-max; 1-85). No thromboembolic events have been reported, but a hypersensitivity reaction (rash) was reported in a patient.

Discussion/Conclusion: The preliminary analysis of the US study further demonstrates the safety and effectiveness profile of rpFVIII in AHA patients. These studies are expected to provide robust real-world data on use of rpFVIII in about 90 patients to obtain better insight on how and in what situations rpFVIII is being used and the optimal dosing regimen in order to personalize therapy in this severe disease.

Disclosure of Interest: R. Crea Employee of: Shire, J.-F. Huang Employee of: Shire.

P182 | Outcomes of the haeminnov ethnographic study: 5 key lessons on the life experience of patients with hemophilia and their relatives

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Introduction: This ethnographic study* focused on patients with hemophilia (PWH), their relatives and their caregivers.

Methods: The aim was to determine which areas of innovation should be focused on in order to improve the management of PWHs and their quality of life.

Results: Five key lessons emerged from the findings:

1. Owning the disease step by step: from informing the parents to caring for the child until he is able to do so himself, this experience-based knowledge is built-up over the entire life of PWHs and their relatives.
2. Dissonance of identity: PWHs are constantly torn between their identity as individuals and their identity as patients, which shapes their relationships with others, with society and with institutions.
3. Challenging quest for identity: a semiological analysis of the codes of masculinity has shown that some PWHs may feel hindered in their ambitions, in that they are unable to fulfill themselves beyond their disease, while others seek to transcend it.
4. Awkward treatment logistics: significance of the burden of logistics for PWHs and their relative with regard to non-automated orders, compulsory travel in addition to the emotional burden associated with treatment, which can give rise to stressful situations.
5. Need for facilitation: insufficient use of innovative and diversified solutions, especially digital, to ease the daily management of hemophilia.

Discussion/Conclusion: The analysis of the data allowed identifying 5 key lessons, which were starting points for innovation and for designing new experiences for patients with hemophilia, their relatives and health professionals.

*Reference to the abstract "HaemInnov ethnographic study to improve the management of patients with hemophilia (PWH): description of the methodology."

Study Sponsor: Roche

Disclosure of Interest: R. d'Oiron Consultant for: Roche, F. GENRE-VOLOT Consultant for: Roche, M. MAKHLOUFI Consultant for: Roche, M. Raymond Consultant for: Roche, T. Sannié: None declared, B. Debaecker: None declared, A. Guyot Employee of: Roche, A. Pruvot Employee of: Roche, K. Ferdows: None declared.

P183 | Modhemos (moderate hemophilia survey), a French multicentric opinion survey on the medical practices in moderate hemophilia: results regarding genetic diagnosis and counseling

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Introduction: There are limited data on medical practices for the management of patients and families with moderate hemophilia.

Methods: To assess opinions and preferences regarding diagnosis, treatment, and follow-up for this group of patients, a questionnaire was sent to physicians of French Haemophilia Treatment Centres. Results regarding genetic diagnosis and counseling are presented here.

Results: A total of 43/82 (52%) practitioners from 26 centers completed the survey.

F8 or *F9* genotype was prescribed by 40/43 (93%) of responders in moderate hemophilia A and 38/43 (88%) in moderate hemophilia B. The main purposes for genotyping were familial inquiry for more than 90% of physicians and the clarification of the severity of hemophilia for half of the responders.

Two additional specific reasons for physicians to prescribe *F8* genotyping were the assessment of the risk for anti-FVIII inhibitor development (33/40, 83% of responders) and the anticipation of the response to desmopressin (10/40, 25%). Despite the moderate severity of hemophilia A, a test to document response to desmopressin was advised by 26/43 (60%) of the physicians, either systematically (9/26, 35%), either according to the basal factor VIII level (12/26, 46%) or the *F8* gene mutation (2/26, 8%).

On a regular basis, the familial inquiry was similar to that of the severe hemophilia for 93% of the physicians. In carriers of moderate hemophilia, a prenatal diagnosis for helping obstetrical management was never (17/38, 45%), rarely (12/38, 31.5%), frequently (5/38, 13%) or always (4/38, 10.5%) proposed by responders. For purposes of a potential termination of pregnancy in case of affected male fetus, prenatal diagnosis was proposed either rarely (16/38, 42%) or never (22/38, 58%).

Discussion/Conclusion: This opinion survey highlights heterogeneous medical practices for the genetic diagnosis and counseling for patients and families with moderate hemophilia in France.

This survey was supported by Octapharma.

Disclosure of Interest: R. D' Oiron Consultant for: Octapharma, B. Guillet Consultant for: Octapharma, M. Trossaert Consultant for: Octapharma, S. Dantin Employee of: Octapharma, F. Genre-Volot Consultant for: Octapharma.

P184 | Combined prothrombin and factor XI deficiency in a Lebanese family

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Introduction: Rare missense mutations in the Prothrombin (*F2*) or Factor XI (*F11*) genes can lead to bleeding disorders with autosomal recessive inheritance. Prothrombin deficiency is typically associated with a severe bleeding tendency, while low plasma Factor XI leads to a milder, more variable bleeding predisposition. Here we report a Lebanese family affected by bleeding and segregating mutations in both *F2* and *F11* genes.

Methods: Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and coagulation factor assays including prothrombin and FXI:C were performed using standard techniques.

Next generation sequencing was made on a gene panel, including the *F2* and *F11* coding regions, using the Custom SureSelectQXT Target Enrichment system (Agilent) on a MiSeq platform (Illumina). Sequence alignments were analyzed with SeqOne software.

Results: The proposita is a 34 year-old woman with a moderate bleeding diathesis and prolonged PT and APTT. Normal coagulation factor activities were measured, except for Prothrombin and FXI:C which were both low at 17% and 24% respectively.

DNA sequencing revealed a homozygous missense mutation in the *F2* gene: c.941G>A or p.Arg314His, and a heterozygous missense mutation in *F11* gene: c.1186C>T or p.Arg396Cys. Large rearrangements of either *F11* or *F2* coding regions were excluded. Low levels of prothrombin and factor XI were measured in several family members.

Discussion/Conclusion: Prothrombin Arg314His was described previously as Prothrombin Padua I (Arg271His, Legacy nomenclature). This mutation is thought to affect the conversion of meizothrombin des-fragment 1 to α-thrombin. Here we measured 17% activity when the Arg314His mutation is present in homozygosity, close to that expected from meizothrombin des fragment 1 alone (~10%). The FXI Arg396Cys mutation has also been reported in a heterozygous patient with FXI:C and FXI:Ag levels of 61% and 83%, respectively. The lower FXI:C measured in heterozygotes from the family described here (24-29%) suggests the presence of a further *F11* mutation, which might have escaped from sequencing, perhaps as a deep intronic variant.

To our knowledge, this is the first description of co-segregation of missense *F2* and *F11* mutations and of homozygous Prothrombin Padua I. It represents a unique opportunity to understand a bleeding predisposition in this combined deficiency, and further genetic characterization is warranted to understand unexpectedly low FXI:C.

Disclosure of Interest: None declared.

P185 | [Correction added on 27 June 2018, after first online publication: the poster abstract P185 has been removed in this version.]

P186 | Measurement of joint status in patients with hemophilia: a systematic review of the measurement properties of hemophilia-specific joint examination scores

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Introduction: Accurate assessment of musculoskeletal status in patients with hemophilia is crucial. Several hemophilia-specific joint examination scores are available, but a complete overview of their measurement properties is lacking. The aim of this systematic review is to provide a comprehensive overview of the measurement properties of hemophilia-specific joint examination scores.

Methods: Medline and Embase were searched for reports on reliability, validity or responsiveness of the World Federation of Haemophilia orthopedic joint score (WFH score), the Colorado Physical Examination score (CPE), the joint examination score by Petrini (PJS) and the Hemophilia Joint Health Score (HJHS). Methodological quality of the studies was assessed by an adapted COSMIN checklist. Evidence on measurement properties was summarized.

Results: The search yielded 2905 unique hits and 98 full text papers were included. The methodological quality of the included studies was limited. Evidence on hypotheses testing was conflicting in most joint scores. Yet, overall moderate evidence for good hypotheses testing properties was found in pediatric populations for the PJS and in adult populations for the HJHS. Limited to moderate evidence exists for responsiveness of the CPE. Internal consistency, reliability, measurement error and structural validity were only reported for the HJHS. Test-retest reliability as well as measurement error were rated as unknown, due to sample sizes below 20 subjects.

Discussion/Conclusion: Only patchy evidence is available on the quality of measurement properties of hemophilia-specific joint scores. Measurement properties of the HJHS were most extensively studied, but significant gaps in evidence for all joint examination scores remain. This review forms the basis for the design of further research specifically aimed at the assessment of measurement properties of joint scores for further improvement of the performance of the scores.

Disclosure of Interest: None declared.

P187 | Long half-life of a non-extended half life product in a patient with severe hemophilia A, requiring double antiaggregation therapy, a case report

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Introduction: Extended half life products enable patients less frequent dosing. Among patients who benefit most from these products are patients requiring higher trough levels. We present a patient with severe hemophilia A requiring double antiaggregation therapy following an acute coronary syndrome. Adequate protection from bleeds was achieved using the patient's already used non-extended half life product, due to its very long half-life.

Methods: One-stage APTT-based assay was used for the measurements of FVIII activity.

Results: Case report: A 76-year old severe hemophilia A patient with diabetes, arterial hypertension, hemophilic arthropathy, renal insufficiency stage 4 and known ischemic heart disease presented with chest pain. Non-ST-elevation myocardial infarction was diagnosed and 2 drug-eluting stents were inserted into left ascending artery. Before the acute coronary syndrome the patient was on prophylaxis with turoctocog alfa 18 IU/kg 3-times per week. Knowing that the patient would need double antiaggregation therapy with acetylsalicylic acid and clopidogrel in addition to coexistent uremic dysfunction of platelets, we aimed (according to recommendations) for a trough level of F VIII above 30%. We planned to switch him to an extended half- life factor VIII. However, by measuring FVIII activity at different time points, we were surprised by the patient's half life of turoctocog alfa of 24 hours. By dosing 54 IU/kg every other day we managed to keep FVIII level above 30% at all times (with peak levels never higher than 150%) and the patient hasn't experienced any bleeds during the next few months.

Discussion/Conclusion: Pharmacokinetics of FVIII widely varies between individuals, reflecting in considerable interindividual variation in FVIII half-life. Currently used extended FVIII half- life products prolong factor VIII half-life by no more than 1.5-1.8 times. With our case we show that also with standard recombinant factors we can achieve high trough levels using alternate day dosing. We confirmed that a trough level of 30% is sufficient to prevent bleeding in patients on dual antiaggregation therapy and a concomitant platelet dysfunction due to severe renal insufficiency.

Disclosure of Interest: None declared.

P188 | Prophylaxis for rare bleeding disorders: FXIII deficiency and congenital afibrinogenemia

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Introduction: FXIII deficiency and afibrinogenemia are both an autosomal recessive rare bleeding disorders, but potentially life-threatening causes of a hemorrhagic diathesis. Bleeding from the umbilical cord 1-19 days after birth can be seen almost 80% of FXIII deficient patients and this early bleeding is also frequently provides an early alert to the congenital afibrinogenemia cases.CNS hemorrhage is common, recurs in approximately 30% of patients, and may be the initial manifestation in patients with severe FXIII deficiency, and it can be seen up to 10-20% patients with afibrinogenemia. To prevent recurrent life threatening bleeding, secondary prophylactic treatment is currently recommended. Every 4-6 weeks FXIII and weekly fibrinogen replacement treatment is usually enough to prevent spontaneous bleeding and increase factor levels above critical levels. Here, we want to evaluate our single center experience with secondary prophylaxis in cases with FXIII deficiency and congenital afibrinogenemia.

Methods: We retrospectively evaluate our database since 2004 and find 12 patient with FXIII deficiency and 13 patient with congenital afibrinogenemia.

Results: Our data revealed 8 male 4 female and a total of 12 patients with Factor XIII deficiency and 7 of them (3F, 4M) were lost to follow up. On the other hand 3 M and 1 girl FXIII deficient patient were receiving monthly prophylaxis without any complication. There were 13 patient (with afibrinogenemia and 5 (3F, 2M) of them were on follow up and 2(F) of them receiving prophylaxis. Three boy (12 years old, 15 years old and 2 years old boy) had a history of previous CNS hemorrhage and 1 girl (27 years old) wants to get pregnant and had a history of recurrent miscarriages. Two patients with congenital afibrinogenemia (3 and 14 years old) had a history of CNS and recurrent mucosal bleeding with an intraosseous hemorrhagic cysts. They are still on prophylaxis without any complication and thrombotic event since 27 months.

Discussion/Conclusion: In conclusion secondary long term prophylaxis for these rare bleeding disorder is safe and effective.

Disclosure of Interest: None declared.

P189 | Quality of life in children and young adults with hemophilia having factor level ≤1%

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Introduction: Aim: To identify the psychological and social characteristics and quality of life (QoL) of hemophiliacs and seeking solutions to improve their QoL by recognizing the problems.

Methods: This is a prospective study of a single center planned to determine the demographic characteristics of the patients with hemophilia A and B (4-25 year-old), who have factor level of ≤1%. Hemophilia-specific, self-reported QoL questionnaires (Haemo-QoL for children and Haemo-A-QoL for >16 years) were administered to the patients and parents. Hepatitis B, hepatitis C and HIV screening was also performed.

Results: Thirty-six patients with hemophilia A, 7 with hemophilia B participated in the study which covered 74.1% of the patients who met study criteria. Twenty-two of the patients were 4-16 year-old, 21 were 17-25 year-old group. Median age of diagnosis was 2.3 (0.2-8.0), 12 (9.5-27), 18 (8-36) and 12 (6-27) months in 4-7-year-old, 8-12 year-old, 13-16 year-old and 17-25 year-old age groups respectively. There were no patients who required crutch, wheel chair or having prosthesis. All the patients older than 14 years completed at least 8 year elementary-education. There were patients in college or graduated from college. Young adults were all employed. 84% of the patients were administering prophylactic factor treatment. In 2 patients (4.6%) hepatitis B carriage was detected. The history of inhibitor development was 5.5% in patients with hemophilia A. The first admission was with cerebral hemorrhage in 7% of the patients and 2.3% was in the newborn period. Radio-synovectomy was performed in 16 patients (37.2%) and arthroscopic-synovectomy was performed in 5 patients (11.6%). There was history of depression in 3 patients (6.9%), in 7 mothers (16.3%) and in 1 father (2.3%). In the Haemo-QoL questionnaire, high scores indicate impaired QoL. In group 1 (4-7 years), compared to older children, family and treatment scores were higher. Mean total Haemo-QoL score of the patients in the 4-16 age group was 34.5.

Discussion/Conclusion: Compared to multi-center European study, 4-7 age group of the present study was negatively impaired. Scores in the family and treatment subdomains were 34.38 ± 24.8 and 24.45 ± 28.1 respectively in the European study vs 58.3 ± 12.9 and 70.8 ± 33.2 in this study. We may suggest that 4-25 year-old hemophiliacs have quite good physical and mental health and they are active in education and business life.

Disclosure of Interest: None declared.

P190 | Intrauterine factor IX replacement and blood transfusion to a mild hemophilia B fetus

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Introduction: Intrauterine fetal blood transfusion is the treatment of choice for severe fetal anemia. The decision on timing of the procedure is based on signs of hydrops fetalis and fetal middle cerebral artery Doppler peak systolic velocity (MCA- PSV). We hereby present a

case of a mild hemophilia B carrier's pregnancy with a fetus with mild hemophilia B, complicated with immune mediated anemia.

Methods: Our patient is a mild hemophilia B carrier with low levels of factor IX (15%). Her past medical history included ulcerative colitis, one induced abortion at an early stage of pregnancy and 1 episode of a corpus luteum bleed which was operated and then re-operated due to excessive bleeding. She was transfused with multiple blood products at this time. When she conceived, CVS sampling found the baby to be hemophiliac.

Results: The woman was followed at high risk pregnancy unit.

At 17 weeks gestation she was found to be Rh immunized. Follow up later showed signs of fetal anemia and hydrops fetalis. Fetal blood transfusion was indicated.

After preparing the woman with IV infusion of Factor IX, the fetal umbilical vein was cannulated under ultrasound guidance. The fetus was infused with 100 units of recombinant factor IX and then with red cells. This procedure was repeated 2 more times. A planned cesarean section was performed at 34 weeks gestation, after a fetal brain MRI and preparation with betamethasone for fetal pulmonary maturation.

An anemic baby with mild hemophilia B was worn. The baby received his 4th FIX infusion prior to circumcision at the age of 8 days and is currently doing well.

Discussion/Conclusion: This is the first case report of in utero blood and FIX transfusion to a hemophiliac fetus. The procedure can be safely done with the collaboration of skilled multidisciplinary team.

Disclosure of Interest: None declared.

P191 | Recombinant FVIII product type and the risk of inhibitor development in previously treated patients with hemophilia A: a systematic review and meta-analysis

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Introduction: Inhibitor development in previously treated patients (PTPs) with severe hemophilia A is a rare but severe complication of FVIII treatment. Evidence on product-related immunogenicity is increasing. A systematic review was conducted assessing the relationship between inhibitor development and recombinant factor FVIII (rFVIII) products in PTPs with severe hemophilia A.

Methods: The following electronic databases were searched; PubMed, Embase, Web of Science, Cochrane database and CINAHL. Longitudinal studies reporting on de novo inhibitor formation in severe or moderately severe (baseline FVIII < 0.02 IU/ml) PTPs with hemophilia A (defined as having > 50 exposure days to FVIII at baseline) were included. Pooled incidence rates of inhibitor development according to product types were calculated using a random intercept Poisson regression model.

Results: 39 cohorts were included. There were 39 inhibitor events over 18 685 person-years of observation. The incidence rate among PTPs was 2.22 per 1000 person-years (95%CI: 1.16-4.26). The pooled incidence rate was 0.99 (CI95: 0.37-2.70) per 1000 p-y for patients treated with Advate, 5.86 (CI95: 0.25-134.92) per 1000 p-y for those treated with Kogenate/Helixate, 1.35 (CI95: 0.66-2.77) per 1000 p-y for Kogenate FS/Helixate NexGen, 12.05 (CI95: 1.53-94.78) per 1000 p-y for Refacto and 4.64 (CI95: 0.82-26.43) per 1000 p-y for Refacto AF.

Discussion/Conclusion: These data suggest that some rFVIII products are associated with increased immunogenicity as compared with Advate in severe and moderately severe PTPs with hemophilia A.

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P192 | Clinical characteristics of hemophilic patients in Ethiopia

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Introduction: Hemophilia is an inherited abnormality of homeostasis due to deficiency of factor VIII and IX which is called hemophilia A and B respectively. In Ethiopia, Generally, there is lack of data related to the prevalence and incidence of hemophilic patients.

Methods: A cross sectional survey was conducted on all patients with hemophilia following up in hematology clinic at Tikur Anbessa hospital from December 1, 2016 up to April 30, 2017 from a total of 57 patients data was collected using structured questionnaires by interview on clinical characteristics. In addition, adequate amount of blood for investigation was drawn Sample blood was tested for HBSAg, HCVAb and HIV Ab using ELISA method.

Results: All patients are male with average age of 17.3 years. Children under the age of 5 years and under the age of 15 years constitute 12.3% and 43.9%, respectively. 36.8% of the patients had bleeding in the joints during initial presentation and 36.8% of all patients were diagnosed incidentally. More than one third (36.8%) of the patients or their caretakers didn't know the type of hemophilia. However, 61.4% were known to be Type A hemophilia and 1.8% was diagnosed to have type B hemophilia. About 60% of the patients didn't know the severity level of the hemophilia. 19.3%), 7.0% and 14.0% of the patients reported that they have severe, moderate and mild form of the disease, respectively.

About 95% of the patients reported joint involvement. Knee was the most commonly affected joint which was reported by 77.2% of the patients. Combination of 2 or 3 types of blood product transfusion

was common modality of treatment. Prevalence of HIV, hepatitis B and Hepatitis C were 0.0%, 3.5% and 5.3%, respectively

Discussion/Conclusion: Diagnosis of hemophilia is delayed and most of the patients had joint complication at the time of diagnosis also there is shortage of factor replacement therapy these indicates that hemophiliacs are not given attention at different level of the responsible body so that awareness and sensitization measures should be implemented to improve the availability of diagnostic facilities and comprehensive hemophilia treatment

Disclosure of Interest: None declared.

P193 | How do carriers of hemophilia with clotting factor deficiency compare with mild male hemophilia patients?

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Introduction: Carriers of hemophilia may exhibit an increased bleeding tendency depending on to their clotting factor. However female hemophilia as a disease entity has so far received less attention than hemophilia in males. In this study we compared clotting factor levels and clinical presentation among carriers with clotting factor deficiency and mild male hemophilia patients.

Methods: Male patients with mild HA or HB and identified hemophilia carriers with a clotting factor deficiency in mild range (FVIII/FIX levels 0.05-0.5 IU/mL) regularly followed at the Cliniques universitaires Saint-Luc, Brussels were enrolled in the study. The following parameters were recorded: basal level of FVIII/FIX, age, trigger for diagnosis, age at diagnosis, bleeding phenotype (evaluation of 12 bleeding symptoms).

Results: 44 carriers (32 HA and 12 HB) and 77 male patients (55HA and 12HB) were identified and compared. Carriers had significantly higher factors levels than male (0.33 IU/ml vs 0.20 IU/ml, $P < 0.0001$). The mean age at diagnosis was lower in male patients compared to carriers (19.18 y (range 1-77) vs 31.63 y (range 2-83) ($P = 0.0052$), respectively). The main trigger for diagnosis in carriers was family screening in relatives of probands (84%) while in male was onset of bleedings complications (42%). As regards the sex-linked hemorrhagic symptoms, menorrhagia was the most frequent (64%) and postpartum hemorrhages was in 34% of pregnancies. When these 2 feminine items were removed from the comparison, the most common bleeding symptoms in both groups of patients were: mucocutaneous bleeding (81% men vs 77% women), bleeding post medical interventions (69% vs 50%) and hematoma (68% vs 34%). Joint bleeds were reported by 4% of carriers and 36% of male patients.

Discussion/Conclusion: Even if carriers are diagnosed later than male patients and the main trigger for the diagnosis was the family screening rather than bleeding symptoms, we found a comparable bleeding phenotype, characterized by mucocutaneous and post injuries bleeding complications. Menstruations and pregnancy represent an intrinsic hemostatic challenge for carriers. Carriers with clotting factor levels in the range of mild hemophilia represent a significant group of patients and should be considered and managed as female hemophilia patients requiring appropriate management and associated with specific challenges that deserve more research.

Disclosure of Interest: None declared.

P194 | Dental procedures under factor cover and/or antifibrinolytics? Experience of a single hemophilia center

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Introduction: A good oral health plays a key role in hemophilia care, as periodontal disease and dental caries predispose to gum bleeding. Dental procedures have a high rate of bleeding and often require administration of prophylactic therapy to prevent hemorrhagic complications

Methods: We evaluated the use of factor concentrates and/or antifibrinolytics in our hospital, to cover dental procedures in hemophilia A and B patients of our Centre, from January 2000 to September 2017. These procedures included dental extraction, alveoloplasty and tarterectomy.

Results: A total of 35 procedures were performed in 8 hemophilia A patients (8 procedures) and 12 patients with hemophilia B (27 procedures). Four patients had severe hemophilia A and 4 moderate. Concerning hemophilia B patients, 3 patients had severe hemophilia, 6 moderate and 3 mild. The mean age was 36.8 years (SD ± 16, 44) in hemophilia A group and 46.3 years (ST ± 11, 85) in hemophilia B group. The hemophilia A group had an average use of 3875 IU FVIII/procedure and in hemophilia B group, 3350 IU FIX/procedure, given in a single dose before the procedure in both groups. Factor administration was associated with tranexamic acid in most patients. None patient had bleeding complications.

Discussion/Conclusion: Despite WFH guidelines advise antifibrinolytic agents and local hemostatic measures to prevent hemorrhagic complications to be enough in most single extractions, our evaluation of this management approach suggests that the use of factor replacement has been a common practice for more complex procedures, in patients not responding to desmopressin, emphasizing that physicians

prefer factor concentrates to cover more complex procedures, than antifibrinolytics alone.

Disclosure of Interest: None declared.

P195 | Reduced ABR and injection frequency in hemophilia A subjects with short endogenous factor half-life on prophylaxis with rFVIIIFc: a-long post hoc analysis

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Introduction: The safety and efficacy of extended half-life recombinant factor VIII Fc (rFVIIIFc; Elocta®) in previously treated adult/adolescent patients with severe hemophilia A were established in the phase 3 trial A-LONG (NCT01181128). Overall, subjects receiving individualized prophylaxis with rFVIIIFc experienced a decrease in annualized bleeding rate (ABR) and injection frequency compared to pre-study prophylaxis with conventional FVIII. The aim of this post hoc analysis was to investigate if subjects with shorter endogenous factor half-life (*t*½) have similar benefits as those with longer *t*½ after transition to rFVIIIFc prophylaxis.

Methods: The analysis included A-LONG subjects on individualized prophylaxis with available information on rFVIIIFc *t*½. Group 1 included subjects with shorter *t*½, defined by the lower quartile, and remaining subjects were in Group 2. Descriptive statistics were used to summarize the data for each group. Analyses were also conducted on the sub-cohort treated prophylactically pre-A-LONG, to allow pre-study comparisons.

Results: Of 117 subjects enrolled in the A-LONG individualized prophylaxis arm, 110 had available information on rFVIIIFc *t*½. Of these, 28 subjects had shorter FVIIIFc *t*½ (cut-off <13.78 hours). Baseline characteristics were similar for Group 1 and 2 (n = 82), except median [IQR] von Willebrand factor (VWF) antigen (Group 1: 85.0 [72.0, 104.5]; Group 2: 134.5 [105.0, 16])) and rFVIIIFc clearance (mL/h/kg), (Group 1: 3.23 [2.72, 3.49]; Group 2: 2.00 [1.72, 2.54]). In the subgroup with sequential PK analyses, Group 1 (n = 5) and 2 (n = 23) had a similar median [IQR] ratio of *t*½ extension with rFVIIIFc compared to conventional rFVIII (Group 1: 1.53 [1.21, 1.55]; Group 2: 1.52 [1.29, 1.74]). Subjects on conventional FVIII prophylaxis pre-study experienced reduced median ABR (Group 1: 7.50 pre-study vs 3.25 on-study; Group 2: 5.00 vs 1.74), and injections per week (Group 1: 3.00 vs 2.33; Group 2: 3.00 vs 1.75) after transition to prophylaxis with rFVIIIFc. The median [IQR] change in weekly factor consumption was 19 IU/kg [-5, 51] for Group 1 and -5 IU/kg [-23, 15] for Group 2.

Discussion/Conclusion: This post-hoc analysis indicates that irrespectively of the patients' endogenous factor *t*½, rFVIIIFc provides patients with similar extension of factor *t*½, and allows for reduction in both ABR and injection frequency.

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P196 | Therapeutic levels of human FVIII in mice and primates and normalization of bleeding in hemophilic mice following gene therapy with bmn 270

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Introduction: Hemophilia A (HA) is a bleeding disorder caused by deficiency of Factor VIII (FVIII) coagulation protein. Severe HA patients have less than 1% of normal FVIII activity. Bleeding episodes in patients are reduced by prophylactic therapy or treated acutely using recombinant or plasma derived FVIII. We have designed a gene therapy vector, BMN 270, using an adeno-associated virus 5 containing a B-domain-deleted human FVIII (hFVIII-SQ) gene with a liver-specific promoter for treatment of severe HA.

Methods: BMN 270 expressing the hFVIII-SQ protein was administered in various mouse models (with or without HA) and monkeys to study the dose response, kinetics, bleeding correction efficacy, hepato-cellular stress, and species translatability of this investigational drug. hFVIII-SQ DNA, RNA and protein in the liver, as well as hFVIII-SQ protein and activity in the plasma, were analyzed for pharmacodynamics; bleeding times and blood loss were measured to assess efficacy; and endoplasmic reticulum (ER) stress markers were analyzed for hepato-cellular stress in mice treated with BMN 270.

Results: BMN 270 injected into hemophilic mice resulted in a dose-dependent expression of hFVIII-SQ protein and a corresponding correction of bleeding phenotype. Similar corrections in bleeding were observed at approximately the same plasma levels of FVIII protein produced either endogenously by BMN 270 or following exogenous administration of recombinant hFVIII-SQ. hFVIII-SQ expression from BMN 270 reached steady-state by 12-weeks post dosing in mice. No evidence of hepato-cellular stress was observed longitudinally. Comparable doses that produced FVIII levels within or above the normal range in mice resulted in FVIII levels that were slightly lower but within the normal range in primates.

Discussion/Conclusion: Our findings demonstrate that a dose-dependent expression of hFVIII-SQ was produced in mice and primates following administration of BMN 270. The FVIII levels that were achieved following a single administration of BMN 270 normalized the bleeding phenotype in hemophilic mice. Even at supraphysiological levels of expression, there was no evidence of hepato-cellular

stress. BMN 270 is currently being investigated as a potential therapy for patients with severe HA.

Disclosure of Interest: S. Bunting Employee of: BioMarin Pharmaceutical Inc, L. Zhang Employee of: BioMarin Pharmaceutical Inc, L. Xie Employee of: BioMarin Pharmaceutical Inc, S. Bullens Employee of: BioMarin Pharmaceutical Inc, R. Mahimkar Employee of: BioMarin Pharmaceutical Inc, S. Fong Employee of: BioMarin Pharmaceutical Inc, K. Sandza Employee of: BioMarin Pharmaceutical Inc, D. Harmon Employee of: BioMarin Pharmaceutical Inc, B. Yates Employee of: BioMarin Pharmaceutical Inc, B. Handyside Employee of: BioMarin Pharmaceutical Inc, C.-R. Sihn Employee of: BioMarin Pharmaceutical Inc, N. Galicia Employee of: BioMarin Pharmaceutical Inc, L. Tsuruda Employee of: BioMarin Pharmaceutical Inc, C. O'Neill Employee of: BioMarin Pharmaceutical Inc, A. Bagri Employee of: BioMarin Pharmaceutical Inc, P. Colosi Employee of: BioMarin Pharmaceutical Inc, S. Long Employee of: BioMarin Pharmaceutical Inc, G. Vehar Employee of: BioMarin Pharmaceutical Inc, B. Carter Employee of: BioMarin Pharmaceutical Inc.

P197 | Management of deliveries in carriers for hemophilia A and low FVIII levels with recombinant FVIIIFc fusion protein

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Introduction: It is well known that activity of coagulation factors rise significantly during pregnancy. Nevertheless some carriers for hemophilia A may have low factor levels and bleeding problems like male patients with mild hemophilia A. These female carriers may also face bleeding complications during delivery and after delivery. We report outcomes of deliveries in 3 carriers of hemophilia A who had previously experienced post partum hemorrhage. The women were treated with Efmoroctocog alfa 2 hours before delivery. We suspected that due to the fc fusion the factor VIII could cross the placenta into fetal blood, and reduce the risk of bleeding in the neonate.

Methods: In 3 female patients we measured FVIII activity before pregnancy, in week 38 of gestation and 4 hours after delivery. 2 hours before delivery 2000 IU Efmoroctocog alfa were given. The cord blood of the neonates (one with severe hemophilia A, 1 wild-type and 2 fraternal twins with mild hemophilia) was taken after birth and a venous blood sample was drawn 1 day after birth to measure FVIII activity. The FVIII activity was analyzed with a chromogenic assay (FVIII chromogenic assay, on the Behring Coagulation System BCS, Siemens healthcare GmbH, Germany.)

Results: In 2 women FVIII decreased during pregnancy by 20% and 28%, respectively. In the other woman we saw an increase of 28%. In the carrier of the severe hemophilia we observed only an increase of 2% after the administration of 2000 IU of FVIII, while in the other 2 with decreased FVIII an increase of 89% and 90% was noted. This was much more effective. In the new born with a mutation for a severe hemophilia A we could not see any effect of the donation of Efmoroctocog alfa. The activity of FVIII was below 1% in the cord blood and the venous blood sample.

We observed no thrombotic complications after the use of Efmoroctocog alfa. The woman delivering the twins by cesarean section experienced a strong post partum bleeding and was successfully treated with tranexamic acid.

Discussion/Conclusion: The infusion of a recombinant FVIII linked to the Fc-region does not affect the FVIII-level of the newborns. It seems, that also these kind of FVIII concentrate does not pass the placenta in a measureable amount.

Disclosure of Interest: None declared.

P198 | Mutation spectrum of F8 gene in Turkish hemophilia A patients: identification of 14 novel mutations

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Introduction: Hemophilia A (HA) is an X-linked inherited bleeding disorder caused by decreased activity of factor VIII (FVIII) due to mutations in the F8 gene. The identification of these mutations is becoming increasingly important in a variety of clinical settings. In this study, we aimed to present the mutation spectrum of F8 gene in Turkish HA patients and to report 14 novel mutations.

Methods: 105 boys and 1 girl with severe HA from 96 unrelated families were molecularly analyzed. First, Intron 22 inversion was screened using IS-PCR method in all patients. In the patients without intron 22 inversion mutation, direct sequencing of the F8 gene was used to

identify the mutations responsible for HA. The variations detected were classified according to ACMG 2015 criteria.

Results: In 49 of 96 HA families (51%), intron 22 inversion was identified. In 39 of the remaining 47 families, 38 different mutations were identified. 22 of all mutations were missense (57.8%), 6 frameshift (15.8%), 5 nonsense (13.1%), 4 splice (10.5%) and 1 inframe deletion (2.6%). Fourteen of these (36.8%) were found to be novel. In 1 patient, exon 14 couldn't be amplified and a complete exon 14 deletion was suspected. For the remaining 7 families found to be negative with the methods used in the study, MLPA and/or intron 1 inversion tests were planned.

Discussion/Conclusion: This study showed the frequency of intron 22 inversion mutation to be similar to those reported in other populations. With the discovery of 14 novel mutations and overall diagnostic rate of 90.6%, this study will make a valuable contribution to the literature.

Disclosure of Interest: None declared.

P199 | Co-administration of a recombinant D'D3 albumin fusion protein extends the half-life of the novel recombinant factor VIII RVIII-singlechain

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Introduction: Von Willebrand factor (VWF) has been the rate limiting step in attempts to extend the half-life of factor VIII (FVIII) used in the treatment of hemophilia A. Recombinant D'D3-FP (rD'D3-FP) is a novel pharmaceutical compound currently in development. rD'D3-FP consists of the D'D3 domain of VWF fused to albumin, designed to be co-administered with the novel recombinant FVIII rVIII-SingleChain. rD'D3-FP aims to compete with endogenous VWF for binding to FVIII at molar excess, and due to its long half-life to enhance the pharmacokinetic (PK) properties of rVIII-SingleChain in the circulation. The objective of these studies was to investigate the PK and pharmacodynamics (PD) of rD'D3-FP, and its impact on the PK of rVIII-SingleChain when co-administered in animals.

Methods: rD'D3-FP was administered intravenously at a dose range of 0.15–30 mg/kg, alone or in combination with rVIII-SingleChain (100–250 IU/kg). The plasma PK of rD'D3-FP, VWF and FVIII (antigen and/or activity levels) was monitored for up to 72–168 hours in FVIII knock-out (ko) mice, rats, rabbits and non-human primates. Thrombin generation and aPTT were also assessed in FVIII ko mice.

Results: The plasma exposure of rD'D3-FP across species was 6 to 60-fold extended when compared with human pdVWF. When compared to rVIII-SingleChain alone, co-administration of rVIII-SingleChain with rD'D3-FP resulted in a dose-dependent terminal half-life extension of 4.3-5.0-fold in non-human primates, 1.4–3.9-fold in rats, 2.1–4.4-fold in rabbits and 1.9–3.3-fold in FVIII ko mice. In line, a prolongation of PD effects, correction of thrombin generation and aPTT, was shown in FVIII ko mice.

Discussion/Conclusion: Co-administration of rVIII-SingleChain with rD'D3-FP improves the PK profile of rVIII-SingleChain in several animal species and prolongs its PD effects.

Disclosure of Interest: S. Pestel Employee of: CSL Behring, E. Raquet Employee of: CSL Behring, M. Mischnik Employee of: CSL Behring, P. Claar Employee of: CSL Behring, A. Andrews Employee of: CSL Ltd., E. Herzog Employee of: CSL Behring, T. Weimer Employee of: CSL Behring.

P200 | Phenotypic and genetic features of type 3 von Willebrand disease: a cohort study of 8 patients

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Introduction: Type 3 von Willebrand disease (VWD) represents the rarest form of VWD in developed countries (<5% of all VWD cases) with severe but variable hemorrhagic symptoms. It is defined here according to the ISTH SSC by VWF Ag, Ricof and VWFCB levels are less than 5 iu/dL and FVIII level is less than 10 iu/dL with inheritance of an autosomal recessive trait.

Methods: The study was designed to evaluate the phenotypic data, including bleeding scores (BS), von Willebrand factor (VWF) laboratory values and genetic features of the cohort of 8 patients with type 3 VWD. A total number of 8 patients were enrolled with the criteria of VWF Ag levels less than 5 iu/dL and of a proven recessive inheritance.

Results: There were 3 male and 5 female among these patients with the mean age of 51.3 (48-56) and 43.4 (21-76) years, respectively. The mean age at diagnosis is 17 months (2 months-3 years). Phenotypic and genotypic features of 8 index cases were summarized in table 1. We found 10 different mutations in 7 patients, 1 patients' genetic test was not assessed. All of the mutations that we identified in VWD3 patients arise independently and are scattered throughout the entire VWF gene. In our cohort of 8 VWD type 3 patients have FVIII levels of 1-7 iu/dL but only 1 patient had primary regular prophylaxis from young ages and 2 patients were on secondary prophylaxis. The most common and specific bleeding symptoms were easy bruising (75%), epistaxis (100%), prolonged bleeding after surgery or minor injury (75%) in all patients and menorrhagia (80%) was common in female patients. The mean HJHS score was found 18.8 (13-28) and 3 of 8 patients were underwent orthopedic procedure.

Discussion/Conclusion: Type 3 VWD is a rare disease, with an estimated incidence of 1 per million. Patients with type 3 VWD present with recurrent spontaneous and traumatic severe bleeding involving both the skin and mucous membrane surfaces and also soft tissues and joints which eventually lead to severe blood induced arthropathy

requiring orthopaedic procedures such as joint replacements. Mucosal bleeds have dominated as the main symptomatology in VWD patients and it is high time to start primary prophylaxis in type 3 VWD patients with FVIII levels <5 iu/dl according to their joint bleeding phenotype. Type 3 VWD is rare and collaborative studies are necessary to gain a better insight.

Disclosure of Interest: None declared.

P201 | Congenital hypofibrinogenemia in a Slovak family with novel missense mutation in FGB gene (TYR368HIS)

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Introduction: Fibrinogen is a complex glycoprotein comprised of 2 sets of 3 polypeptides (Aα, Bβ and γ), encoded by *FGA*, *FGB*, and *FGG*, which are clustered in a 50-kb region on chromosome 4q32. Homozygous or heterozygous mutations in the 3 fibrinogen genes can lead to congenital hypofibrinogenemia. Most causative mutations in *FGB* are missense or nonsense mutations in the highly conserved C-terminal domain of the β-chain. Functional studies of mutant Bβ-chains revealed the importance of individual residues as well as 3-dimensional structures for fibrinogen assembly and secretion.

Methods: To identify the causative mutation in a Slovak family (a 62-year-old patient with congenital hypofibrinogenemia and his 3 children) peripheral blood samples were collected from all 4 subjects. Standard coagulation tests, fibrinogen functional activity with fibrinogen antigen fibrinolysis activity and rotational thromboelastometry were performed. All exons and exon-intron boundaries of the fibrinogen genes were amplified by PCR followed by direct sequencing. The novel mutation was confirmed by reverse sequencing and analyzed with Swiss-PdbViewer, SIFT and PolyPhen-2.

Results: Functional fibrinogen and fibrinogen antigen levels were 0.50 g/l. Low clot amplitude at 10 minutes of EXTEM and FIBTEM and also low maximum clot firmness of both EXTEM and FIBTEM correlated well with low functional level of fibrinogen. We also examined the 3 children of the patient. Functional fibrinogen and fibrinogen antigen levels were in the range 1.00-1.40 g/l. Analysis of *FGB* exon 7 in the patient with congenital hypofibrinogenemia identified a novel homozygous missense mutation c.1102T>C (p.Tyr368His) in the highly conserved C-terminal domain of the β-chain. As expected, all 3 children of the patient were heterozygous for this mutation.

Discussion/Conclusion: While quantitative fibrinogen disorders are mostly caused by null mutations, missense mutations in *FGB* also lead to fibrinogen deficiency. These mutations clustered in the highly conserved β-chain have highlighted the importance of this structure for fibrinogen hexamer assembly and secretion. Interestingly, patients homozygous for β-chain C-terminal missense mutations are mostly afibrinogenemic. Our report of a novel homozygous mutation p.Tyr368His leading to hypofibrinogenemia contributes to the better comprehension of the complexity of fibrinogen disorders.

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P202 | Surgical interventions in patients with hemophilia: Outcome of treatment at a single center in low-resource settings

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Introduction: Despite significant progress in management of patients with hemophilia, surgery in these patients is a challenge especially in low-resource settings. In this study, we evaluated the management of patients with hemophilia undergoing surgical interventions at the Children's Hospital 1 in Ho Chi Minh, Vietnam.

Methods: Clinical features, selection of products for treatment and outcome of patients with hemophilia A or B under 16 years of age undergoing surgical interventions were analyzed in a prospective descriptive study conducted from Jan 2016 to Jun 2017.

Results: Of 30 children (17 severe, 8 moderate and 5 mild; aged 3-9 years) undergoing surgical interventions, 25 (83.3%) were hemophilia A and 5 (16.7%) were hemophilia B. Surgical procedures in these patients were operative debridement of soft tissue injury (30%), tooth extraction/intervention for oral injury (26.7%), cleft lip and cleft palate surgery (10%), craniotomy for evacuation of the acute subdural hematoma (10%), removal of appendicitis (6.7%), surgical operation of hemophilic pseudotumor (6.7%), diagnostic biopsies (6.7%), drainage of hemothorax (3.3%). Only 2 case with severe hemophilia A had inhibitors confirmed before surgery. Non-inhibitor patients and inhibitor patients were treated with a median total dose of 566 IU FVIII/IX/kg and 2307 IU FVIII/kg respectively. The median length of hospitalization was 8 days for non-inhibitor patients and 14 days for inhibitor patients. For hemostatic coverage

of surgical interventions, of the hemophilia A patients, 16 (64%) were treated with either factor VIII concentrate or factor VIII concentrate in combination with cryoprecipitate and 9 (36%) were treated exclusively with cryoprecipitate. Of the hemophilia B patients, 2 (40%) were treated with either factor IX concentrate or with factor IX concentrate in combination with plasma and 3 (60%) were treated exclusively with plasma. Good wound healing rates accounted for 76.7% and no deaths were reported.

Discussion/Conclusion: Factor concentrates are expensive; cryoprecipitate and plasma are still the mainstay of therapy in many developing countries. Surgical interventions in patients with hemophilia need a multidisciplinary approach to decide the best treatment options to ensure safety, minimize risk of bleeding, help patients recover from complications and improve their quality of life.

Disclosure of Interest: None declared.

P203 | Challenges of management of refugee children with congenital factor deficiencies

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Introduction: Refugee patients with congenital factor deficiencies (CFD) are faced with problems such as delayed diagnosis, inability to access specialist care, inadequate treatment and associated joint damage, more often than other patients. Here, we present the demographic data, treatment, outcome and problems in management of refugee children in Istanbul, Turkey.

Methods: Hemophilia and rare factor deficiency patients from 2 centers caring refugee patients between 2011 and 2017 were included.

Results: Of 526 congenital factor deficiency patients, 20 refugee patients were included (18 male, 2 female). Mean age of the patients was 12 ± 10.5 years (Range 1.3-40 years). Nineteen were from Syria and one was from Egypt. Fifteen had history of coagulation disorder in the family. Nine had hemophilia A (HA), 5 had hemophilia B (HB), 2 had factor VII (FVII) deficiency, 2 had afibrinogenemia and 2 had von Willebrand disease (vWD). Two HA, 3 HB, 2 vWD and 2 afibrinogenemia patients were consanguineous. Three hemophilia patients were diagnosed due to excess bleeding at circumcision, 11 hemophilia patients were diagnosed after joint bleeding or muscle hematoma. Six (2 vWFD, 2 FVII, 2 afibrinogenemia) were diagnosed after mucocutaneous bleeding. Mean age of the diagnosis was 2.2 years (Range 2 days-17 years). Only 1 patient from Egypt was treated with specific factor concentrate on demand before migration. Rest of the patients were treated with fresh frozen plasma (FFP) on demand in their country. No information on exposure days was available. In Turkey, all patients were treated with factor concentrate after diagnosis if required. No inhibitor was detected in any of the patients. Six patients had target joints.

Discussion/Conclusion: The number of refugees is increasing worldwide due to conflicts and war which affect many public health issues. Over 2 million refugees are estimated to migrate to Turkey in recent years. Chronic diseases in refugees cause a substantial burden to the health systems of the host countries. Patients are confronted with language barriers, problems in compliance to treatment, shelter and psychosocial problems. Medical records, factor exposure days, previous treatment, inhibitor history or viral infections are unknown to health care staff caring factor deficiency patients. Analysis of care of refugee patients with CFD is needed to inform future responses.

Disclosure of Interest: None declared.

P204 | Mutation analysis of hemophilia A in Russia

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Introduction: Hemophilia A is one of the most widespread X-linked inherited bleeding disorders. This pathology has a wide range of clinical severities associated with type and location of the causative factor VIII gene defects. Nowadays more than 3000 different mutations are described. Two thirds of patients have a familial history of the disease, in one third of cases it appears sporadically. The mutation analysis is extremely important for sporadic hemophilia, as it could exclude the carriage in proband's mother, and for carriers planning IVF (in vitro fertilization). This study is the first large-scale mutation analysis of hemophilia A patients in Russia.

Methods: We analyzed 174 unrelated patients mostly with severe hemophilia A. DNA was extracted from blood using phenol-chloroform method. Our analysis began with the detection of 2 most widespread inversions 22 (LD-PCR method, Liu et al., 1998 modified) and 1 (as described in Bagnall et al., 2002). If both inversions were absent, we sequenced all 26 exons of the factor VIII gene and functionally important fragments including promoter region and polyA signal.

Results: In 99 patients we found inversion 22, in 7 patients – inversion 1 (3 patients with abnormal inversion), in 66 patients – other mutations. In 2 patients we found no gene defects. Two of patients with hemophilia and detected mutations were women. Among 66 patients without inversions we found 58 different mutations: missense mutations (32, prevailing), nonsense (10), frameshift (7), splicing mutations (5), deletions and indel mutations without frameshift (2) and 2 large deletions. In 3 patients we found 2 mutations simultaneously.

Discussion/Conclusion: All mutations detected in this study were distributed uniformly along the FVIII gene. As expected, significant part of missense and nonsense mutations occurred in CpG

hot spot dinucleotides (17 out 42). We found 2 other mutation hot spots located in oligoA tracts of exon 14. Microdeletion c.3637delA (p.Ile1213Phefs*5) was detected in 5 unrelated patients and was associated with 3 different haplotypes of factor VIII gene's alleles, which shows the polyphyletic origin of this mutation. For 2 found large deletions (del Ex6 and del Ex6-12) we determined breakpoints, which were in both cases located within or nearby Alu-repeats. For 5 families with sporadic hemophilia we excluded the carriage in proband's mother. Twenty-eight mutations were previously not described.

Disclosure of Interest: None declared.

P205 | Observatory of patients with von willebrand disease treated with human coagulation FVIII/VWF complex (opale study)

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Introduction: Describe the hemostatic efficacy of human coagulation FVIII/VWF complex (hFVIII/VWF) (Voncento®) in the prophylaxis and treatment of hemorrhage or surgical bleeding in a French cohort of patients with inherited von Willebrand disease (VWD).

Methods: National observatory of patients with inherited VWD who received treatment with hFVIII/VWF in France.

Results: Forty-six patients (61% female) aged 46.2 ± 19.7 years were enrolled between May 2016 and July 2017. VWD types were distributed as follows: type 1 (30.4%), type 3 (17.4%), type 2B (15.2%), type 2M (15.2%), type 2N (10.9%), type 2A (6.5%), type 2B/2N (2.2%) and type 3/2N (2.2%). One patient received prophylactic treatment 2 injections/week for 4 months with good efficacy. Ten patients received preventive prophylaxis regimen within 3 months period (1-3 injections per week) with excellent (20%) or good (60%) efficacy, 1 patient received preventive prophylaxis regimen with hFVIII/VWF for 1 year (1 injection per month) with good efficacy and tolerability. Nine patients received on demand treatment with excellent (11.1%) or good (88.9%) efficacy. Thirty patients received hFVIII/VWF before and after surgery with excellent (60%) or good (40%) efficacy. One delivery was managed with excellent efficacy. Only 3 adverse events (AEs) were reported: 2 cases of headaches and 1 case of deep vein thrombosis (following orthopedic surgery, on D10 after last infusion of hFVIII/VWF and with FVIII:C levels always < 1 IU/mL after surgery).

Discussion/Conclusion: hFVIII/VWF (Voncento®) was effective and well-tolerated in the prevention and treatment of hemorrhage and surgical bleeding in a French cohort of patients with inherited VWD.

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P206 | Hematocrit effect on the accuracy of teg functional fibrinogen assay

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Introduction: Thromboelastography (TEG) functional fibrinogen (FF) assay is one of just a few methods which enable rapid determination of fibrinogen concentration directly in a whole blood (WB) sample. The test takes ≈10 minutes, and its result (referred to as "Fibrinogen Level", or FLEV) is claimed to be an equivalent to plasma fibrinogen concentration. Many authors report a weak correlation (0.4-0.6) between TEG FF and von Clauss assay results. The present study demonstrates that hematocrit (HCT) is the most significant factor affecting the accuracy of TEG FF and suggests a simple correction method.

Methods: Thirty-six normal healthy donors were recruited. For each blood draw, 3 test samples were prepared: "WB" comprising native HCT levels; "low-HCT" sample and "high-HCT" sample. High-HCT samples were obtained by admixing 350 μL PPP to 1 mL WB. Low-HCT samples were obtained by removing 350 μL PPP from the supernatant layer of 1 mL WB samples centrifuged at 3000 *g* × 10 mins, and then re-mixing the contents by gentle rotation. The above 3 samples differ in terms of HCT levels, but contain equivalent amounts of plasma fibrinogen. Thus, TEG-FF results are assumed to be the same for all 3 solutions derived from one original WB sample. The new calculated HCT levels are to be as follows: HCT, HCT/0.65 and HCT/1.35 respectively. Von Clauss assay was conducted in parallel using PPP samples on Delta™ KC4 coagulometer.

Results: HCT effect is statistically significant (paired *t* test $P < 0.01$ between 3 groups). Mean FLEV is 3.2 ± 0.5 g/L in WB group; 3.8 ± 0.6 g/L in low-HCT group; and 2.1 ± 0.5 g/L in high-HCT group. The estimated HCT effect is at least as high as ±17% (for 0.25 < HCT<0.6) and comparable to total level of TEG FF inaccuracy reported previously by some authors.

The linear regression model is built in a form FLEV/FClauss=1.83*(1-HCT), where R2 = 0.87. In general, FLEV tends to overestimate real

fibrinogen levels up to being 5.7% (*t* test $P < 0.05$), and the minimum error of the TEG FF corresponds to HCT level of 0.45.

Discussion/Conclusion: The study demonstrates that varying HCT levels have a significant impact on TEG FF, producing distorted test results. This effect can be corrected using simple linear regression model, provided that HCT level is known. This work was supported by Enterprise Ireland (Grant CF-2016-0401) and the European Regional Development Fund (ERDF).

Disclosure of Interest: None declared.

P207 | MRI can accurately detect low concentrates of blood in synovial fluid: preliminary in vitro results

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Introduction: Joint bleeding is the hallmark of hemophilia, but reliable non-invasive methods to differentiate bleeding from non-bleeding episodes are lacking. Especially minimal and subclinical bleedings are difficult to establish, but will affect joint health. Standard Magnetic Resonance Imaging (MRI) settings are unable to detect limited amounts of intra-articular blood. We hypothesized that dedicated MRI settings may detect low concentrates of blood in synovial fluid. The aim of this study is to evaluate a dedicated MRI protocol to detect low concentrates of blood in synovial fluid.

Methods: Samples with different ratios of synovial fluid from patients with rheumatoid arthritis and blood from a healthy volunteer (collected in li-heparin tubes) were scanned within 12 hours on an 1.5 Tesla MRI using settings aimed at measuring the long T2-relaxation times of fluids. Samples with 0, 5, 10, 25, 50, 75 and 100% blood were used. Paramagnetic properties of samples were quantified using T2-measurements with 95% confidence intervals (CI).

Results: T2-relaxation times varied tenfold from 706 ms (CI 696-715) for 100% synovial fluid to 88 ms (CI 80-95) for 100% blood. This wide variation in MRI T2-relaxation allow differentiation of synovial fluid with different ratios of blood. Samples with limited amounts (10-25%) of blood could be identified and differentiated from samples of 100% synovial fluid and samples with >25% blood. Statistically different MRI measurements were found between the sample containing 100% synovial fluid and the sample containing 10% blood.

Discussion/Conclusion: We showed that MRI can detect low concentrates of fresh blood in synovial fluid in vitro. Further clinical studies are needed before MRI can be used as a validated and non-invasive reference standard for (minimal/early) joint bleeding.

Disclosure of Interest: None declared.

P208 | Circumcision in children with severe hemophilia A: Is single pre-operative dose of factor VIII replacement effective?

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Introduction: Most surgical and invasive procedures can be performed safely in patients with hemophilia with factor replacement therapy. Current guidelines recommend to keep factor VIII level between 50–60% for 2–4 days for circumcision [(1)]. This was mainly based on expert opinions and surveys. Over the past 5 years we used mainly a single pre-operative dose of factor VIII 25 IU/kg with adequate local hemostasis.

Methods: The current study was done to report the prophylactic method used for circumcision in Oman and to study whether 1 single preoperative dose of factor VIII is effective in establishing hemostasis. A Retrospective study that includes 2 main referral hospitals in Oman during the period January 2010- December 2016. Electronic patient records were reviewed and missing data were collected through phone interviews. Data included age at circumcision, method of circumcision, factor replacement doses, local hemostatic use, post circumcision bleeding and readmission.

Results: We identified 63 patients who undergone circumcision during the identified period. Data were complete for 40 patients. The age at circumcision ranged between 3 weeks-11 years (Mean 37.2 ± 33.5 months), the method used was plastibell method in all patients younger than 3 month of age (4 patients; 10%) and surgical method in older age group (90%). All older patients had cautery at the surgical site to prevent bleeding. Sixty percent of patients received a single dose of factor VIII 25 IU and the remaining 40% received post-operative factor doses every 8 hours for 24-48 hours (These patients were done earlier before we adopt the single pre-op dose prophylaxis. 1 patient developed post circumcision bleeding from those who received pre and post factor VIII doses post circumcision bleeding and needed readmission after 96 hours.

Discussion/Conclusion: Single dose of factor VIII may be effective in establishing hemostasis for circumcision and can result in a major reduction in the cost. Since circumcision site is visible, instructions to report back to the hospital in case of postoperative bleeding should be given to patients' guardians.

Reference: C. Hermans et al. Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations. Haemophilia (2009), 15, 639–658.

Disclosure of Interest: None declared.

P209 | Preferences between surgical or medical treatment in hemophilia patients with spontaneous epidural hematoma may vary

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Introduction: Spinal epidural hematoma (SEH) is a rare and potentially disabling process, especially for hemophiliacs. Treatment options should be carefully considered for such rare and difficult cases. We report 3 cases of SEH in hemophiliacs who had different treatment and various prognosis.

Methods: We examined the clinical courses and prognoses of 3 hemophilia A patients with SEH. They had been treated either conservatively or surgically.

Results: Of these 3 severe hemophilia A patients, one particular patient had antibodies to Factor VIII. The SEHs, all of which developed spontaneously, were identified by magnetic resonance imaging (MRI). An 8-month-old boy, who was presented with non-traumatic acute-onset irritability, was found to have SEH at the level of C1-S1 on MRI and then diagnosed as having hemophilia. The other 2 patients had posterior neck pain as their initial symptom, while their MRI scans identified an SEH extending from C1 to T2 and from C3 to C5, respectively. The time intervals from the onset of the initial symptom to the time of first clotting factor administration for these 3 patients were 17 hours, 27 hours, and 36 hours, respectively. Clotting factor concentrates to reach 100% factor level or adequate doses of bypassing agents were administered. Two patients, who had been managed conservatively, were fully recovered within 2 months. However, 1 patient, who presented with progressive neurologic abnormalities at the time of diagnosis, had to undergo surgery and developed non-spontaneous breathing and quadriplegia postoperatively. One pediatric patient developed transient inhibitors to Factor VIII after treatment.

Discussion/Conclusion: Early diagnosis and immediate aggressive replacement therapy are crucial in the management of SEH. Owing to high morbidity and mortality, it is imperative for clinicians to decide on optimal management for such SEH cases and in accordance with a patient's condition. The best strategies for good prognosis are still being debated.

Disclosure of Interest: None declared.

P210 | Gastrointestinal bleeding in congenital factor deficiencies

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Introduction: Gastrointestinal Bleeding in patients with congenital factor deficiencies (CFD) is a life–threatening condition. Despite its clinical importance, little has been published on the frequency and complication. We evaluated CFD patients with gastrointestinal bleeding at our centre.

Methods: In a retrospective review of 432 patients with CFD followed at our centre from 1990 to 2017. We identified 22 episodes of gastrointestinal bleeding in 18 patients. Information of patients with gastrointestinal bleeding were retrieved from patient files and from the records contained in the electronic information processing environment created after 2005.

Results: Thirteen of the patients were males and 5 were female. The age range was between 3-27 years. The levels of Factor:C were as follows: 10 (55.6%) patients; <1%, 2 (11.1%) patients; 1-5% and 6 (33.3%) patients; >5%. There were eleven VII deficiency, 2 factor X, 1 von Willebrand Disease, 1 hemophilia A, 1 hemophilia B, 1 factor XIII and 1 afibrinogenemia. All patients had 1 bleeding episode, except 4 patients with 3 FVII and 1 von Willebrand Disease. Seven of cases had endoscopic examination and 6 had gastric biopsy. Helicobacter pylori was obtained in 6 biopsy material. The treatment consisted of appropriate factor replacement, fresh frozen plasma and appropriate antibiotics. The mean duration of therapy with clotting factor concentrate was 4 days. The mean duration of hospitalization was 4 days. Prophylaxy was applied 5 patients (3 patients with FVII deficiency and 2 patients with FX deficiency). The prophylaxis periods of our patients range between 1-8 months. Six patients continue routine prophylaxis regimen. Development of inhibitors and thrombotic incidents were not observed during bleedings and prophylaxy treatments.

Discussion/Conclusion: Gastrointestinal bleeding still may be life-threatening. Early diagnosis and effective factor replacement therapy is important to decrease the complication. Prophylaxis is justified to prevent recurrent bleed.

Disclosure of Interest: None declared.

P211 | Is there still a concern for hepatitis C in patients with hemophilia?

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Introduction: Transfusion Transmitted Infection (TTI) continue to be a problem in many parts of world and multitransfused patients of beta thalassemia major and hemophilia are at a particularly increased risk of TTI. This study was conducted to assess prevalence of Hepatitis C virus (HCV), Hepatitis B virus (HBV) and Human Immunodeficiency virus (HIV) among hemophilia patients in Gilan province.

Methods: In this cross-sectional study, all hemophilia patient records were evaluated in Gilan, North of Iran. Sources of data were health centers of province and territories, blood transfusion organization, general hospitals and private clinics. Demographic and results of serologic tests such as HCV-Ab, HIV-Ab، HBs-Ag were entered in check

list .At first Enzyme-linked Immunosorbent Assay (ELISA) were performed in all cases and recombinant Immunoblot Assay and finally PCR were done for patients with positive results of ELISA. Data analyzed with SPSS ver 18.

Results: One-hundred eighty nine hemophilic patients underwent the study with mean age 26.7 ± 16.6 years, from 2-83 years, 163 patients (86.2%) were male. The most popular blood groups were A+ and O + (32.8% &).Among these patients only 6 patients (3.2%) were positive for HCV Ab. None of them was positive for HIV Ab or HBs-Ag tests. All HCV positive patients were above 20 years old (from 23-57 years).

Discussion/Conclusion: these findings show that the strategies for prevention of Transfusion Transmitted Infection and safety of blood products in this respect have indeed been successful.

Disclosure of Interest: None declared.

P212 | Sirolimus experience in the treatment of acquired hemophilia A with inhibitor: case report

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Introduction: Acquired hemophilia A is a bleeding disorder which results from inhibition of factor VIII, which occurs due to autoantibodies. There are numerous possible underlying causes, still, 50% of acquired hemophilia cases remain idiopathic. Treatment may involve management of bleeding, underlying causes and immunosuppression.

Methods: In this study we report an idiopathic acquired hemophilia case presented with recurrent bleeding who successfully treated with sirolimus.

Results: A 16 month-old girl presented with failure to thrive, recurrent and severe skin and mucosal bleeding She had hypotonia, microphthalmia, depressed nasal bridge and delayed development. She had only prolonged aPTT, low factor VIII (0.5%), and inhibitor of factor VIII positivity. vWF antigen, vWF activity, lupus anticoagulant, C3, C4, ANA, anti-dsDNA, were normal. She was started on 1 mg/kg.day of prednisolone and 1 month later, she tested negative for factor VIII inhibitor. On the seventh day after steroids were discontinued, she has ecchymosis and prolonged aPTT. Inhibitors of factor VIII at 25.6 BU were positive again. Subsequently, methylprednisolon, cyclophosphamide, rituximab, cyclosporine treatments were given to the patient due to recurrent bleeding, low Factor VIII level and inhibitor positivity. Every time the inhibitor became positive again and bleeding occurred. The latest post-cyclosporine gingival hypertrophy has developed and immunosuppressive treatment was discontinued but the inhibitor was positive again after 3 months. Mycophenolate mofetil started but no response was obtained. Bypass medication was given to the patient who was unresponsive and had frequent bleeding episodes, but bleeding was difficult to control. Finally, sirolimus was started for inhibitor eradication to the patient, inhibitor negative at 1 month of treatment. Patients who have not experienced bleeding episodes for 2 months are still negative for inhibitor and sirolimus is continuing.

Discussion/Conclusion: Acquired hemophilia is an important cause of potentially serious bleeding and has numerous possible underlying etiologies. Sometimes an underlying cause may not be found. Despite the steroids, rituximab, cyclophosphamide and mycophenolate mofetil treatments used as immunosuppressive therapy in patients with high inhibitor levels, sirolimus may be a good option in patients who have inhibitor positivity and whose bleeding cannot be controlled.

Disclosure of Interest: None declared.

P213 | Unconvincing reduction of inhibitor titers during first Latvian ITI experience with high-dosage coagulation factor regime

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Introduction: Immune tolerance induction (ITI) protocols are standard-of-care and remain to be very costly for health system, still long-lasting for patients and families.

Methods: Case report

Results: A severe form of hemophilia A (factor VIII <1%) was diagnosed in 10-month-old male with history of bruising. The boy's mother had excessive menstrual bleeding, and diminished level of FVIII (36%). Treatment with first-generation recombinant coagulation factor (*Recombinate*) was initiated at 12 months of age due to ankle hemarthrosis. At the age of 1 year 7 months prophylactic treatment with 25 IU/kg was started once weekly per peripheral venous access. During first 2 months of early toleration phase more prominent subcutaneous bleedings were noticed. In May 2016 after 16 exposure days high-titer non-transient inhibitors (20 BE) were diagnosed. Attempt to correct the acute coagulopathy with high-dose (100 IU/kg) coagulation factor failed. Treatment with FEIBA was initiated at acute bleeding episodes and for coverage at Port-a-Cath implantation. Parental education for use of Port-a-Cath were performed 6 months later preparing for realization of ITI, when titer of inhibitors had declined noticeably. In December 2016 after parental consent ITI with typical high-dosage protocol using twice-daily infusion of *Recombinate* was started. During ITI, inhibitor titer levels were monitored closely. Results demonstrated anamnestic response shortly after initiation of ITI, with a maximum documented inhibitor level of 41 BE/ml. During ITI the patient had 2 episodes of bleeding (1 spontaneous, 1 posttraumatic) and 1 surgery (removal and replacement of new Port-a-Cath

due to decubitus over portal in August 2017. During whole ITI period negative titers of inhibitors were diagnosed in 2, 6 and 10 months after treatment initiation, but were raising again very quickly in low-titer range. Due to very slow dynamics and persistent inhibitor titers, treatment was switched to pdFVIII end of October 2017, 11 months after starting ITI. During whole period of ITI the parent's treatment compliance was excellent, very few hemorrhagic episodes were observed.

Discussion/Conclusion: Our first ITI experience was challenging for patient, family, medical staff and healthcare system, especially considering the low national output for healthcare in Latvia.

Disclosure of Interest: None declared.