Objective: Post-traumatic stress disorder (PTSD) is a serious mental health condition that affects people who have survived a terrifying physical or emotional event. There are three main clusters of symptoms: those related to re-experiencing the event; those related to avoidance and arousal; and the distress and impairment caused by the first two symptom clusters. Most people consider PTSD a complication suffered by military war veterans. However, this disorder can impact anyone who has gone through a traumatic experience - including children. In fact, more than 3 million children in the U.S. are believed to have PTSD. Children with severe hemophilia that require frequent infusions of clotting factor may become “shell shocked” from repeated trauma, similar to that of a soldier. These children can face a lifetime of stress and anxiety due to this trauma. Trauma Focused Cognitive Behavioral Therapy and family support are two treatments that are available to help these children (and their families cope and accept their condition and treatment).

Methods: Case study

- An 8 year old boy with a history of severe hemophilia A with high inhibitor titers and an allergy to Factor VIII. Child also has right knee and right ankle target joint/hemarthrosis.
- Child is fearful of needles. Obtaining IV access at the hospital requires conscious sedation and multiple people holding him down. He has become very anxious and shows avoidant behaviors when he is asked to talk about his infusions.
- He is frequently in and out of the hospital. Keeping current with class work has been a challenge and a tutor was needed to assist.
- Trauma Focused Cognitive Behavioral Therapy with a pediatric psychologist was provided along with pool therapy and family support.

Summary:

- The family and pediatric psychologist observed a transformation in the patient’s self-esteem and sense of control.
- The patient has made great strides building up his self-esteem and confidence so he has some control over his infusions.
- Following therapy the child continues to make progress with infusions.
- Interested in attending hemophilia camp to learn self-infusion.

Conclusions: Trauma Focused Cognitive Behavioral Therapy and family support are helping to build the patient’s confidence, self-esteem, and having a sense of control over his infusions. The patient has been helped to alleviate his fears and increase a sense of empowerment.
Prevalence of Depression in US Patients with Hemophilia A Compared with a General Medical Population: A Retrospective Database Analysis

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Objective: Prevalence of clinical depression in persons with hemophilia (PWH) has been reported to be from 0%–50%. Most papers studied fairly small numbers of PWH; many had no controls and used instruments not validated for depression. One recent paper, using the Patient Health Questionnaire-9, a validated instrument for depression, reported a prevalence of 37% in 41 adult PWH. Our objective was to determine the prevalence of depression in PWH in the United States.

Methods: Using the MarketScan® Commercial and Medical Research databases, we compared depression prevalence in 2506 PWH and 7518 controls. Male patients with hemophilia A were identified using an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code (ICD-9-CM 286.0) and were matched (based on age, eligibility months in the study, region, and health plan type) in a 1:3 ratio with controls (no hemophilia diagnosis). Evidence of depression was determined using ICD-9-CM 296.20–296.26, 296.30–296.36, and 311 codes. Chi-square tests were used to compare frequencies.

Summary: PWH had a statistically significant increase in depression prevalence overall and in age groups 50–59 years and 60–69 years and a numerical increase in all other age groups except 18–29 years (Table). The delta between PWH and controls steadily increased between ages 30 and 69 years.

Table. Patients with Major Depressive Disorder

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Controls, n (%)</th>
<th>PWH, n (%)</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–17</td>
<td>38 (1.68)</td>
<td>16 (2.13)</td>
<td>0.4279</td>
</tr>
<tr>
<td>18–29</td>
<td>117 (7.36)</td>
<td>32 (6.04)</td>
<td>0.303</td>
</tr>
<tr>
<td>30–39</td>
<td>62 (8.23)</td>
<td>25 (9.96)</td>
<td>0.3998</td>
</tr>
<tr>
<td>40–49</td>
<td>90 (11.76)</td>
<td>37 (14.51)</td>
<td>0.2502</td>
</tr>
<tr>
<td>50–59</td>
<td>90 (9.77)</td>
<td>44 (14.33)</td>
<td>0.0265</td>
</tr>
<tr>
<td>60–69</td>
<td>78 (10.36)</td>
<td>40 (15.94)</td>
<td>0.0175</td>
</tr>
<tr>
<td>≥70</td>
<td>52 (10.83)</td>
<td>22 (13.75)</td>
<td>0.3177</td>
</tr>
<tr>
<td>Total</td>
<td>527 (7.01)</td>
<td>216 (8.62)</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

Conclusions: Commercial claims databases have limitations, including coding errors and inability to verify accuracy of diagnoses. However, in PWH versus a 3:1 control group in a US commercially insured sample that may not be representative of the overall population, depression prevalence was greater in PWH, reaching a peak of 16% in those aged 60–69 years. Awareness of this comorbidity is important as the hemophilia population ages in an era of declining healthcare-delivery resources.
Don't Push Your Luck! Educational Board (not Bored) Game for Families Living with Hemophilia

Andrea Kennedy, Brenda Riske, Lisa Semple, Kerri Alderson, Vanessa Bouskill, Janice Karasevich, Sheri van Gunst

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Objective: This poster outlines evaluation of an educational family board game, “Don't Push Your Luck!” designed to inspire discussion about hemophilia, and help school-age children learn about decision-making. Since children with hemophilia have a life-long disorder, this game provides a resource to help them learn how to make decisions for transitions to self-care.

Methods: This game was developed based on recommendations by school-age children from previous research on partnership roles in hemophilia care. In the game, each player takes on the role of a child with hemophilia, exploring choices and consequences in everyday experiences. A multi-site, mixed method research project was coordinated by Mount Royal University, with sub-sites in Canada and United States. In phase I, the board game prototype and questionnaires from boys (n=3) and parents (n=5) living with hemophilia and boys (n=3) and parents (n=5) living with cystic fibrosis was refined. In phase II, we evaluated the revised version of the board game with children who were living with hemophilia and their household family members over age 8 years. The primary objective was to explore how playing an educational board game affected school age children's engagement in decision-making for self-care. Children and parent perspectives were compared in the way the board game affects engagement in decision-making for children's hemophilia self-care. Recommendations for future board game development were solicited. Purposive sampling was used to recruit household family members (n=50), including at least one parent/guardian (n= 22) and children aged 8-12 years living with hemophilia (n= 16). Two researchers visited homes to play the game, interview families, observe their responses to the game, and provide pre and post-game questionnaires on decision-making and Haemo-Quol Index© quality of life, and post-game enjoyment. Audio recordings and field notes were documented to record participant observation. Questionnaire items on decision making, quality of life observations, and game enjoyment were analyzed using descriptive statistics. Qualitative analysis of written, verbal and observed behaviours was summarized in thematic categories provided further evaluation of the board game intervention.

Summary: Comparisons between children and adults were analyzed. Findings indicate that this game is an enjoyable and effective resource for school-age families to engage in discussions relevant to hemophilia self-care skills and decision-making.

Conclusion: This board game is an interactive, developmentally appropriate resource for families with school-age children who are living with hemophilia to facilitate engagement and conversation about everyday life experiences in preparation for their transition to adult self-care.

This project was generously funded by an unrestricted grant from Bayer Healthcare.
Rates of falls, injurious falls, and activity restriction due to fear of falling in adults with hemophilia

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Objective: To describe the rates of falls, injurious falls, and activity restriction due to fear of falling in a population of patients with hemophilia.

Methods: As part of a study on identifying fall risk in patients with hemophilia, subjects completed a self-administered questionnaire inquiring about fall history over the previous 12 months.

Summary: 75 patients with hemophilia between the ages of 18 and 85 completed the questionnaire. 59 (79%) of these patients had hemophilia A, and 16 (21%) had hemophilia B. 34 (45%) had severe disease, 17 (23%) had moderate disease, and 24 (32%) had mild disease.

25 (33%) of the subjects reported a fall within the last 12 months. The average and median ages of the subjects who fell were 46 and 45 respectively, while the average and median ages of the non-fallers were 41 and 39.5 respectively. Of the 25 patients who fell, 11 (44% of fallers or 15% of total sample) reported an injury caused by the fall. 12 patients (16%) reported restricting activity due to fear of falling. The majority of subjects who reported a fall or injurious fall had mild disease (55 %.), with an average age of 45 and median age of 46.5. The majority of subjects who restricted activity due to fear of falling had mild disease (50%), with most subjects who restricted activity reporting a fall in the previous 12 months (58%).

Conclusions: Fall rates in hemophilia patients in this study (33%) are similar to or higher than the fall rates found in community dwelling adults 65 years and older (22-33%), although the subjects in this study were younger. Injurious fall rates found in the study (15%) are higher than non-fatal injurious fall rates described in adults age 65 and up (5-11.5%), and similar to those found in adults with arthritis age 45 and up (16.2%). Subjects in this study with mild disease were more likely to fall and to be injured. Activity restriction due to fear of falling (16%) was lower than that found in older adults in other populations (20-60%).

This study suggests that fall risk screening may be an important component of the comprehensive evaluation of patients with hemophilia, including those with mild disease. These results should be confirmed in a larger population of patients and across different treatment centres. Further research into optimal fall risk screening, in-depth assessment and treatment in this population is warranted.
Hemophilia of Georgia's Preventive Dental Program

Gail Day, Deniece Chevannes

Hemophilia of Georgia, Atlanta, GA, United States Minor Outlying Islands

Objective:

1. Create a preventive program to address the dental needs of people living with a bleeding disorder that have no dental insurance coverage or substandard dental insurance coverage.
2. Provide an opportunity for people living with a bleeding disorder access to dental cleanings and treatment of other dental concerns.
3. Increase access to dental care in rural communities of the state and provide ongoing preventive dental care services to people living with a bleeding disorder.

Method:

Studies show that oral hygiene has a direct correlation to optimal physical health. According to objectives developed by Healthy People 2020, oral health should be a main focus with targets addressing children and adult dental care.

Hemophilia of Georgia (HoG) recognizes the importance of good dental care and researched ways to address this need in the bleeding disorder community. HoG decided to develop a preventive dental program for Georgia's bleeding disorder population. The HoG preventive dental program offers two dental cleanings per year to any client with no dental insurance or substandard dental coverage. Additionally, HoG nurses annually provide at minimum 15 medical in-services to dental providers educating them about hemophilia and other bleeding disorders. The preventive dental program is promoted at numerous HoG events and program information is mailed annually to HoG clients. The two dental cleanings and other dental treatments received by clients are tracked to determine utilization of the program and to determine if clients in rural communities have access to preventive dental services.

Summary:

The preventive dental program was started in 2011 and to date 95 clients have applied and been approved for the program. Of the 95 clients on the preventive dental program ten (10) reported that they have not seen a dentist for a cleaning in over ten years. Forty-nine (49) clients reported that they have had a cleaning in the past three to five years; six (6) clients reported having a cleaning in the past six months to a year. Thirty (30) clients were unsure when they last had a cleaning.

Of the 95 clients on the preventive dental program fifty-one (51) have gone for their first cleaning. Twenty-seven (27) clients have completed their second cleaning. Seventeen (17) clients needed additional dental treatment such as; root canals, extractions, and fillings.

The 95 clients on the preventive dental program twelve (12) clients were under the age of eighteen, twenty (20) clients were between the ages of eighteen and twenty-five, twenty-three (23) clients were between the ages of twenty-six and thirty-five, nineteen (19) clients were between the ages thirty-six and forty-five, and twenty-one (21) clients were between the ages of forty-six and seventy-seven.

Of the 95 clients on the preventive dental program approximately 36 clients reside in the metro-Atlanta area and 59 clients are outside metro Atlanta in rural Georgia.

HoG outreach nurses have provided 47 medical in-services to dental providers educating them about bleeding disorders.
The average cost of a cleaning is $156.00 and all 95 clients met the Federal Poverty Guidelines of 250% or below.

**Conclusion:**

Developing a specific program to address dental needs has proven effective in capturing clients all over the state, in particularity those in rural areas that may have difficulty accessing care. Providing outreach education to dental providers regarding the care of bleeding disorder clients has been shown to be important and beneficial to the bleeding disorder community. Based on the results, HoG’s preventive dental program will continue to address the dental needs of Georgia’s bleeding disorder population by providing dental care to all who are in need.
Home infusion/specialty pharmacy inhibitor management program leads to patient/provider collaboration to facilitate enhanced program and patient outcomes.

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Walgreens Infusion Services, Deerfield IL, USA

Objective: To evaluate the impact of interventions in a focused home infusion/specialty pharmacy based inhibitor management program on patient outcomes including, adherence, retention, prescriber communication.

Methods: From our bleeding disorders patients’ databases between April 1, 2013 and March 31, 2014 (12 month period), prescriptions and assessment records were analyzed for patients with hemophilia A or B with inhibitors and those with acquired inhibitors. 49 unique patient records were reviewed, care managers were interviewed, and interventions were highlighted.

Results: 44 patients had Hemophilia A with an inhibitor, 2 had an inhibitor to Hemophilia B and 3 had acquired hemophilia. Hemophilia A patients had a diagnosis of severe hemophilia A (39), Moderate (2), Mild (2). 1 Hemophilia B patient was severe and the other moderate. Total number of active inhibitor patients on service (with a detectable Bethesda Unit titre) increased from 22 to 30 over this same period. 8 patients left service during the year due to insurance changes (4), and transfer to HTC’s 340B program (4). At the beginning of the study period, a multidisciplinary inhibitor management team (HTC experienced RN’s, RPh, SW, PT, Patient Advocate, and Hispanic Coordinator) was assembled and goals and processes for patient review and intervention were established. Monthly and ad hoc patient review meetings were implemented. Multiple barriers to adherence were encountered including immigration issues, language barriers, transportation issues, potential for caregiver burnout, storage and security of product concerns, relocations, product allergies, and needle phobia. Team worked collaboratively with HTC and other prescribers to intervene successfully in these issues. Interventions included long term twice daily nursing, securing an immigration attorney, hemophilia experienced translators, social worker, and physical therapist interventions, links to foundations for financial support, product bridge for insurance lapses, lab monitoring and reporting to HTC for remote patients, obtaining equipment (locking refrigerator) and protective supplies/ cooling compression cuffs. 30 patients received immune tolerance therapy during the study period. Of these, 25 were treated by an HTC and 5 were not. 10 patients on ITI achieved an “undetectable” inhibitor status during the study period. 8 were followed by an HTC and 2 were not. No patients were lost to therapy/management. All patients maintained positive interactions with prescribers and follow up visits.

Conclusion: Inhibitor patients can be very challenging to manage. A focused, multidisciplinary inhibitor management team can extend the comprehensive model to the home, promote patient/prescriber/treatment team collaboration, and target interventions that enhance outcomes.
Kids A-LONG: Safety, Efficacy, and Pharmacokinetics of Long-Acting Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Previously Treated Children with Hemophilia A.

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Objective: Kids A-LONG was a global, multi-center, open-label phase 3 study that evaluated the safety, efficacy, and pharmacokinetics (PK) of rFVIIIFc in previously treated patients aged <12 years with severe hemophilia A (<1 IU/dL FVIII activity).

Methods: All participants had ≥50 prior exposure days (EDs) to FVIII, and no history of FVIII inhibitors. Participants were to be treated with twice-weekly rFVIIIFc prophylactic infusions (Day 1, 25 IU/kg; Day 4, 50 IU/kg), with adjustments to dose (≤80 IU/kg) and dosing interval (≥ every 2 days) as needed by the investigator. A subset of participants (<6 years of age, n=25; 6 to <12 years of age, n=35) underwent sequential PK evaluations with FVIII (50 IU/kg), followed by rFVIIIFc (50 IU/kg). The primary endpoint was development of inhibitors (neutralizing antibodies). Secondary endpoints included PK, annualized bleeding rate (ABR) and number of infusions required to control a bleed.

Summary: The study enrolled 71 participants from 23 centers (<6 years, n=36; 6 to <12 years, n=35); 94.4% of participants completed the study. Prestudy, 89% of participants received FVIII prophylaxis, the majority (74.6%) of whom required ≥3 infusions per week. The median time on study for treated subjects (n=69) was 26 weeks; 61 participants had ≥50 EDs to rFVIIIFc. No participant developed inhibitors to rFVIIIFc. Overall, the pattern of adverse events reported on rFVIIIFc treatment was typical of the population studied; no serious adverse events were assessed as treatment-related by the investigator. The terminal half-life (arithmetic mean [95% CI]) in participants aged <6 years and 6 to <12 years was 12.67 (11.23, 14.11) hours and 14.88 (11.98, 17.77) hours, respectively. The relative increase in half-life over prior FVIII therapy was ~1.5-fold, consistent with the increase in half-life seen in the A-LONG study of adults and adolescents. Median (IQR) ABR was 1.96 (0.00, 3.96) overall, and 0.00 (0.00, 0.00) for spontaneous bleeds. Median total weekly dose and dosing interval were 88.1 IU/kg and 3.5 days, respectively. 83.7% and 93.0% of bleeding episodes were controlled with 1 or 1–2 infusions, respectively (median dose per bleeding episode: 54.9 IU/kg).

Conclusions: rFVIIIFc was well-tolerated, efficacious for prophylaxis and treatment of bleeding, and resulted in low bleeding rates. The extended half-life compared to FVIII and the safety profile were generally consistent with that observed in the Phase 3 study in adults and adolescents. rFVIIIFc offers the potential of prolonged dosing intervals and fewer infusions for children with severe hemophilia A.
Depression in children with severe Hemophilia- a pilot study

Golan Gaby, Kenet Gili

The Israeli National Hemophilia Institute Sheba Medical Center, Ramat Gan, Israel

Children with severe Hemophilia (CWH) suffer pain and inconvenience due to the required IV factor concentrates' injections and mostly exhibit poor quality of life. These children don't have any hope that their life will improve in the future. Most of them keep the Hemophilia a secret; therefore they are unable to get any emotional support from their peer group. These parameters are known stressors and triggers leading to depression, especially among children and adolescents (due to their lack of mature psychological defense mechanisms). The consequences of depression might be hazardous, since such children may neglect their medical treatment, leading to further deterioration of their medical state.

Objective: We compared the depression level of children with Hemophilia to healthy children of the same age and background.

Methods: Depression was evaluated using a standard validated questionnaire of depression that was developed by A. Beck - the CDI. We compared 20 children with severe Hemophilia with 25 non-Hemophiliac children.

Summary: The calculated score for degree of depression was 7.6 for CWH vs age matched controls with a score of 12.32. The mean of normal populations is around 9. Parametrical T test for Equality of Means = 0.013.

This is the first reported study objectively addressing the issue of depression in CWH.

Conclusions: We found the opposite of what we had expected: The children with Hemophilia were rated significantly much less depressed then the children without Hemophilia. This finding merits further validation in future larger studies and must be examined very carefully, due to the complexity of the psychological defense mechanisms.
The Medical Home Neighbor: The Intermountain Hemophilia and Thrombosis Center’s Experience with Quality Improvement via the Children’s Health Improvement Collaborative Medical Home Demonstration Project in Utah

Kate Colbath¹, Heidi Lane², Chuck Norlin¹

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Objective: Patient-centered medical home (PCMH), a team-based model of practice involving patients, families, providers and care team members, focuses on high quality, efficient, and patient-centered care. The purpose of this project was to implement appropriate elements of the PCMH model in the care delivered by the Intermountain Hemophilia and Thrombosis Center (IHTC).

Methods: The IHTC, as a medical home neighbor, participated in a 3 ½ year (5/2011-11/2014) Children’s Health Improvement Collaborative Medical Home Demonstration (MHD) that involved 3 specialty and 9 primary care practices in Utah. IHTC focused on both MHD-wide and practice-specific quality improvement (QI) goals. Our QI team included the IHTC core multidisciplinary team and a parent partner and medical home coordinator (MHC) who were funded by the MHD. The MHD led four sequential, 8-12 month projects: “Improving Collaboration Among Pediatric Generalists and Specialists,” “Implementing Care and Self-Care Plans for Children with Chronic Conditions,” “Improving Healthcare Transitions for Children with Special Health Care Needs,” and “Sustainability.” Practice-specific projects targeted goals established via a needs assessment and parent partner input. Plan-Do-Study-Act (PDSA) cycles were facilitated by the MHC and a practice coach from the MHD. Continuing education and peer support were provided via learning sessions, webinars, and ongoing mentorship.

Summary: IHTC met all MHD-wide and practice-specific goals. Selected MHD-wide improvements included: completion of the patient history prior to new consultation (improved from ~15% to 95%); patient self-care plans (0% to 97%); and youth with an up-to-date transition tool (0% to 100%). To address “sustainability,” IHTC will continue using QI, implementing the PCMH model, and will maintain the MHC as a member of the care team. Practice-specific strategies resulted in improved efficiency and family-centered approach to the annual comprehensive clinic visit (3½ hour visit decreased to 2 hours with reduced redundancy), reduced no-show/cancellations (~33% to 10%), established means for continuous individual patient/family feedback, and a formalized IHTC-specific emergency preparedness plan (currently in progress).

Conclusions: Via participation in the MHD, the IHTC learned that QI is both realistic and rewarding. Essential components for ongoing improvement include: specific, defined and measurable goals; a QI leader; parent/consumer input; and participation by all clinical team members. The PCMH model provides a framework for meaningful change for patients, families, and clinical practice.

Acknowledgments: Funded in part by a CHIPRA Quality Demonstrations grant: CFDA 93.767 from the U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services.
Hemophilia Inhibitor PUP Study (HIPS)

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Objective: Hemophilia A is a congenital bleeding disorder caused by a deficiency of a blood-clotting protein, factor VIII (FVIII), and is treated with replacement therapy using FVIII concentrate products. The prevention and treatment of bleeding symptoms is confounded by the development of FVIII neutralizing antibodies, or inhibitors, in about 30% of patients with severe hemophilia after exposure to FVIII concentrate (Wight 2003). Hemophilia A patients who develop inhibitors experience a substantial decline in health (Morfini 2007), and their cost of care increases considerably (Nerich 2008). Genetic and environmental risk factors for inhibitor formation have been identified, but more information is necessary to effectively predict and prevent inhibitors. Furthermore, mechanisms of inhibitor formation and conversely, immune system tolerance to FVIII among patients with hemophilia who do not develop inhibitors, are poorly understood, limiting the ability to develop sound therapies to overcome inhibitors.

Methods: The Hemophilia Inhibitor PUP Study (HIPS) is an investigator-initiated, international, multi-center, observational study to evaluate the longitudinal changes in immunity upon exposure to FVIII in patients with severe hemophilia A previously untreated with FVIII concentrates. Eighteen hemophilia treatment centers in the U.S. and Europe have qualified to enroll patients in the study. Study candidates must have severe hemophilia A (FVIII level < 0.01 IU/ml), no other clinically significant chronic disease(s), no prior exposure to blood products or clotting factor concentrates, and weigh ≥ 3.5 kg. Each participant will receive a single source of recombinant FVIII (Advate) during the first 50 FVIII exposure days, and treatment dosing and regimen will be determined by his hematologist. Each subject will have eight study visits during the first 50 FVIII exposure days or three years, whichever occurs first. During these visits subjects will receive a physical exam during which approximately 7 ml of blood will be taken. These blood samples will be tested for FVIII inhibitor (Nijmegen-modified Bethesda assay), characterization of FVIII-specific T-cell signatures, epigenetic markers of immune status, RNA expression profiles, and determination, quantification, and affinity testing of anti-FVIII antibodies Ig isotypes and IgG subclasses.

Conclusions: The goal of HIPS is to advance the understanding and detect early biomarkers of FVIII inhibitor development, and allow for better risk assessment and strategies to avoid inhibitor development in patients with hemophilia A. The study is open for enrollment.
Modelling the transfer of rFVIIa procoagulant signal from tissue factor to platelets

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Objective: Although hemophiliacs have normal initial hemostatic and platelet responses, they suffer from re-bleeding likely due to a deficient propagation phase of coagulation and require treatment with recombinant Factor VIIa (rFVIIa) minutes to hours after the initial vessel wall injury. It remains debated whether a TF-dependent or platelet-dependent rFVIIa mechanism overcomes this deficiency. Tissue factor (TF) is the more efficient enzymatic cofactor at sub-pharmacological rFVIIa doses, suggesting dominance of the TF mechanism. Nevertheless, the commonly accepted cell-based model of hemostasis postulates the importance of the lipid mechanism because of potentially limited TF availability during post-bleeding rFVIIa infusion due to rapid TF inhibition by TF pathway inhibitor (TFPI) and obstruction by the pre-existing hemostatic plug. Previous attempts to study rFVIIa action in vitro have failed to effectively separate the TF-dependent coagulation response from the platelet-dependent action of rFVIIa. Therefore, we have developed a new in vitro model that more accurately reflects the on-demand rFVIIa treatment through physically separated TF-led initiation and platelet-led propagation to determine if and how the TF mechanism may be limited.

Methods: A two-layered thrombin generation assay was developed where various dosages of rFVIIa in plasma (2nd layer) were added on top of an already formed TF-initiated clot (1st layer). Inhibitors to TF and various procoagulant enzymes, e.g. activated Factor X and thrombin, were also added to the rFVIIa infusion mixture (2nd layer).

Summary: A transfer of procoagulant signal from the pre-existing clot (1st layer) to fresh plasma with rFVIIa (2nd layer) was found and was dose-dependent on rFVIIa. Inhibition of TF by TFPI was not fast and was not complete after at least 30 minutes because addition of anti-TF antibodies to the 2nd layer blocked the rFVIIa dose response. In contrast, transfer of coagulation enzymes from the TF-initiated clot to the rFVIIa-containing layer had no contribution to the hemostatic effect of rFVIIa.

Conclusions: Our novel two-layered TGA model of the cell-based model of hemostasis suggests that TF may be an active participant in rFVIIa action during on-demand rFVIIa treatment one hour after initial clot formation. Further studies will evaluate the use of platelets and various lipid compositions and its effect on the two-layered TGA dose-response of rFVIIa action.

Disclosure: This is an informal communication and it represents authors’ own best judgment. These comments do not bind or obligate FDA.
Systematic review of clinical trial results assessing health-related quality of life in hemophilia patients receiving prophylaxis

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Introduction and Objective: Prospective clinical trials have demonstrated the efficacy of prophylaxis in reducing bleeding episodes in hemophilia A and B patients and those with inhibitors. However, data, predominantly from observational studies, have suggested more equivocal effects on health-related quality of life (HRQoL) [Buchbinder 2013]. The present review examined the impact of prophylaxis on HRQoL as measured during prospective trials.

Methods: We conducted a systematic literature review of prospective studies evaluating the efficacy of prophylaxis in hemophilia using factor VIII, factor IX, or bypassing agents. Applying the inclusion criteria, we selected studies which evaluated HRQoL via validated instruments and summarized key data.

Results: A total of 12 studies (hemophilia A [n=7]; hemophilia B [n=2]; inhibitors [n=3]) met all inclusion criteria and were reviewed. Of these studies, the investigational products were Advate (n=2), Kogenate (n=2), NovoEight (n=2), Eloctate (n=1), Rixubis (n=1), Aprolix (n=1), Feiba (n=2), and NovoSeven (n=1). HRQoL was assessed using one or a combination of the following instruments: SF-36 (n=3), EQ-5D (n=5), Haemo-QoL (n=2), Haem-A-QoL (n=3), Haemo-QOL-A (n=2) and general pain VAS (n=1). Seven of the 12 studies reported significant improvement in ≥1 HRQoL measure following prophylaxis. Advate, Rixubis and Feiba prophylaxis (among good responders with ≥ 50% bleed reduction) demonstrated statistically significant and clinically meaningful improvement in the physical component and certain domain(s) scores of the SF-36 (Valentino 2012; Windyga 2013; Gringeri 2013). Additionally, prophylaxis with Feiba showed clinically meaningful and/or statistically significant improvements in HRQoL (EQ-5D, Haemo-A-QoL) and general pain scores (VAS) (Antunes 2014; Stasyshyn 2014). Although, a previous Kogenate study indicated non-significant change in HRQoL measures (Collins 2003), recently published results from the SPINART trial demonstrated statistically significant and clinically meaningful improvement in several domains of the Haemo-QoL-A (Hong 2014). Prophylaxis with Eloctate and Alprolix resulted in non-significant change in the HRQoL measures used in their respective trials (Wyrwich 2013). Statistical and clinical significance were not reported for prophylaxis treatment with NovoEight (Santagostino 2014). Prophylaxis with NovoSeven showed a non-significant trend towards improvement in all dimensions of the EQ-5D but statistical improvement in general health status (EQ-VAS) (Hoots 2008).

Conclusion: Results from Advate, Kogenate, Rixubis and Feiba trials offer robust evidence of clinically and statistically significant improvement in HRQoL in hemophilia patients treated with prophylaxis.
Point-of-care musculoskeletal ultrasound is critical for the diagnosis of hemarthroses and soft tissue inflammation in adult patients with painful hemophilic arthropathy.

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Objective: Using point-of-care musculoskeletal ultrasound (MSKUS), we previously demonstrated that patient and physician assessments were unreliable in determining bleeding during acute painful joint episodes. Here we delineated by MSKUS pathophysiological soft tissue changes that may contribute to pain, and investigated to what extent MSKUS findings and functional or radiographic joint status correlate with markers of inflammation.

Methods: We used the GE Logiq e BT11 US-module with high frequency 8-13 MHz linear transducer and real time spatial compound imaging capability for grey scale and Power Doppler examinations. We analyzed all MSKUS examinations performed between 05/2012 and 08/2013 in 34 adult hemophilia patients (mean age 39.3 years) seen at our Hemophilia Treatment Center. Findings were correlated with Hemophilia Joint Health Scores (HJHS), Pettersson Scores, hsCRP, and von Willebrand Factor (VWF) activity and antigen levels. Spearman correlation coefficient and Wilcoxon Mann-Whitney tests were used. P-values ≤0.05 were considered significant. Acute and persistent pain was defined as lasting ≤7 days and >7 days, respectively.

Results: Sixty-five examinations were performed. Seventy percent of patients had severe hemophilia. Mean Pettersson scores were 22 of 78 and HJHS were 22 of 124. Joints most commonly examined were knees and ankles (72%), with most examinations (72%) performed for persistent pain. Effusions were present in 48% of painful joints. Of those effusions, 90% were bloody during acute and ~50% during persistent pain episodes. Synovitis (+/-tendinitis, enthesitis or bursitis) was observed in 66% of all MSKUS examinations. Synovitis and hemarthrosis coincided in 20% of examinations. In exams revealing hemarthrosis, synovitis was present in 68%. In acute hemarthrosis, synovitis was present in 55% and, with persistent pain, synovitis was present in 80%. Although total and joint-specific HJHS and Pettersson scores were higher in patients with synovitis, only the joint-specific Pettersson score was significantly higher (mean score 3 vs 6.5). HsCRP, VWF activity and VWF antigen levels correlated significantly with joint-specific Pettersson scores (Cr ~0.4) and total HJHS (Cr ~0.6), but not consistently with synovitis.

Conclusion: Inflammation and bleeding were prominent findings in painful hemophilic arthropathy. One-fifth of persistently painful joints were diagnosed with hemarthroses, which were almost always associated with synovitis. Inflammatory markers correlated to some extent with joint findings, but were diagnostically not helpful. We conclude that sensitive imaging technology such as MSKUS is critical to precisely diagnose causes of pain in hemophilic arthropathy with a need for personalized care that includes tailored clotting factor replacement and/or novel anti-inflammatory strategies.
Safety and efficacy of a recombinant factor IX (BAX326*) in pediatric previously-treated patients with hemophilia B

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Objectives: This prospective clinical trial was conducted to assess the safety, hemostatic efficacy and pharmacokinetic (PK) profile of a recently developed recombinant factor IX (BAX326*) in pediatric previously-treated patients (PTPs) with severe or moderately severe hemophilia B.

Methods: PTPs aged <12 years with severe (FIX level < 1%) or moderately severe (FIX level ≤ 2%) hemophilia B were eligible for enrollment. BAX326 was administered as prophylaxis twice a week over 6-months, and on demand for treatment of bleeds. Efficacy was evaluated by treatment response rating (excellent, good, fair, none) and annualized bleeding rate (ABR). PK assessments after one 75 ± 5 IU/kg infusion of BAX326 were assessed using a non-linear mixed model (population PK) approach. IR was measured as part of the PK evaluation 30 minutes after the initial PK infusion and at 5, 13 and 26 weeks after the initial infusion.

Summary: Nine subjects (39.1%) had no bleeds during the study. A total of 26 bleeds occurred (mean ABR 2.7 ±3.14, median 2.0), of which 2 were spontaneous. Fewer bleeds occurred in joints than in non-joint sites (19 non-joint vs. 7 joint bleeds). Hemostatic efficacy was excellent or good in >96% of bleeds, and the majority (88.5%) resolved after 1-2 infusions. The median IR (IU/dl)/(IU/kg) at the initial PK assessment was 0.685 (range: 0.31-1.00). As expected, a higher IR was observed in association with increased patient age; IR was slightly lower in subjects < 6 years (median 0.591; range: 0.31-0.75), than in subjects aged 6 to <12 years (median 0.714; range: 0.51-1.00). IR was consistent over time. There were no adverse reactions, no thrombotic events and no hypersensitivity reactions. None of the subjects treated (N=23) developed inhibitory or specific binding antibodies against FIX.

Conclusions: BAX326 is efficacious and safe as prophylactic treatment as well as for bleed control in pediatric hemophilia B patients.

*Licensed in the USA and Australia (Rixubis®; Baxter Healthcare Corp., USA).
An Initiative to Implement Quality Improvement Measures for Hemophilia Treatment Centers

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**Objective:** Quality improvement (QI) consists of systematic and continuous actions that lead to measurable improvement in healthcare services and health status of targeted patient groups. To perform effective QI, key health measures must be identified and tracked over time. The Cystic Fibrosis Foundation’s (CFF’s) QI Initiative monitors four key health measures for each of its >110 accredited care centers. While the U.S. Hemophilia Treatment Center (HTC) network is optimally organized to undertake a similar program, no initiative to do so currently exists. The Indiana Hemophilia and Thrombosis Center (IHTC) envisions such an initiative. To that end, the current study aimed to determine what metrics are best suited to evaluate the effectiveness of the IHTC’s hemophilia program, with the secondary objective to propose these measures to the HTC community.

**Methods:** The IHTC’s electronic medical record was accessed for 2008-2011 for males with hemophilia A and B. Data extracted included demographics, insurance status, factor deficiency/severity, primary product, treatment regimen, inhibitor status, BMI, adherence as measured using VERITAS-Pro and VERITAS-PRN, days missed from school/work, port status, contacts with the IHTC, history of orthopedic procedures, history and emergence of arthropathy, hospitalizations, and HIV/hepatitis C status. An extensive report was created showing descriptive graphs of all data points. A panel of experts in hemophilia care and statistical analysis convened to review the measures and tentatively identify the most informative ones.

**Summary:** The following measures were introduced in a presentation to IHTC clinical staff as the most critical metrics reflecting care quality: 1) percent of patients attending comprehensive clinic per year; 2) percent of patients with arthropathy in a new joint by age, disease severity, and treatment regimen; 3) percent of patients with existing arthropathy and with arthropathy in a new joint in a given year, by inhibitor status; 4) number of days missed from school/work; and 5) percent of inhibitor patients tolerized.

**Conclusions:** The QI measures described here are under consideration and will continue to be refined. To propose implementing a QI initiative in the HTC network may create ambivalence amongst HTCs reluctant to share performance and outcome data. The CFF has overcome these tensions by focusing their initiative to increase, promote, and share improvements in care; not to generate competition or criticize poorer performing centers. Our study similarly seeks to promote information sharing in a manner that will enable all HTCs to improve outcomes and quantify the effectiveness of the HTC comprehensive care model.
The effects of FXIa on clot formation and lysis in the thrombin generation assay

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**Objective:** Assaying thrombin generation (TG) in real time using fluorogenic substrates has been a popular approach for developing a true global hemostasis assay. Benefits over other assays include assessment of global hemostasis potential, not just the level of coagulation factor deficiencies. Recent experiments in our laboratory have suggested that adding factor XIa to the assay improves the sensitivity and robustness of this assay approach. Its effects on clot formation and lysis are also being assessed.

**Methods:** To expand the utility of the TG test, we optimized the reaction mixture and protocol. We add FXIa to the substrate/calcium mixture as previous experiments in our laboratory have shown FXIa needs to be added during or after plasma recalcification in order to maintain activity. We are also observing, concurrently with TG by fluorescence, absorbance as a direct measurement of fibrin generation (FG). Congenitally FV, FVII, FVIII, and FIX-deficient plasma were supplemented with their respective purified factors to give known level of factor deficiency. Tissue plasminogen activator (tPA) and thrombomodulin (TM) are also added to our assay to induce and allow observation of clot lysis and thrombin-dependent lysis inhibition. We run equivalent samples on Thrombinscope’s Calibrated Automated Thrombinography (CAT, Stago USA) platform to assess our variations from the current standard protocol.

**Summary of results:** Adding FXIa improves the robustness and sensitive range of the TGT as applied to clotting factor deficiencies. For FVIII deficiency, adding FXIa results in thrombin peak heights begin rising at lower factor concentrations and increases in thrombin peak heights. For FIX deficiency, the addition of FXIa gives a dose-dependent thrombin maximum response that would otherwise be absent or weak. However, FV deficiency showed dose-dependent TG trends with or without FXIa, while the addition of FXIa eliminates dose-dependent TG trends in FVII deficiencies. These trends are seen both using our in-house TGT and CAT. The addition of tPA and TM do not appear to produce additional factor-dependent TG or FG responses under conditions tested, while they diminished the factor-dependent time to peak thrombin trend for FIX-deficient plasma.

**Conclusions:** The addition of FXIa to the TGT gives us a more sensitive assessment of global hemostasis in intrinsic pathway deficiencies and reveals patterns not seen using current standard protocols.

Disclaimer. The authors are employees of the US Food and Drug Administration (FDA). This presentation is an informal communication and represents authors’ own best judgment. These comments do not bind or obligate FDA.
Identification of Previously Unreported F8 and F9 Gene Mutations in Hemophilia Subjects From the Phase 3 Clinical Trials of rFVIIIFc and rFIXFc

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Objective: Hemophilia A and B are X-linked bleeding disorders caused by the deficiency of clotting factor VIII or IX, respectively. Mutations in the F8 gene can result in hemophilia A while mutations in the F9 gene can lead to hemophilia B. The objective of this analysis was to evaluate the F8 and F9 genotypes of subjects screened for enrollment in the phase III clinical trials of rFVIIIFc in hemophilia A (A-LONG) and of rFIXFc in hemophilia B (B-LONG).

Methods: The F8 and F9 genotypes of 170 subjects with severe hemophilia A and 114 subjects with severe hemophilia B, respectively, were compared with several genotype databases (HAMSTeRS, [Hemophilia A Mutation, Structure, Test and Resource Site], CHAMP [CDC Hemophilia A Mutation Project], and King’s College London Hemophilia B database), as well as with the NCBI human F8 and F9 sequences.

Summary: Among 170 subjects with hemophilia A, inversions in intron 22 (Int22inv) were identified in 36%, nucleotide substitutions in 39%, frameshift mutations in 21%, Int1inv in 3%, and an in-frame duplication in 1 subject. Previously unreported mutations (frameshift, missense, nonsense, and splice site changes) were found in 24 subjects, with 2 unrelated subjects having the same mutation, resulting in 23 novel mutations being identified. Among 114 subjects with hemophilia B, the majority (86%) had some form of substitution mutation (missense, nonsense, splice-site change), consistent with previous reports. Thirteen previously unreported mutations were identified, including 10 substitutions (7 missense, 2 nonsense and 1 splice-site change), 1 deletion, and 2 insertions.

Conclusions: In this analysis, 23 previously unreported mutations in the F8 gene of subjects with severe hemophilia A and 13 in the F9 gene of subjects with severe hemophilia B were identified. Identifying mutations allows for prenatal diagnosis and identification of carrier status. These results will lead to further enhancement of databases for hemophilia A and B mutations and may assist in clarifying the relationship between genotype, phenotype, and pathophysiology in individuals with hemophilia.
Mobilizing Patients Towards Positive Health Management Through Motivational Interviewing

Mary Jane Frey, Michelle Witkop, Susan Zappa, Chris Guelcher, Sonia Nasr

Objective: Patient health outcomes are strongly correlated with management of their health condition. In chronic disease management, example hemophilia, a clinician often encounters situations where despite what the patient is instructed to do, there is resistance to follow directions, thus compromising the potential benefits of their treatment regimen.

The objective of these interventions was to test out motivational interviewing (MI) as an alternative communication approach to traditional advice giving in especially difficult, yet common, hemophilia patient situations.

Methods: Four case studies are reported, each with a different nurse, patient, and desired behavioral change. In each case study, the clinician had received education on the use of MI in health care settings. Multiple Tools and Paradigms were used with patients at different life stages, and in need of making changes in their self-care and disease management. The clinicians avoided traditional directive approaches and adopted collaborative methods that guided the patient to take responsibility for achieving their own health goals. Patients were followed post intervention to determine longevity of the success achieved through this intervention.

Results Summary: In each case, the use of MI enabled the clinician to work collaboratively with the patient or caregiver, to evoke their own reasons for change, to elicit change planning, and to mobilize them towards healthier choices in managing their condition.

Case study 1: pediatric setting - Use of Engaging Microskills (Open Questions, Affirmations, Reflections, Summaries) with a parent to empower their child to start self-infusion.

Case study 2: pediatric setting - Use of MI Rulers to motivate an adolescent to choose a more appropriate sport activity.

Case study 3: Transition setting - Use of MI Spirit, especially partnership and honoring autonomy, with an adolescent.

Case study 4: Adult setting - Use of EPE (Elicit Provide Elicit Approach) with an adult who was not adherent to his prophylaxis regimen.

Conclusions: MI was confirmed as a successful therapeutic approach with a variety of resilient clinical cases where traditional directive approaches had been unsuccessful. The use of MI created an open and trusted communication channel between the clinician and the patient or caregiver, concluding with a change plan agreement. Clinicians felt more fulfilled with their jobs and more satisfied with the result of their intervention. With appropriate education about this methodology, clinicians can use it with their patients where a behavioral change is required to achieve better therapeutic outcomes.
Objective: To analyse real world FVIII dosing and treatment interval patterns in patients with haemophilia A. A secondary objective was to compare the observed dosing patterns with the dosing regimens for rFVIII and rFVIIIFc evaluated in clinical studies.

Methods: A retrospective analysis was conducted using aggregate Specialty Pharmacy Provider (SPP) records from Nov 2013 through Mar 2014. SPP data included 63 different attributes for each prescription, including trade name, National Drug Code (NDC), drug quantity shipped, prescribed infusion dose, days supplied, and dose frequency. Patients were considered eligible for the analysis if they received a shipment of any FVIII product. Patients were excluded from the analysis if they were being treated episodically, for immune tolerance induction, or their pharmacy records did not specify a prescribed infusion dose. Patients with missing or extremely abnormal weights were also excluded. The patient's weekly consumption was calculated for each shipment record by multiplying the prescribed infusion dose by the dose frequency and dividing the product by the patient’s weight, resulting in the patient’s average weekly prescribed dose (IU/kg/week). Patients were also categorized according to their dosing interval.

Summary: The analysis included 520 hemophilia A patients with a median age of 18 (range: 1-77) and median weight of 63.5 kg (range: 8-161 kg). Pharmacy dispensing records represented 227 distinct prescribers across 43 states. FVIII therapies evaluated included Advate®, Recombinate®, Helixate® FS, Kogenate®, Hemofil and Xyntha®. The average weekly consumption across all therapies was 108.0 IU/kg/week (95% CI, 104.6-111.5). Dosing frequency ranged from once-daily to once-weekly with three times/week and every other day as the most common dosing intervals, representing 81.3% of patient records. For patients infusing thrice-weekly, the average infusion dose was 35.1 IU/Kg. Only 15.4% of the population was infusing ≤ two times per week. Clinical trials for Advate report weekly consumption of 110.3 IU/kg (31.4 IU/kg administered QOD). Two prophylactic regimens were evaluated for rFVIIIFc in A-LONG. In the last 3 months of this study, the median weekly consumption was 77.7 IU/kg for the individualized prophylaxis and the median weekly dose of 65.5 IU/kg for the weekly prophylaxis regimen.

Conclusions: Pharmacy dispensing records support the clinical trial dosing intervals of rFVIII products currently requiring every other day or thrice-weekly dosing; however, real-world dosing (IU/kg/week) may be greater. This may result in unpredictability for payers who are responsible for healthcare budgets.
Real-world Dosing Patterns of Factor in Hemophilia B Patients

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Objective: To analyse real-world FIX dosing and treatment interval patterns. A secondary objective was to compare the observed dosing patterns with the dosing regimens for FIX products evaluated in clinical studies.

Methods: A retrospective analysis was conducted using aggregate Specialty Pharmacy Provider (SPP) records from 2012 through Q12014. SPP data included 63 different attributes for each prescription, including trade name, NDC, quantity shipped, prescribed infusion dose, days supplied, and dose frequency. Patients were considered eligible for the analysis if they received a shipment of any FIX product. Patients were excluded from the analysis if they were being treated episodically, for immune tolerance induction, or their pharmacy records did not specify a prescribed infusion dose. Patients with missing or extremely abnormal weights were also excluded. The patient’s weekly consumption was calculated for each shipment record by multiplying the prescribed infusion dose by the dose frequency and dividing the product by the patient’s weight, resulting in the patient’s average weekly prescribed dose (IU/kg/week). Patients were also categorized according to dosing interval.

Summary: The analysis included 118 hemophilia B patients with a median age of 20 (range: 2-63) and median weight of 55.4 kg (range: 9.5-129 kg). Pharmacy dispensing records represented 78 distinct prescribers across 29 states. FIX therapies evaluated included Benefix®, Alphanine®, Mononine®, and Rixubis®. The average weekly consumption across all therapies was 139.0 IU/kg/week (95% CI, 128.7-150.3). Dosing frequency ranged from every other day to once weekly. Twice weekly was the most common dosing interval, representing 56.8% of patient records. According to clinical trial data and FDA labelled dosing for FIX therapies, lower weekly consumption may be expected. For BeneFIX the mean weekly consumption was 80.6 IU/kg, 40.3 IU/kg administered twice-weekly. For Rixubis the mean weekly consumption was 88.9 IU/kg, 49.4 IU/kg administered 1.8 times/week and a US dosing recommendation of 40-60 IU/kg dosed twice-weekly. Two prophylactic regimens have been evaluated for Alprolix™. In the last 3 months of B-LONG, in the weekly prophylaxis arm, the overall median dose on study was 40.5 IU/kg. The individualized interval prophylaxis arm had a median weekly dose of 50.0 IU/kg, 100 IU/kg administered every 14 days. No real world dosing is available for Alprolix due to its recent approval.

Conclusions: Dosing regimens evaluated in the real world for conventional FIX products indicate greater consumption than reported in clinical trials. This may result in unpredictability for payers who are responsible for healthcare budgets.
Global Assessment of Knowledge and Practices in the Diagnosis, Classification, and Management of Hemophilia among Pediatric Providers.

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Objective: Knowledge gaps among clinicians regarding diagnosis, classification, and/or management in hemophilia can potentially delay diagnosis/referral and lead to adverse clinical outcomes. A study was undertaken to identify hemophilia clinical practice gaps among pediatricians.

Methods: A global, hemophilia-specific continuing medical education-accredited clinical practice assessment survey was developed based on current evidence-based consensus guidelines and best practices, including guidelines from the National Hemophilia Foundation and the World Federation of Hemophilia. The assessment included both knowledge- and case-based, multiple-choice questions that healthcare providers completed confidentially online between March 21, 2014 and April 16, 2014. Areas such as appropriate triggers for initiating prophylaxis and use of physical therapy were assessed. Responses from pediatric providers were de-identified and aggregated prior to analyses.

Summary: 817 pediatricians (42% of total respondents) completed the survey, from the following locales: North America (29%), Asia (23%), Europe (16%), Middle East (13%), Africa (9%), Central/South America (6%), and Australia (3%). Academic (36%), private practice (26%), community hospital (24%), community clinic (9%), and hemophilia treatment center (1%) practice settings were identified. For most responses, the proportion of incorrect responses appeared to be consistent regardless of whether pediatricians indicated professional interaction with hemophilia patients (Group A: 60%) or not (Group B: 40%). Pediatrician knowledge gaps included (% incorrect responses): classification of severity of hemophilia (28% A v. 39% B; P=.0030); optimal use of prophylactic therapy, e.g., when to initiate (29% A v. 30% B; P=.83), at what dose (16% A v. 17% B; P=.93); likelihood of inhibitors (51% A v. 55% B; P=.14); and adolescent care, e.g., adherence (25% A v. 22% B; P=.33), transitioning (14% A v. 14% B; P=.36), and long-term prophylaxis (76% A v. 76% B; P=.68). Differences in correct responses were observed when comparing Australia, Europe, and North America versus Africa, Asia, Central/South America, and the Middle East on topics such as classification of severity of hemophilia (P<.0001) and when to initiate prophylaxis (P=.04), although knowledge gaps existed in both groups. A low level of confidence in ability to identify when to use prophylaxis was reported among 42% [95% CI: 40%-46%] of pediatricians. The top barriers to the administration of prophylaxis included cost and lack of availability of FVIII or FIX (41% and 26% for all respondents, respectively).

Conclusions: Substantial knowledge gaps permeate pediatric clinical practice in the diagnosis and optimal care of hemophilia. Educational efforts tailored to the practice setting and geographic locales are warranted.
Retrospective Database Analysis of the Prevalence of Cardiovascular Comorbidities in a US Patient Population with Hemophilia A: Confirmation of Findings

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Objective: A previous retrospective study of the MarketScan® claims database reported increased prevalence and earlier onset of cardiovascular (CV) comorbidities in patients with hemophilia A compared with patients without hemophilia. Our study was designed to confirm these findings in a second population of male patients with hemophilia A in the United States.

Methods: Male patients with hemophilia A and continuous insurance coverage were identified by ICD-9-CM code 286.0 using the PharMetrics LifeLink claims database (IMS Health) of patient records from January 1, 2008 to December 31, 2011. Patients with hemophilia A were matched 1:3 with controls for sex, age, plan type, geographic region, and eligibility months in the study period. The prevalence of CV comorbidities (identified by ICD-9-CM codes) was compared between matched cohorts. Statistical significance was calculated using Fisher’s exact test.

Summary: Overall, 1050 patients were included in the hemophilia A cohort and 3150 in the control cohort (Table). Prevalence of hemorrhagic stroke, ischemic stroke, coronary artery disease, myocardial infarction, hypertension, hyperlipidemia, arterial thrombosis, and venous thrombosis was significantly higher in the hemophilia A cohort (all \( P \leq 0.016 \)). Increased prevalence of CV comorbidities was consistent across most age groups, and patients with hemophilia A experienced CV comorbidities at an earlier age than those without hemophilia.

Table: Cardiovascular comorbidities in patients with hemophilia A

<table>
<thead>
<tr>
<th>Comorbidities, %</th>
<th>PharMetrics Integrated Database</th>
<th>MarketScan Database</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hem (n=1050)</td>
<td>GHP (n=3150)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.3</td>
<td>13.2</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>15.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>9.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>4.9</td>
<td>0.3</td>
</tr>
</tbody>
</table>

GHP=general health population; Hem=patients with hemophilia A.
**Conclusions:** This second retrospective study of claims databases confirmed an increased prevalence and earlier onset of CV comorbidities in patients with hemophilia A. These findings support increased screening in patients with hemophilia for CV comorbidities at an earlier age than recommended for the general population.
Dosing Flexibility in Prophylaxis Regimens With Bayer's Sucrose-Formulated Recombinant Factor VIII: Experience From Postmarketing Surveillance Studies

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Objectives: Factor VIII (FVIII) prophylaxis regimens for severe hemophilia A that allow more flexible dosing than the standard 3-times-weekly regimen while maintaining efficacy may improve adherence. This analysis compared the clinical efficacy of once- or twice-weekly versus ≥3-times-weekly prophylaxis dosing of Bayer’s sucrose-formulated recombinant FVIII (rFVIII-FS) in patients with severe hemophilia A.

Methods: Data from 3 postmarketing studies were pooled. Patients with severe hemophilia A and no history of inhibitors who were receiving ≥1 prophylaxis infusion/wk of rFVIII-FS for ≥80% of a prophylaxis observation period (≥5 months) were included. Patients were categorized based on age (<18 and ≥18 years) and physician-assigned treatment regimens of 1–2 prophylaxis injections/wk (n=63) or ≥3 prophylaxis injections/wk (n=76). Descriptive statistics were determined for annualized bleeding rates (ABRs) by dosing group and age subgroups.

Summary: Median (quartile 1; quartile 3) ABR for all bleeds was 2.0 (0; 4.0) in the group receiving 1–2 prophylaxis injections/wk and 3.9 (1.5; 9.3) in the group with ≥3 prophylaxis injections/wk. Similarly, median ABRs for joint, spontaneous, and trauma-related bleeds were numerically lower in the group receiving 1–2 prophylaxis injections/wk. The trend toward lower ABRs in the group with 1–2 prophylaxis injections/wk was observed in both age subgroups, although ABRs were somewhat higher in patients ≥18 vs <18 years. Zero annualized bleeds were reported by 30% and 7% of patients in the groups with 1–2 prophylaxis injections/wk and ≥3 prophylaxis injections/wk, respectively.

Conclusions: These data demonstrate that bleeding control can be achieved in some patients with severe hemophilia A using a <3-times-weekly prophylaxis dosing regimen and that physicians’ judgment based on bleeding phenotype can successfully direct the frequency of prophylactic dosing.
Joint Outcomes by Magnetic Resonance Imaging After Treatment With Bayer’s Sucrose-Formulated Recombinant Factor VIII in the SPINART Study: Results at the 3-year Evaluation Timepoint

Walter Hong, David Raunig, Charles Peterfy, Michael Werk, Marilyn J. Manco-Johnson, Bjorn Lundin

Objective: Joint status was assessed in the 3-year SPINART study, which compared routine prophylaxis versus on-demand treatment in adults with severe hemophilia A. We report joint outcomes at year 3 obtained using magnetic resonance imaging (MRI).

Methods: The open-label, randomized, controlled, parallel-group, multinational SPINART study enrolled males aged 12–50 years with severe hemophilia A who had ≥150 exposure days with any factor VIII (FVIII) product, no inhibitors, no prophylaxis for >12 consecutive months in the past 5 years, and 6–24 documented bleeding events or treatments in the previous 6 months. Patients were treated with Bayer's sucrose-formulated recombinant FVIII (rFVIII-FS), either on demand or as prophylaxis (25 IU/kg 3 times weekly, with dose escalation by 5 IU/kg permitted once per year). MRI was performed at baseline and year 3 to evaluate the structure of 6 index joints. Each MRI was read by 3 radiologists blinded to treatment assignment who independently completed the extended MRI (eMRI) scale; higher eMRI scores indicate greater joint structure damage. The score for each joint was based on the readers’ median change score for each of the 45 eMRI scale items when comparing MRIs from different timepoints. Total patient score was derived; change from baseline in total patient score was prespecified as the first in a hierarchy of 2 secondary endpoints. Between-group comparison was made using constrained longitudinal data analysis. Data are presented for the intent-to-treat population.

Summary: Of 84 patients enrolled (42 per treatment group), MRI data were available for 38 on-demand and 41 prophylaxis patients. Least squares (LS) mean change from baseline to year 3 on the eMRI scale total score was 0.96 for on demand and 0.79 for prophylaxis (LS mean difference, –0.17; 95% CI, –0.92 to 0.59; P=0.66). LS mean change from baseline to year 3 for on demand and prophylaxis was 0.06 and 0.01 for the eMRI soft-tissue domain (LS mean difference, –0.04; 95% CI, –0.18 to 0.10; P=0.53) and 0.90 and 0.78 for the eMRI osteochondral domain (LS mean difference, –0.12; 95% CI, –0.82 to 0.58; P=0.74).

Conclusions: In adults with severe hemophilia A, progression of structural joint damage was not significantly different between patients using rFVIII prophylactically or on demand over a 3-year follow-up period, although less progression was seen with prophylaxis.
SPINART Trial 3-Year Results With Bayer’s Sucrose-Formulated Recombinant Factor VIII: Improved Joint Function and Health-Related Quality of Life in Adults Using Prophylaxis

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Objective: Joint status and health-related quality of life (HRQoL) were assessed as part of the 3-year SPINART study, which compared routine prophylaxis versus on-demand treatment in adults with severe hemophilia A. We report SPINART joint outcome results obtained using the Colorado Adult Joint Assessment Scale (CAJAS) and HRQoL data from Haemo-QoL-A assessments.

Methods: The open-label, randomized, controlled, parallel-group, multinational SPINART study enrolled male patients aged 12–50 years with severe hemophilia A who had ≥150 exposure days to any factor VIII (FVIII) product, no inhibitors, no prophylaxis for >12 consecutive months in the past 5 years, and 6–24 documented bleeding events or treatments in the previous 6 months. All patients were treated with Bayer’s sucrose-formulated recombinant FVIII (rFVIII-FS), either on demand or as prophylaxis (25 IU/kg 3 times weekly, with dose escalation of 5 IU/kg permitted once per year). CAJAS assessments were performed at baseline and years 1, 2, and 3. The physiotherapists performing CAJAS assessments were blinded to patient treatment assignment, bleeding history, and previous joint assessment data. Change from baseline to year 3 in CAJAS total score was prespecified as the second of 2 secondary endpoints; higher CAJAS scores indicate worse joint function. Haemo-QoL-A was completed at baseline, month 6, and years 1, 2, and 3; higher Haemo-QoL-A scores indicate better HRQoL. Between-group comparison was made using constrained longitudinal data analysis. Data are presented for the intent-to-treat (ITT) population.

Summary: 84 patients (42 prophylaxis, 42 on demand) comprised the ITT population; Haemo-QoL-A data were available for 41 and 42 patients, respectively. For CAJAS total score, least squares (LS) mean change from baseline to year 3 was 0.63 for on demand and −0.31 for prophylaxis (LS mean difference, −0.94; 95% CI, −1.61 to −0.26; P=0.0072). LS mean change in CAJAS total score for the on-demand and prophylaxis groups was 0.19 and −0.46 at year 1 and 0.34 and −0.57 at year 2, respectively. For Haemo-QoL-A total score, LS mean change from baseline to year 3 was −6.00 for on demand and 3.98 for prophylaxis (LS mean difference, 9.98; 95% CI, 3.42 to 16.54).

Conclusions: In adults with severe hemophilia A, joint function and HRQoL improved continuously over 3 years with prophylaxis compared with on-demand use.
BCR11

Production and Characterization of BAX 855, PEGylated rFVIII with Extended Half-Life

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Objective: Baxter has developed BAX 855, a PEGylated form of Baxter’s recombinant full length FVIII (rFVIII) product based on the ADVATE™ manufacturing process. Here we describe its manufacturing and structural and functional characterization.

Methods: A rFVIII intermediate of the ADVATE™ manufacturing process is the starting material for the conjugation process for preparing BAX 855 by proprietary PEGylation technology from Nektar Therapeutics. Similar technology has been successfully employed for marketed and licensed PEGylated drug products and drugs in clinical use. The manufacturing process for BAX 855 comprises several steps, including controlled PEGylation followed by cation exchange chromatography. Final formulation uses the same excipients as ADVATE™. BAX 855 was characterized by a number of analytical methods, focusing on the elucidation of the primary structure, posttranslational modifications, PEGylation site distribution and three-dimensional structure. The overall hemostatic potency of BAX 855 in FVIII-deficient plasma was assessed by conventional FVIII 1-stage clotting and chromogenic assays and with a thrombin generation assay. The tenase cofactor activity of FVIII was determined by measuring the kinetics of FXa generation. Binding of BAX 855 in comparison to ADVATE™ was determined to its ligands VWF and low-density lipoprotein-receptor-related protein (LRP).

Summary and Conclusions: BAX 855 is a full-length rFVIII with extended half-life. PK studies in different animal species and humans with hemophilia A display longer survival of BAX 855 compared to ADVATE™. Our analyses show that BAX 855 can be manufactured reproducibly without changes to the protein structure characteristic for a fully functional full-length rFVIII molecule. The process is suited to manufacture BAX 855 in large scale and showed a good batch to batch consistency, ensuring an equivalent product quality for each batch. BAX 855 has a specific activity similar to that of rFVIII in ADVATE™ and PEGylation degrees in the range of 2 to 3 mol PEG / mol rFVIII. SDS-PAGE and Western blot analysis of BAX 855 confirm PEGylation and demonstrate an increase in the molecular weight of the various FVIII domains.

In comparison to ADVATE™ the functional properties of BAX 855 were fully retained except for binding to LRP, indicating that PEGylation did not have an impact on the functional properties of rFVIII. The latter might explain why BAX 855 shows prolonged survival in the circulation of hemophilic species and patients with hemophilia A than ADVATE™.
CR21

3-Year Results From SPINART: Prolonged Reduction of Bleeding With Prophylaxis Using Bayer’s Sucrose-Formulated Recombinant Factor VIII

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Objective: In the 3-year SPINART study, routine prophylaxis and on-demand treatment were compared in adults with severe hemophilia A. We report final SPINART efficacy and safety results after 3 study years.

Methods: The open-label, randomized, controlled, parallel-group, multinational SPINART study enrolled males aged 12–50 years with severe hemophilia A who had ≥150 exposure days with any factor VIII (FVIII) product, no inhibitors, no prophylaxis for >12 consecutive months in the past 5 years, and 6–24 documented bleeding events or treatments in the previous 6 months. All patients were treated with Bayer’s sucrose-formulated recombinant FVIII (rFVIII-FS), either on demand or as prophylaxis (25 IU/kg 3 times weekly, with dose escalation by 5 IU/kg permitted once per year). The primary efficacy endpoint, bleeding frequency (number of all bleeding episodes at 1 year), has been previously reported. Endpoints reported here are total and annualized numbers of all bleeding episodes, joint bleeding episodes, spontaneous bleeding episodes, and trauma-related bleeding episodes. Between-group comparisons of bleeding frequency were made within the framework of a negative binomial regression model to account for different follow-up times of patients who discontinued prematurely, with stratification variables (presence of target joints at baseline, number of previous bleeding episodes at baseline) included in the model. Safety variables included adverse events (AEs), serious AEs, and inhibitor development.

Summary: 84 patients (42 prophylaxis, 42 on demand) comprised the intent-to-treat population. The total number of all bleeding episodes during the 3-year study was significantly lower with prophylaxis versus on demand (median, 2.0 vs 96.5, respectively; P<0.0001). Annualized number of all bleeding episodes (median [quartile 1; quartile 3], 0.7 [0; 1.6] vs 37.4 [24.1; 52.6]), total joint bleeding episodes (median, 1.0 vs 67.0), and joint bleeding episodes per year (median, 0.3 vs 27.3) were all lower with prophylaxis versus on demand. The numbers of spontaneous and trauma-related bleeding episodes were also lower with prophylaxis versus on demand. Observed AEs were consistent with the established rFVIII-FS safety profile. No patient developed inhibitors.

Conclusions: Long-term prophylaxis with Bayer’s rFVIII-FS is efficacious in decreasing bleeding episodes, including joint bleeding episodes, in adults with severe hemophilia A. 75% of prophylaxis patients had <2 bleeding episodes per year during the 3-year study. No inhibitors were reported.
Dosing Routines and Bleeding Rates Before and Following Treatment with rFVIIIFc in the A-LONG Clinical Study

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Objective: Recombinant factor VIII Fc fusion protein (rFVIIIFc) uses a natural pathway to extend the half-life of FVIII. In the phase 3, international A-LONG trial (N=165), rFVIIIFc was shown to have an extended half-life (19.0 hours, geometric mean) compared with recombinant FVIII (rFVIII; 12.4 hours); bleeding rates were low with rFVIIIFc and no confirmed inhibitors were observed. Here we examine the relationship between A-LONG subjects’ self-reported pre-study FVIII routines and on-study rFVIIIFc routines to give health care providers data that may inform treatment decisions.

Methods: Subjects in this analysis (n=80) were ≥12 years of age, had severe hemophilia A (<1% endogenous FVIII activity), and were treated ≥6 months in the individualized prophylaxis arm (starting dose 25 IU/kg rFVIIIFc on day 1 and 50 IU/kg on day 4; dose and/or dosing interval adjusted to maintain trough levels of 1-3%). Self-reported pre-study FVIII schedule and dose, weekly factor use, and bleeding rates were compared with corresponding parameters for rFVIIIFc during the last 3 months on-study. Population pharmacokinetic models, developed using pharmacokinetic data from subjects in the phase 1/2a and 3 clinical trials of rFVIIIFc, enabled simulation of different doses and dose intervals and were used to predict the proportion of patients with FVIII troughs ≥1% for a given dosing routine.

Summary: The most common pre-study dosing interval was 3 times per week (n=65). There was a decrease in number of prophylactic infusions used per week with rFVIIIFc on-study in 99% (79/80) of subjects. Median pre-study FVIII and on-study rFVIIIFc weekly factor use were comparable: 78.0 and 79.2 IU/kg/week, respectively. The median annualized bleeding rate was reduced from 6.0 pre-study to 0.0 on-study with rFVIIIFc (P <0.001). Population pharmacokinetic simulations showed that a greater proportion of subjects are predicted to maintain a trough level ≥1% with rFVIIIFc compared with rFVIII for each dosing routine evaluated (Table). A US subject subgroup analysis (n=33) showed similar trends towards reduction of infusion frequency and low bleeding rates.

Conclusion: Compared with their self-reported pre-study prophylaxis routine, subjects receiving rFVIIIFc prophylaxis had fewer weekly infusions and lower bleeding rates with similar FVIII weekly factor use. The data suggest that patients may be empirically converted from rFVIII prophylaxis to rFVIIIFc prophylaxis using their current FVIII routine as a guide, without loss of clinical efficacy or the need for extensive individual pharmacokinetic analysis.
A Prospective Case-Control Study of Bleeding Phenotype in Hemophilia A Carriers

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Objective: Hemophilia A carriers have historically been thought to demonstrate normal hemostasis. Recent data demonstrates that despite normal factor VIII ((FVIII) activity (>0.50 IU/mL) Hemophilia A carriers demonstrate an increased bleeding tendency. To better define the extent bleeding symptoms in Hemophilia A carriers, we have tested the hypothesis that adult obligate Hemophilia carriers have an increase in clinically relevant bleeding symptoms, as measured by validated quantitative assessment tools, when compared to a control population.

Methods: A cross sectional, case-control study was performed comparing obligate Hemophilia A carriers to normal controls. Women were excluded from the study due to a personal history of known bleeding disorder, inherited or acquired thrombophilia, pregnancy, or autoimmune disorder. Questionnaire assessment included a general bleeding questionnaire, modified Tosetto bleeding score and Pictorial Bleeding Assessment Chart (PBAC). Laboratory assessment included complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen activity, FVIII activity (FVIII:C), von Willebrand factor antigen level, ristocetin cofactor, platelet function analyser-100™ (PFA-100) and ABO blood type. Descriptive (frequencies, mean, median, maximum and minimum values) and comparison (Chi-Square and Mann-Whitney U) analysis was performed.

Summary: 87 women were included, 44 Hemophilia A carriers and 43 controls. Age was similar between the two groups; the median age was 36.7 years (24.5 – 59.6), as were additional demographic features. Laboratory results demonstrated a statistically significant difference in FVIII:C between the two groups (77 versus 138%, p value < 0.001). Additional assessment for hemostatic abnormalities was non-concerning for both groups. Carriers reported a higher history of bleeding events (43.6 versus 7.3%, p value < 0.001). Modified Tosetto bleeding scores were higher in carriers (5 versus 1, p value < 0.001); carriers demonstrated increased post-surgical bleeding (48.3 versus 9.1%, p value = 0.001) and post-partum hemorrhage (30.8 versus 9.8%, p value = 0.018). Carriers demonstrated significantly higher PBAC scores (423 versus 182.5, p value = 0.018), heavier menses (72.7 versus 32.3%, p value = 0.001), and increased OCP use as a consequence of heavy menses (488.5 versus 20.5%, p value = 0.023).

Discussion: Our study demonstrates that Hemophilia A carriers exhibit increased bleeding symptoms when compared to controls. Our assessment utilized two validated quantitative assessment tools, both of which demonstrated higher scores in Hemophilia A carriers. Carriers demonstrated increased bleeding events that resulted in increased medical and surgical intervention. Further studies are necessary to fully understand the bleeding phenotype in this population and optimal management techniques.
Extended-interval Dosing with rFIXFc Is Associated With Low Bleeding Rates and a Reduction in Weekly Factor Use

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Objective: Recombinant factor IX Fc fusion protein (rFIXFc) is the first FIX product with a prolonged half-life approved in adults and children with hemophilia B for control of bleeding episodes, prophylaxis, and perioperative management. In the phase 3 B-LONG trial (N=123), rFIXFc was shown to have a prolonged half-life (82.1 hours) and time to 1% (11.2 days [50 IU/kg dose]) compared with rFIX (half-life, 33.8 hours; time to 1%, 5.1 days [50 IU/kg dose]); bleeding rates were low with rFIXFc and no inhibitors were observed. Here we examine the relationship between B-LONG subjects' pre-study FIX and on-study rFIXFc prophylaxis routines.

Methods: Subjects in this analysis (n=26) were ≥12 years of age, had severe hemophilia B (≤2% endogenous FIX), were on pre-study prophylaxis, and were treated ≥6 months in the weekly prophylaxis arm (starting dose 50 IU/kg rFIXFc every 7 days; dose adjusted to maintain trough levels of 1-3%, or as clinically indicated). Patient-reported pre-study FIX schedule and dose, weekly factor use, and bleeding rates were compared with corresponding parameters for rFIXFc during the last 3 months on-study. Population pharmacokinetic models, developed using pharmacokinetic data from subjects in the phase 1/2 and 3 trials of rFIXFc, enabled modelling of different doses and dose intervals and were used to predict time to 1% and proportion of patients with FIX troughs ≥1%.

Summary: The most common pre-study dosing interval was twice weekly (73%). Median weekly FIX use decreased by 52% from 80 IU/kg FIX pre-study to 39 IU/kg rFIXFc (P<0.0001). The annualized bleeding rate was reduced from 5.5 pre-study to 2.9 on-study with rFIXFc (P=0.047). A US subject (n=7) subgroup analysis showed similar trends towards reductions in FIX consumption with low bleeding rates upon switching to rFIXFc. The figure demonstrates the higher trough levels predicted with rFIXFc compared with rFIX for 50 IU/kg once-weekly dosing. Further population pharmacokinetic modelling predicted that 95% of individuals receiving 50 IU/kg rFIXFc once-weekly would have FIX levels that do not dip below 1% at any time, while a rFIX routine of 50 IU/kg twice-weekly would be needed to keep FIX levels above 1% in a similar proportion of individuals.

Conclusion: Compared with their pre-study prophylaxis regimen, subjects on once-weekly
Safety of BAX 855, a Polyethylene Glycol (PEG) Conjugated Full-Length Recombinant Factor VIII Product

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Objectives: Biopharmaceuticals are an emerging branch of therapeutic agents. Their short half-life, rapid elimination and ability to induce a specific immune response, however, may impair their applicability. These disadvantages have been overcome by chemical modification with polyethylene glycol (PEG), which has enhanced the PK and safety of several marketed proteins since the 1990s. PEGylation uses metabolically stable PEG polymers, often with a molecular size of 5-60 kDa.

PEGylated rFVIII candidates include PEG-protein-conjugates with a minimal amount of PEG attached to the protein. Baxter and Nektar are developing BAX 855, a PEGylated full-length recombinant (r) FVIII based on the FVIII molecule used for Baxter’s licensed rFVIII (ADVATE). Due to the high potency of FVIII, the absolute amount of conjugated PEG applied with PEG-FVIII is within the range of µg per kg body weight and week. PEGylation was optimized to retain functionality of the FVIII molecule and improve its pharmacokinetic properties.

PEGs ≤20 kDa are rapidly cleared mainly via the kidneys and excreted into urine. Over time, the protein portion of the PEG-FVIII conjugate is degraded by proteolysis leaving a PEG portion which is rapidly eliminated.

Methods: Preclinical safety, toxicokinetics and formation of anti-product antibodies were assessed in rats dosed intravenously at 350 or 700U/kg BAX 855 every other day, and in macaques receiving 150, 350 or 700U/kg BAX 855 every five days, for 28 days.

Like other non-degradable entities, physiological clearance mechanisms of PEG may include liver macrophage uptake. Clearance by macrophages in mammals has been reported to cause vacuolization at high cumulative doses. Generally, vacuoles were shown to consistently resolve over time, with no cellular damage, inflammation at the vacuolization site or functional deficits of affected tissues, and are therefore regarded to not affect the safety of PEGylated therapeutics.

Summary: No systemic adverse effects or vacuolizations were observed after 28-day intravenous administration with BAX 855. Therefore, 700 U/kg was considered the no observed adverse effect level in these studies.

Conclusions: This favorable safety profile provides the basis for proceeding with human trials.
A Study Evaluating the Impact of myCubixx, an Innovative Factor Inventory Management and Storage System, with Selected Outcomes on People with Hemophilia A

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Objectives: Home treatment has advanced the care of patients in the management of their hemophilia. Currently, patients/caregivers must be in close communication with their pharmacy to ensure adequate factor supply. In addition to keeping track of factor supply, patients are required to maintain an infusion/bleed log to optimally manage their bleeding condition. Studies examining patient adherence to prophylaxis treatment regimen and maintaining an infusion log suggest that adherence to these aspects of treatment are sub-optimal. The myCubixx system, a refrigerated storage device, is an innovative factor inventory management, storage and infusion/bleed logging system that utilizes radio frequency identification (RFID) technology to automatically identify, log and transfer data to key clinical and pharmacy stakeholders in the hemophilia community. To demonstrate the utility of this new technology, a pilot study was developed to evaluate the usability, satisfaction and impact on selected patient outcomes of the myCubixx system in hemophilia A patients.

Methods: This study is a prospective, observational, non-controlled, 6-month study to evaluate the use of the myCubixx system for up to 110 patients with hemophilia A. In addition to assessing overall usability of the system, this study also examines changes in access to treatment, adherence to prescribed treatment, maintenance of an infusion/bleed log, and satisfaction, before and after 6 months of utilizing the myCubixx system. FVIII utilization during the study period will also be compared to the 6 months prior to receiving the myCubixx system. Each pharmacy will also report their level of satisfaction with various aspects of myCubixx.

Summary: Patients from 2 specialty pharmacy practice organizations and 1 hemophilia treatment center are currently being recruited for this study.

Conclusion: This study explores the use of technology to facilitate factor inventory management and automatic logging of bleed/infusion to support the optimal management of persons with hemophilia.
Study Design of a Phase 3, Open-Label Trial of the Safety and Efficacy of Recombinant Factor VIII Fc Fusion Protein for the Prevention and Treatment of Bleeding Episodes in Previously Untreated Patients With Severe Hemophilia A

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Objective: The safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) for the prevention and treatment of bleeding episodes in previously-treated patients (PTPs) with severe hemophilia A was demonstrated in the phase 3 A-LONG study; no A-LONG subjects developed inhibitors. The risk of inhibitors with FVIII in previously-untreated patients (PUPs) has been documented to be higher than in PTPs, ~30% vs 2–3 per 1,000 patient/years, respectively. Thus, it is important to assess the risk of inhibitor formation with rFVIIIFc in PUPs. In addition, immune tolerance induction (ITI) has been used successfully in some patients developing inhibitors against FVIII products. This report describes the study design to evaluate the safety and efficacy of rFVIIIFc for the prevention and treatment of bleeding in PUPs with severe hemophilia A.

Methods: In this open-label, single-arm, multicenter, phase 3 study, eligible subjects are males aged <18 years and weighing ≥3.5 kg, with severe hemophilia A (<1 IU/dL FVIII activity). The primary endpoint is occurrence of inhibitor development. Selected secondary endpoints include number of bleeding episodes, number of infusions and dose per infusion required to resolve a bleeding episode, rFVIIIFc consumption, and response to ITI. Approximately 125 subjects will be dosed. The initial prophylaxis regimen may be chosen by the investigator (dose: 20–80 IU/kg), with adjustments made based upon pharmacokinetics and bleeding. Dosing for treatment of bleeding will target ~40%–100% peak FVIII activity. ITI is allowed for subjects developing an inhibitor after exposure to rFVIIIFc; rFVIIIFc will be dosed at 200 IU/kg/day for ITI (regimen based upon high-dose treatment recently used in the International Immune Tolerance study of other FVIII products). Successful immune tolerance is defined as negative inhibitor titers on 2 consecutive tests, with an incremental recovery ≥66% of expected value (based on individual’s baseline FVIII recovery assessment) and a half-life of ≥6 hours.

Summary: At study completion, ≥100 subjects will have reached ≥100 rFVIIIFc exposure days. This prospective study of rFVIIIFc in PUPs will be reflective of real-world conditions due to the dosing flexibility allowed to investigators.

Conclusions: Results from this study, including the incidence of inhibitor formation and the use of ITI in this patient population, will broaden the knowledge base from which to best treat patients. Publication of study designs such as this is important for increasing awareness among researchers, and advancing clinical trial design.
ACS05

Study Design of a Phase 3, Open-Label Trial of the Safety and Efficacy of Recombinant Factor IX Fc Fusion Protein for the Prevention and Treatment of Bleeding Episodes in Previously Untreated Patients With Severe Hemophilia B

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Objective: In patients with hemophilia B using factor replacement therapy, inhibitor development may be associated with serious allergic reactions and hinder effective treatment of bleeding. Previously-untreated patients (PUPs) are particularly at risk; therefore, it is important to assess inhibitor formation in PUPs treated with new FIX preparations. Recombinant factor IX Fc fusion protein (rFIXFc), approved in the US, was demonstrated to be safe and efficacious for the prevention and treatment of bleeding episodes in previously-treated patients aged ≥12 years with severe hemophilia B in the phase 3 B-LONG study. No B-LONG subjects developed inhibitors. This report describes the design of a study that evaluates the safety and efficacy of rFIXFc for the prevention and treatment of bleeding episodes in PUPs with severe hemophilia B.

Methods: Subjects eligible for this open-label, single-arm, multicenter, phase 3 study are males aged <18 years and weighing ≥3.5 kg, with moderately-severe to severe hemophilia B (≤2 IU/dL FIX activity; target enrollment: ~60 subjects). The primary endpoint is occurrence of inhibitor development. Secondary endpoints include number of bleeding episodes, number of infusions and dose per infusion required to resolve a bleeding episode, and rFIXFc consumption. Where commercially available, subjects may have had 1–3 prior rFIXFc infusions for bleed treatment. The recommended prophylaxis regimen is 50 IU/kg weekly; however, actual dosing is investigator-determined, with adjustments made based on pharmacokinetics and bleeding frequency. The target for dosing for treatment of bleeding is 25%–100% FIX activity, depending on severity. Scheduled inhibitor tests are at 5, 10, 15, 20, 50, and 100 exposure days. Immune tolerance induction (ITI) is allowed for subjects developing an inhibitor (investigator-chosen rFIXFc dosing regimen). Successful immune tolerance is defined as negative inhibitor titers on 2 consecutive tests and incremental recovery ≥66% of expected value (based on individual’s baseline FIX recovery assessment).

Summary: At study completion, ≥40 subjects will have reached ≥100 rFIXFc exposure days. Because limited prior exposure to study drug is allowed and investigators have dosing flexibility, this study design parallels real-world conditions.

Conclusions: Because of its associated complications, inhibitor development is a serious concern for PUPs. The results of this study, the first of a long-acting approved FIX product in PUPs, will provide important information regarding rFIXFc efficacy and risk of inhibitor development in this population. Publication of such study designs increases researchers’ awareness and can facilitate advancement of clinical trial design.
Gingival Bleeding and Oral Hygiene of Women with von Willebrand Disease

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Objectives: To determine the relationship between von Willebrand disease (vWD), dental plaque, and gingival bleeding in women with vWD and to determine the oral hygiene habits and dental care utilization in women with vWD.

Methods: Consenting adult women with vWD (n=40) will have been recruited for this study. A questionnaire was given with 34 items covering topics such as dental care utilization, oral health quality of life, and oral hygiene habits. A brief oral examination was performed on each subject to assess which surfaces of the six Ramfjord teeth presented with dental plaque, and which surfaces bled upon flossing. Information was also gathered about each subject’s medical history, including the type of vWD, severity, and last von Willebrand factor levels.

Summary: Data is still being collected for this study. Data collection will be completed on June 30. The data gathered so far shows that the majority of women who participated in this study have a high plaque score, yet minimal bleeding with flossing, when a gentle c-wrap flossing technique was performed.

Conclusions: Results of this study are expected to show that the bleeding disorder has minimal effect on the amount of gingival bleeding that occurs with a c-wrap flossing technique. It’s possible that conclusions may be made that correct flossing technique can be performed in a manner that does not, in itself, cause gingival bleeding. This can perhaps assist in increasing the amount of people with bleeding disorders that floss, diminishing the fear that many people with bleeding disorders have of causing excessive bleeding with flossing.
Safety and Effectiveness of Anti Inhibitor Coagulation Complex (AICC) in Routine Clinical Management: a Post-Authorization Safety Study (PASS)

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Objective: The development of inhibitors is the most serious complication in the treatment of hemophilia and their management remains challenging. Activated prothrombin complex concentrate, AICC [FEIBA], has been a key therapeutic option for the prevention and management of bleedings in individuals with hemophilia and inhibitors for over three decades and has been approved in more than 60 countries with a prophylaxis indication in more than 40, including the US. In 2008, a second, independent virus removal/inactivation step (35 nm nanofiltration) was added to the vapor heat treatment as a part the manufacturing process of FEIBA.

The FEIBA NF PASS was developed to prospectively monitor, in routine practice, the safety and effectiveness of FEIBA in the treatment of subjects with hemophilia and inhibitors. This prospective, observational surveillance program documented adverse events (AEs) and hemostatic effectiveness of FEIBA. An additional aim was to identify real-world treatment patterns for managing hemophilia with inhibitors with regular FEIBA prophylactic dosing.

Methods: An electronic data collection system was utilized to monitor the safety and effectiveness of FEIBA NF in subjects for 12 ± 2 months. Informed consent was obtained for all subjects and the study was conducted according to the Declaration of Helsinki and its amendments.

Summary: The study was conducted in 40 study sites in 8 countries in Europe (EU), as well as in the US and Canada. The last subject out in the study was in October 2013 and data base lock occurred in February 2014. Of the 92 subjects who were screened, 81 were treated, and 75 completed the study. At enrollment, 85.2% of subjects were diagnosed with congenital hemophilia A, 12.3% with acquired hemophilia A (AHA) and 2.5% with congenital hemophilia B. At baseline, FEIBA was prescribed to 45 subjects as regular prophylaxis, and 36 were prescribed on-demand treatment for bleeding episodes. Overall hemostatic efficacy rating by the physician was excellent or good for 90.1% of subjects. Treatment-related serious AEs reported were hemarthrosis in one subject, deep venous thrombosis and thrombophlebitis superficial in a second, and device-related infection in the third. All were associated with on demand treatment.

Conclusions: The FEIBA PASS has provided an opportunity to collect data for individuals with hemophilia and inhibitors during routine care, and serves as an invaluable tool for documenting the safety and effectiveness in a variety of clinical settings including prophylaxis, surgery and bleed management during immune tolerance induction (ITI).
Bleeding Risk for the Active Person with Hemophilia: A Comparison of Factor VIII Treatment Regimens

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Background: Bleeding risk during physical activities for persons with hemophilia has been shown to be reduced with adequate factor levels (Broderick 2012). With extended half-life Factor VIII and IX products offering opportunities for longer intervals between infusions, it is important to understand the bleeding risk for patients who have an active lifestyle.

Objective: To evaluate the relative risk of bleeding between prophylaxis schedules using recombinant Factor VIII (rFVIII) vs. rFVIII-Fc among different patient physical activity profiles

Methods: A mathematical model based on the literature was developed. Factor levels were estimated using a one-compartment pharmacokinetic model (Collins 2010). Half-life and incremental recovery values were taken from a crossover study of rFVIII and rFVIII-Fc (Mahlangu 2014). Five prophylaxis regimens were evaluated: two common to rFVIII (30IU/kg every other day (EOD); 35IU/kg 3x/week) and three studied in the rFVIII-Fc pivotal trial (2x/week: 25IU/kg covering 3 days and 50IU/kg covering 4 days per week; 50IU/kg every 5 days; 65IU/kg 1x/week). Activities such as swimming, running and wrestling were classified as Type 1, Type 2, and Type 3 in Broderick 2012, derived from the NHF “Playing It Safe Brochure” (Anderson 2005). Risk of bleeding by activity category and factor level at time of activity was calculated using the odds ratio values from Broderick 2012. Three hypothetical patient activity profiles were evaluated: Consistently Active (M-Sun: Type 2 activities), Regular Exerciser (M-F: Type 2 activities, Sat-Sun: Type 1 activities), and Weekend Warrior (TThSun: Type 1 activities, MWF: Type 2 activities, Sat: Type 3 activities). For each regimen, the infusion schedule with the lowest bleeding risk for each patient activity profile was selected. The relative bleeding risk vs. the best prophylaxis regimen was estimated and compared for the activity profiles.

Results: rFVIII 30IU/kg EOD and 35IU/kg 3x/week achieved the two lowest bleeding risk for all three patient activity profiles. Compared to rFVIII every other day, bleeding risk was increased by 20%, 25% and 46% for the Consistently Active patient prescribed rFVIII-Fc twice per week, every 5 days, and 1x/week, respectively. Compared to rFVIII 3x/week, bleeding risk was increased by 20%, 30% and 44% for the Regular Exerciser and by 21%, 32% and 45% for the Weekend Warrior prescribed rFVIII-Fc 2x/week, every 5 days, and 1x/week, respectively.

Conclusion: This model suggests that active patients characterized with the above profiles may have reduced bleeding risk with rFVIII compared to extended half-life FVIII dosing regimens evaluated in this analysis.
The Impact of Reduced Treatment Frequency: Qualitative Evaluation of Adherence and Outcomes in Chronic Disease Management

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Background: Adherence is a key factor of chronic disease management that influences clinical outcomes. However, as patient adherence is a behavioral outcome defined by attributes and interactions between patient and treatment characteristics, mechanisms to improve patient adherence are multifactorial. To validate the impact of reduced treatment frequency on patient adherence and clinical outcomes, real-world comparative data is needed. By analyzing the impact of reducing treatment frequency in other chronic, specialty disease areas, insights can be applied to extended half-life products in hemophilia.

Objective: To Conduct a literature search and qualitative review assessing if treatment frequency has been linked to adherence and outcomes in chronic disease states with injectable biologics.

Methods: A qualitative search was conducted using PubMed to identify evidence for injectable therapies with reduced administration frequency from 2000-2014. Keyword search terms included: dosage forms, administration and dosage, adherence, compliance, injectable drugs, clinical outcomes. Assessment of whether less frequent dosing has been linked to adherence and clinical outcomes was provided.

Results: The search yielded 58 publications. Articles on long-acting anti-psychotics for schizophrenia and bipolar disorder represent the majority (n=41), followed by interferon beta for multiple sclerosis (n=5). The remaining articles covered the following chronic disease areas: insulin for diabetes, anti-TNFs for immunological disorders, naltrexone for opioid and alcohol dependency, antithrombotic agents for thromboprophylaxis, or were not disease specific. This review focuses on the first two disease areas which had the most robust real-world evidence. Summaries of results measuring adherence and outcomes are provided.

Schizophrenia and bipolar disorder: (n=36) Observational studies and a recent systematic review comparing long-acting injection with daily oral therapy in schizophrenia patients indicates that longer-acting therapies have been associated with better adherence and outcomes, specifically defined as a reduction in the relative risk of relapse by 30%.

Multiple sclerosis: (n=5) Higher adherence for once-weekly intramuscular injection (Avonex) compared to subcutaneous injection (Rebif) 3x/weekly was documented in a prospective longitudinal adherence study but did not include assessment of clinical outcomes. However, in a drug class review pooling data from four RCTs, once-weekly administration was found to be less efficacious than 3x/weekly subcutaneous injection in relapse outcomes.

Conclusion: Patient differences and disease complexity suggest that therapeutic enhancements providing less frequent administration may have positive effects in only some disease states. Evidence supporting the proposal of less frequent treatment administration resulting in improved adherence and outcomes will need to be demonstrated for extended half-life products in hemophilia A and B.
The expression of codon-optimized blood coagulation factor VIII using a lentiviral system

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Methods: Based on a lentiviral vector, we generated two constructs of the BDD-FVIII cDNA, wild-type (WT) and codon-optimized (CO). Three cell types, BHK-M, SK-Hep-1 and CHO were transduced with the constructs and tested for FVIII expression. Upon testing, the CHO cells were subjected to additional rounds of transduction/clone selection for the highest levels of FVIII expression. For the lab-scale FVIII production, the cells were cultivated as adherent cultures and the media was collected daily. The secreted FVIII was analyzed by Western-blotting, ELISA and one-stage clotting assay. The results were compared to those of a licensed BDD-FVIII used as standard.

Summary: In BHK-M cells, both WT and CO variants of BDD-FVIII were secreted in a single-chain (unprocessed) form. In SK-Hep-1 and CHO cell lines, both variants of FVIII were secreted fully processed, i.e. in heterodimers of heavy (BDD) and light chains similar to those of plasma-derived FVIII. From the CHO cells, several clonal lines secreting WT and CO variants of BDD-FVIII were obtained with yields of 0.1-0.7 mg/L/24 h and 0.4-1.2 mg/L/24 h, respectively. Two clonal lines, each for WT and CO variants of BDD-FVIII, demonstrated stable levels of secretion for more than 20 days of cultivation in the same flasks. The functionality of both FVIII forms was confirmed by assays of FVIII activity in the media with similar specific activities.

Conclusions: Our data indicate that high levels of FVIII expression can be achieved using codon-optimization in a lentivirus-based platform. Our approach is an alternative to the one based on the amplification of the FVIII gene using dihydrofolate reductase/ methotrexate selection. In addition, by using adherent cells we bypassed the need for specialized equipment (rollers, shakers or bioreactors), and made it possible to obtain sufficient quantities of BDD-FVIII for research. Potentially, our approach can also be used to improve commercial manufacture of FVIII products.
Using oral history for patient education: The Gift of Experience II: Conversations with Parents about Hemophilia

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Introduction and Objectives: We previously used oral history methods to capture the experience of older men with hemophilia. In a follow up project, we have developed, The Gift of Experience II: Conversations with Parents about Hemophilia (GOE), a book that documents parents' experiences raising a child with hemophilia A or B from birth to age six. Their experiences provide insight into the emotional, financial, medical, social and spiritual challenges that families confront. The intent is to normalize parents' feelings and reactions and offer hope that they will manage what might seem overwhelming at first.

Materials and Methods: Eighteen parents agreed to be interviewed by one of three interviewers. The interviewees all had children with hemophilia A or B between the ages of four and twelve and received treatment at the Boston Hemophilia Center. The interviews were taped and transcribed. The interviewer focused on the ways in which parents reacted and adjusted to the diagnosis, learned how to medically manage the disease, coped with the effects on the marriage and family, managed decisions about childcare and school, explained hemophilia to their young child, and handled financial challenges. Quotations were extracted from the oral history transcripts. Interviewees had editorial and approval rights for the quotations. All participants signed consent.

Results: The GOE is a collection of quotations extracted from the oral history transcripts. The book succeeds in offering insight, a practical support and a guiding light to families whose child is newly diagnosed with hemophilia. It covers pertinent issues that parents face in raising a child from birth to six. It includes a glossary of terms for new families

Conclusion: The GOE concentrates on helping families learn from other parents' experiences what challenges lay ahead and how to manage these challenges. With the benefit of knowing others' experiences, families have a blueprint for normalizing their own thoughts and feelings and anticipating and resolving challenges. This promotes a healthy adjustment for families living with a child who has hemophilia. For those families who are not lucky enough to have local community support, this book functions as a literary support group.
New insights from modeling FVIII Kinetics of Native vs. Extended Half-life FVIII Products - Comparing FVIII Coverage under Various Dosing Scenarios

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Introduction: Extended half-life factor VIII (FVIII) products currently in development require a careful evaluation of dosing options given that the pharmacokinetics of weekly FVIII levels, including FVIII peak and trough levels, have been shown to play a role in bleeding occurrence.

Methods: Pharmacokinetic (PK) modeling was conducted using published literature and clinical trial data. Published population PK models for recombinant full length DNA, plasma and albumin free FVIII (octocog alfa, rAHF-PFM) and recombinant B-domain-deleted FVIII Fc fusion product (efraloctocog alfa, rFVIIIFc) were used. All calculations were performed assuming linear pharmacokinetics. Dosing frequencies assessed were every 2 days with rAHF-PFM and every 3, 4, 5 or 7 days with rFVIIIFc. Dosages assessed were 30 IU/kg of rAHF-PFM and 30, 40, 50 or 65 IU/kg of rFVIIIFc. Results were generated for a hypothetical patient aged 30 years, with 70 kg body weight, exhibiting a VWF level of 118 IU/dL and a hematocrit of 45%. Time spent below 1% and 3% per week and time spent above 10% and 20% per week were assessed and compared for each scenario.

Summary: Compared to 30 IU/kg of rAHF-PFM dosed every other day, a patient on rFVIIIFc would spend more time per week below 1% FVIII level when dosed every 5th day up to 50 IU/kg and when dosed every 7th day at any dose within the range tested. Moreover, even when increasing the dosing frequency to 30 IU/kg of rFVIIIFc every 3rd day, or when dosing rFVIIIFc up to 65 IU/Kg every 4th, 5th and 7th day the patient’s plasma FVIII level will drop below 3%. When looking at time per week spent above higher FVIII levels, the model patient would spend more time above 10% when dosed with rAHF-PFM at 30 IU/kg every second day as compared to rFVIIIFc dosed every 3 days at 30IU/kg, and every 4, 5 and 7 days at any dose within the range tested (≤65 IU/kg). Likewise, this patient will also spend more time above 20% with rAHF-PFM every other day than with rFVIIIFc dosed every 4 days at 40 IU/kg and every 5 days at 50 IU/kg and every 7 days at 65 IU/Kg.

Conclusion: These data indicate that choice and optimal dosing of FVIII products require a better understanding of individual pharmacokinetics in order to avoid that patients would spend extended time at levels insufficient to protect them from bleeding, particularly subjects with a more active lifestyle.
The use of combination therapy with plasma derived and recombinant factor VIII in patients with hemophilia A: a single institution experience

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Objective: Factor VIII (fVIII) infusions are the treatment of choice for hemophilia A. The majority of pediatric patients in the US are treated with recombinant fVIII (rfVIII) which does not contain von Willebrand Factor (VWF). Plasma derived fVIII (pdfVIII) products that contain varying amounts of VWF are also approved to treat patients with hemophilia, and studies have shown an association between VWF level and fVIII half-life. In our patient population we had several patients for whom a switch to a VWF containing pdfVIII product was considered. However, the volume of infusion of the pdfVIII product was a road block to treatment for these children. Here we report our single institution experience using combined therapy with rfVIII and pdfVIII mixed in a single syringe.

Methods: The electronic charts of pediatric patients with hemophilia A at the Emory University/Children’s Healthcare of Atlanta were reviewed as part of IRB approved studies for patients with hemophilia A or hemophilia A with inhibitors. Baseline patient characteristics, reasons for product change, compliance to therapy, and need for central line placement before and after product change were collected.

Summary: We identified 5 patients that were treated with combined therapy with rfVIII and pdfVIII. Three patients with moderate to severe hemophilia and no active inhibitors were switched from rfVIII to combination therapy. Two of these patients had low VWF levels with risotocitin cofactor activities of 35% and 49% and shortened half-life. The other had a normal level of 80% but poor clinical response to rfVIII. All patients were initially switched to pdfVIII but all 3 had difficulty peripherally infusing the large volume. In addition one patient had trough VWF levels >400%. All 3 patients were switched to combination therapy with pdfVIII and their previous rfVIII product. One patient who had previously needed a CVAD for rfVIII dosing had a new CVAD placed for continued access issues. The other two patients were teenagers with severe hemophilia A and high titer inhibitors. Both were partially tolerized and had better laboratory response to pdfVIII but neither could infuse the large volume peripherally. Both patients were able to infuse the combined therapy peripherally, however, one had a temporary PICC line placed due to increased infusion frequency around a bleed.

Conclusions: Combination therapy with rfVIII and pdfVIII was tolerated by all 5 patients. Lower infusion volumes resulted in increased rates of peripheral infusions when compared to pd-fVIII alone.
Ongoing Prospective ADVATE Immune Tolerance Induction Registry (PAIR) Continues to Demonstrate Success Rates Consistent with Published Literature

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Objectives: PAIR is an ongoing, global, non-interventional, post-authorization safety surveillance designed to collect information on ADVATE safety and effectiveness in immune tolerance induction (ITI) therapy in routine practice.

Methods: From July, 2007 to April, 2011, individuals with hemophilia A and inhibitors were enrolled in 10 countries. The primary objective is to assess the incidence of adverse events (AEs) related to ADVATE during ITI therapy. Secondary objectives are incidence of central venous access device (CVAD)-related complications, and success rates of ITI therapy. Maximum observation period for ITI is 33 months plus a 12 month follow-up.

Summary: As of April 1, 2014, 36 of 44 subjects (81.8%) completed ITI therapy, 28 (63.6%) of which completed the 12 month follow-up. Six subjects withdrew prior to completing ITI therapy. Dosing regimens were: ≥200 IU/kg/day (n=4, 9.1%); 131-199 IU/kg/day (n=3, 6.8%); 90-130 IU/kg/day (n=26, 59.1%) and <90 IU/kg/day (n=11, 25.0%). During the observation period, 337 bleeding episodes and 273 AEs were reported for all enrolled subjects (N=44). Of these AEs, 52 (19.0%) were serious and none were considered related, while 15 (5.5%) were non-serious and related. CVAD complications were common; 32 subjects experienced one or more CVAD-related AE such as hospitalization, line infection, line malfunction, line removal, and pain following port-a-cath bleed. Of the subjects that completed ITI, 21 achieved negative titer levels, two experienced a high to low titer conversion, seven failed to achieve negative titer, and six were un-assessable per protocol. After 18 months therapy, Kaplan Meier estimates of success for achievement of first negative titer was 65.4% (asymptotic 95% CI: 48.7-81.5%, n=36) for the completer group. Rates were higher for the per protocol analysis set (72.2%, CI: 54.6-87.5%, n=30), and slightly lower for the full analysis set (63.5%, CI: 48.0-78.7%, n=44).

Conclusions: These interim outcome results are consistent with previous reports from PAIR and other published data on ADVATE in ITI. No new ADVATE related safety issues have been seen. The last two participating subjects will end observation within the next year.
Real World Utilization and Cost of aPCC versus rFVIIa Among Hemophilia Patients with Inhibitors in the US

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Introduction and Objective: Limited information exists in the recent literature capturing real-world utilization and cost of bypassing agents among hemophilic patients with inhibitors in the US. The present study compared the cost of on-demand and prophylaxis treatment between aPCC and rFVIIa among inhibitor patients with severe hemophilia.

Methods: A retrospective analysis of two large US specialty pharmacy databases was conducted using dispensing data over a 28-month period (Jan. 2012 to April 2014). Subjects were included if they had a diagnosis of hemophilia A or B (ICD-9 code 286.0 or 286.1) that was classified as severe and ≥12 months of consecutive prescription claims for only bypassing agents. For patients who switched between bypassing agents or between on-demand (OD) and prophylaxis (P) during the observation period, observations of ≥6 months with consistent prescriptions were selected and analyzed independently. Bypassing agent utilization was annualized and normalized by patient weight (kg). Cost was calculated using 2013 Redbook® US wholesale acquisition costs (aPCC=$1.81/U and rFVIIa=$1.77/µg) and compared by product and regimen using non-parametric statistics.

Results: A total of 78 subjects with 84 observations met the inclusion criteria. Median age was 20 years old (range 2-64) and median time between the first and last prescription filled was 20.5 months. Approximately 34.5% of the subjects were on aPCC (44.8% [OD] and 55.2% [P]) and 40.5% were on rFVIIa (85.3% [OD] and 14.7% [P]). The remaining subjects (25%) were on various combinations of aPCC and rFVIIa. Median annualized utilization for aPCC and rFVIIa was 7,183U/kg (2,186U/kg [OD] and 9,612U/kg [P]) and 13,838µg/kg (9,493µg/kg [OD] and 27,245µg/kg [P]), respectively. Median annualized cost/kg was significantly lower (p=0.0071) among patients treated on-demand with aPCC ($3,956/kg) compared to rFVIIa ($16,801/kg). Similarly, median annualized cost/kg was also significantly lower (p=0.0093) among patients treated prophylactically with aPCC ($17,399/kg) compared to rFVIIa ($48,223/kg). Overall, median annualized cost/kg for on-demand and prophylaxis treatments was 76.5% and 63.9% lower, respectively, with aPCC compared to rFVIIa. Furthermore, there was no significant difference (p =0.6438) in median annualized cost/kg between aPCC prophylaxis and rFVIIa on-demand.

Conclusion: Overall, these data suggest that the annualized treatment cost with aPCC is significantly lower compared to that of rFVIIa for both on-demand and prophylaxis regimens. For each patient treated on-demand or prophylactically with rFVIIa, approximately 3-4 patients could be treated with aPCC at comparable cost. Additionally, the median rFVIIa on-demand patient could be prescribed aPCC prophylactically to reduce bleeding episodes without significant cost implications.
Pain and Arthropathy Impact Quality of Life of Young Adults With Hemophilia (ages 18-30) in the United States: Observations From the Hemophilia Experiences, Results and Opportunities (HERO) Study

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Objective: To assess quality of life, self-reported comorbidities, health-related quality of life (HRQoL), and impact of hemophilia on activities of young adult (YA) patients with hemophilia (PWH).

Methods: Analysis of US YA-PWH respondents (aged 18-30) in the international HERO study conducted in 2010-2011. US respondents were recruited through NHF, Facebook, and e-mail. An independent ethics board approved the US survey.

Summary: Of 189 adult PWH HERO respondents in the United States, 66 were aged 18-30 years, 74 were aged 31-40 years, and 49 were older than 40 years. The median (interquartile range) age of YA-PWH was 26 (22-28), and had hemophilia A (58%), hemophilia B (21%), or hemophilia with inhibitors (21%). Most were Caucasian (77%). Half were on prophylaxis (50%), with the remainder treated on-demand alone (24%) or with occasional short-term prophylaxis (24%). Compared with PWH older than 40 years, YA-PWH less frequently self-reported bone/skeletal/arthritis (41% vs 67%), chronic pain (38% vs 57%), and viral comorbidities (20% vs 65%). On EQ-5D-3L, 62% of YA-PWH reported no difficulties with mobility, 71% no difficulties with usual activities, and 94% no difficulties with self-care. In contrast, 68% reported moderate and 5% extreme pain/discomfort, and 33% reported some/moderate and 8% extreme anxiety/depression. On EQ-5D-VAS, 53% reported VAS scores of 80-90-100 (vs 24% for PWH >40 years). Surprisingly, 89% reported pain interference with daily activities in the past 4 weeks, with 9% reporting it was extreme/a lot. More YA-PWH had pain only with bleeding than PWH older than 40 (42% vs 18%), with 14% citing pain all the time and 39% reporting pain all the time and worse with bleeding. YA-PWH reported seeking psychological treatment in the prior 5 years (26%), frequently related to hemophilia (71%). When asked about specific activities, YA-PWH reported participating in lower-risk (80%), intermediate-risk (61%), and higher-risk activities (27%); older PWH reported 82%, 45%, and 16%, respectively.

Conclusions: YA-PWH in the United States are less likely than older PWH to report arthritis, chronic pain, or viral diseases; yet, HERO results suggest these remain important problems for this age group. Pain appears to be perhaps the most significant; only 11% did not report pain interference in the past 4 weeks, and only 27% reported no pain/discomfort at the time of the survey. Additionally, 33% reported some/moderate depression. The relationship of intermediate- and high-risk activities to the rates of reported pain and arthritis is unclear.
Hemophilia Impacts Relationships and Employment of Young Adults (ages 18-30) in the US Hemophilia Experiences, Results and Opportunities (HERO) Study

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Objective: To assess impact of hemophilia on relationships and employment during the transition to adulthood in young adult (YA) patients with hemophilia (PWH).

Methods: Analysis of US YA-PWH respondents (aged 18-30 years) in the HERO study.

Summary: Of 189 US adult PWH HERO respondents, 66 were aged 18-30 years (median: 26). Most lived in large cities (52%) or suburban areas (29%); 73% reported household income of <$60,000/year. Some (32%) were married or in long-term relationships; 20% lived alone. Negative impact on relationships was reported by 32%; 62% predicted an impact in the future, 62% cited difficulty understanding issues, and 52% worry about supporting a family. Only 9% had children; 77% wanted to have children. Only 45% received genetic counseling from the HTC; of those, 60% felt it was helpful. Most were very/quite satisfied with support of partners/spouses (95%), family (92%), and friends (86%). Negative reactions telling friends were reported by 41%; 59% reported most/all of their friends knew about their hemophilia. Most (78%) were employed with 57% reporting office work. One fifth (20%) reported being disabled, and 14% received disability benefits. The majority (74%) reported negative impact on employment; 39% reported moderate/very large impact. Many (43%) reported current treatment allows them to work in most situations, 37% selected a job based on their needs, 29% were helped to obtain a job, 20% were not hired, and 18% lost a job due to hemophilia. Only 36% received advice from the HTC on work/employment, mostly on what to do if a bleed occurs at work (71%), suitable jobs (67%), when (63%) and what (33%) to tell an employer, and workplace precautions (46%). Fifty-eight percent found the advice helpful. Only 37% reported most/all of their colleagues know about their hemophilia; 38% reported a select few or 1-2 and 26% none. Most were very/quite satisfied with the support of colleagues at work/school (82%). Most YA-PWH (62%) were members of an organization or online (48%) or other (35%) support group.

Conclusions: During the transition to independent adults, YA-PWH are likely planning for family and careers. Many reported negative impacts on relationships and employment, highlighting a need for career counseling. YA-PWH are supported by friends and colleagues, but this may be a limited group. HTCs are an underutilized resource for addressing these issues, with perhaps online peer-support networks playing a larger role during this transition to adulthood and independence.
Treatment, Outcomes, and Access to Care Among Young Adults (ages 18-30) With Hemophilia in the US Hemophilia Experiences, Results and Opportunities (HERO) Study

Angela Lambing, Chris Guelcher, Michelle Witkop, Angela Forsyth, Sarah Hawk, Neil Frick, Randall Curtis, Laureen Kelley, Michelle Rice, David Cooper

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Objective: To assess treatment of young adult (YA) patients with hemophilia (PWH) and issues around access to and use of factor and comprehensive care.

Methods: Analysis of US respondents aged 18-30 years in the international HERO study conducted in 2010-2011.

Summary: Of 189 adult PWH HERO respondents in the United States, 66 were aged 18-30 years. More YA-PWH were on prophylaxis (50%) than on-demand alone (24%) or with occasional short-term prophylaxis (24%). Only 27% used treatment medication exactly as prescribed, with 27% a little less, and 21% varying (sometimes more/less). Twenty-six percent reported issues with access to factor in the prior 5 years due to availability or affordability, with 82% citing financial issues. YA-PWH reported a median of 2 bleeds in the prior month and median (IQR) annual bleed rate of 9.5 (12-22) bleeds. Similar to older adults, 80% of YA-PWH reported that a single joint suffers more bleeds than others; the most common joints reported were the ankle (77%), elbow (26%), and knee (21%). YA-PWH rated perceived disease control (1-10 scale, 10=most control) as median (IQR) 8 (7-9). HTC visit frequency was median (mean) 1 (1.66) per year. Similar to older adults (aged >40 years), 21% of YA-PWH reported difficulty in visiting the HTC. Accessibility was the most common reason (79%)—distance to travel (57%) or time to travel (29%); time constraints were more commonly reported by YA-PWH (57%), including being unable to get time off work (50%). When identifying health care professionals (HCPs) involved in management of their hemophilia, YA-PWH named hematologists (83%), nurses (67%), social workers (48%), counselors/psychologists (30%), and physical therapists (26%). The majority were satisfied with care provided by HCPs. YA-PWH reported being very/somewhat knowledgeable about hemophilia (91%). When looking to the future (pessimistic=1 to optimistic=7), YA-PWH were generally optimistic, with median (IQR) 5 (5-7).

Conclusions: YA-PWH in the United States are more likely to be on prophylaxis than older adults, but less likely to use medication exactly as prescribed. Additional research is warranted to better understand why prescribed regimens are not followed. Despite 50% prophylaxis use, bleeding occurred ~1-2 times/month and YA-PWH reported high perceived disease control. During this period of transition to independence, it is important to note one quarter reported issues around access to treatment and one fifth reported difficulty in visiting the HTC. YA-PWH were satisfied with care, but infrequently reported social workers and physical therapists as part of management.
Addressing patient concerns about product switching in hemophilia A: Evaluating turoctocog alfa data from the guardian™ clinical trial program

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Objective: Patients with hemophilia A are often reluctant to switch their factor VIII (FVIII) product for a variety of reasons. Despite the lack of evidence to support this, the concern that switching may increase the risk of inhibitor development remains.¹,² We aimed to address patient concerns and perceptions about product switching using data from clinical trials of turoctocog alfa (NovoEight®), a new B-domain truncated recombinant FVIII (rFVIII). The focus was on the questions: “Will I develop an inhibitor?” “Will I bleed more after switching product?” “If I bleed, can it be treated quickly and effectively?”

Methods: Safety and efficacy of turoctocog alfa were studied in phase 3 trials of previously treated patients (PTPs) with severe hemophilia A (n=213) (guardian™1: adults/adolescents 12-65 years;³ guardian™3: children 0-11 years).⁴ All patients switched to turoctocog alfa prophylaxis (25-50 IU/kg every second day or 25-60 IU/kg three times weekly) from other FVIII products. Breakthrough bleeds were treated on-demand with turoctocog alfa (aiming for 0.50 IU/mL plasma FVIII activity). Long-term safety and efficacy of turoctocog alfa are being investigated in patients completing guardian™1 or guardian™3 in the guardian™2 extension trial.⁵

Summary: No patients receiving turoctocog alfa developed confirmed inhibitors. In guardian™1 and guardian™3, the median annualized bleeding rate (ABR) was 3.7 and 3.0 bleeds/patient/year among adults/adolescents³ and children,⁴ respectively. Three-year interim results from guardian™2 showed that ABR decreased over 6 months and stabilized with continued turoctocog alfa prophylaxis; overall median ABR across all patients was 1.7 bleeds/patient/year.⁵ Furthermore, turoctocog alfa successfully resolved the majority of bleeding episodes reported by adults/adolescents (84%; 403/477 bleeds) and children (94%; 116/123 bleeds) in guardian™1 and guardian™3, with most bleeds controlled with 1-2 infusions (89%; 446/499 bleeds [adults/adolescents]; 95%; 120/126 bleeds [children]).³⁴

Conclusions: Patients on turoctocog alfa prophylaxis did not develop inhibitors after switching from their previous product. Additionally, the ABR was similar to that reported previously for full length rFVIIIs⁶,⁷ and was maintained at a low level over time. Breakthrough bleeds were treated effectively with turoctocog alfa. Turoctocog alfa was well tolerated and effective with low immunogenicity in PTPs. Overall, the evidence on switching is reassuring for patients.

Changes in Healthcare Resource Utilization and Haemophilia Related Events in Patients Diagnosed with Haemophilia A

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Objective: To evaluate changes in healthcare resource utilization and haemophilia related events among patients diagnosed with haemophilia A between 2008 and 2012.

Methods: This retrospective study analyzed data from the Humedica de-identified electronic medical record database between January 2008 and December 2012. Male patients diagnosed with hemophilia A (ICD-9-CM 286.0) receiving treatment with a clotting factor were eligible if they 1) were ≥18 years of age 2) did not receive Factor IX therapy and 3) did not have a diagnosis of Von Willebrand while receiving factor VIII therapy containing von Willebrand factor. All patient level resource utilization was converted to utilization per patient year. Resource utilization was then compared across time periods using repeated measures analysis of variance (ANOVA). The annualized number of haemophilia related events (haemophilic arthropathy or other joint related events) was calculated for each year. McNemar's chi-square test was used to compare the frequencies across years.

Summary: 136 patients contributing 375 patient-years were included in this study. Office/clinic visits accounted for the majority of healthcare encounters annually; 7.5 all-cause visits per year and 2.2 haemophilia related visits per year. The number of annual all-cause office/clinic visits for Haemophilia A patients decreased significantly over time from 12.5 visits in 2008 to 5.9 visits in 2012 (p=0.0404), while haemophilia A-specific annual visits decreased from 4.0 to 1.5 (p=0.1991) during the same period. On average haemophilia A patients had less than 1 inpatient and emergency room visits per year, which did not change significantly over time (p=0.6371 and p=0.4845, respectively). Over the 5-year period, haemophilic events occurred in 30.93% of patient years, changed from 23.81% in 2009 to 34.09% in 2011 (p=0.6658).

Conclusions: Office/clinic outpatient visits among patients diagnosed with haemophilia A has decreased overtime. However, the rate of haemophilia related arthropathies and other associated events have remained high. Further analysis is needed to understand how to best manage patients diagnosed with haemophilia A and reduce the proportion of patients who develop reduced joint mobility due to bleeding into joints.
A Comparison of US Prophylaxis Rates Shows Lower Prescribing for Severe Hemophilia B Patients than Severe Hemophilia A Patients

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Objectives: The objective of this study was to compare the rate of prophylaxis between severe hemophilia B and severe hemophilia A patients.

Methods: A retrospective cross sectional study was conducted using a large US specialty pharmacy dispensing database and 16 months of data (January 2013 to April 2014). Patients with ICD-9 diagnosis codes 286.0 (hemophilia A) or 286.1 (hemophilia B), who filled a prescription for any FVIII or FIX product were included. Prophylaxis patients were defined by having at least one prophylaxis dispensing record, while on-demand patients were defined by those without any prophylaxis dispensing record during the study period. Descriptive statistics were used to report patient characteristics and the percent of prophylaxis and on-demand patients by hemophilia A and B. Logistic regression was used to compare the rate of prophylaxis between severe hemophilia A and severe hemophilia B, while controlling for age.

Results: A total of 1565 hemophilia A patients and 376 hemophilia B patients were included in the analysis. A higher percentage of hemophilia A patients had severe hemophilia than hemophilia B patients (63.1% vs. 45.0%, P<0.0001). The mean age for severe hemophilia patients was 24.6 and 22.8 years, respectively (P=0.04). Overall, more severe hemophilia A patients were on prophylaxis compared to severe hemophilia B patients (80.3% vs 73.4%, P=0.04). When controlling for age, severe hemophilia A patients were significantly more likely to be on prophylaxis compared to severe hemophilia B patients (OR=1.63, P=0.02).

Conclusion: Severe hemophilia B patients were less likely to be prescribed prophylaxis compared to severe hemophilia A patients. Efforts should be made so the benefits of prophylaxis are extended to more hemophilia B patients.
Does Quality of Life improve with successful immune tolerance induction? An illustrative case report.

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Objective: Having a family member with a chronic disease often increases the burden in the family with more hospital visits, treatment administration, and increased expenses. Management of hemophilia patients with inhibitors can be very complex and challenging. Health-related quality of life (HRQoL) has become a recent focus of research in hemophilia. Data on the HRQoL of congenital hemophilia patients with inhibitors and their caregivers is limited.

Methods: We report a case study of a 36 year old male diagnosed as a neonate with hemophilia A, who, at age 6 months, developed a high titer inhibitor. His titer levels ranged from 99 BU/ml to in the thousands. Throughout a 30 year period, he experienced frequent bleeding episodes with several severe bleeds requiring extended hospitalization and intensive care management. He completed a majority of his schoolwork from a hospital bed and was unable to hold a steady job. He used factor VIII (FVIII) bypassing agents on demand to manage the bleeding episodes. As an adult, immune tolerance induction (ITI) failed with recombinant FVIII (rFVIII). QoL was poor for this husband and father of two children due to extremely limited mobility and inability to provide household income. He needed double knee replacement but insurance coverage for the surgery was denied due to the presence of the inhibitor. ITI therapy was switched to human plasma-derived FVIII with double viral inactivation (Koate-DVI) 10,000 units per day with successful tolerization in 8 months; his inhibitor was undetectable. He is currently on a prophylactic regimen of 3000 units twice a week, has not experienced any adverse events, and has had no major bleeds and only one minor bleed in 4 years.

Summary: Successful immune tolerance induction (ITI) was achieved in a 32 year old adult male with hemophilia A with daily self-infusion of human FVIII therapy containing naturally occurring von Willebrand factor. This patient's QoL has significantly improved since initiation of a home-based ITI protocol with Koate-DVI. He has been able to have double knee replacement surgery with major improvement in mobility and started his own successful national business.

Conclusions: Advances in therapies continue to improve the longevity and quality of life of patients with hemophilia A. Increased or maintained HRQoL are essential goals in health care among patients with a chronic disease. This case study demonstrates the importance of well-disciplined ITI therapy with a human plasma FVIII product for hemophilia A patients with inhibitors.
Comorbidities among Adults with Hemophilia: Hemophilia Utilization Group Studies (HUGS V)

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Objective: To investigate the prevalence of comorbidities among adults with hemophilia in the Hemophilia Utilization Group Studies (HUGS)

Methods: Standardized interviews were conducted for two prospective cohort studies HUGS-Va (hemophilia A) and HUGS-Vb (hemophilia B) at six and ten US Hemophilia Treatment Centers, respectively, between 2005 and 2011. Clinical records were reviewed. Information captured included self-reported comorbidities, sociodemographics, treatment patterns and other clinical characteristics. Overweight and obesity were defined as body mass index (BMI) 25-29 kg/m² and BMI ≥30 kg/m², respectively. The prevalence of comorbidities was calculated. The association of comorbidities with hemophilic severity, age and type of hemophilia were assessed using appropriate statistical methods for categorical or continuous variables.

Summary: The analyses included a total of 213 adults (HUGS-Va: n=147, HUGS-Vb: n=66) aged 20 to 65 years (mean±standard deviation: 36.6±12.9). Approximately, 64% of hemophilia A and 44% of hemophilia B individuals had severe hemophilia. The five most prevalent self-reported comorbidities were liver disease/hepatitis (66%), overweight/obesity (60%), arthritis (51%), human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) (24%), and hypertension (23%). The individuals in the hemophilia A sample were more likely to report liver disease/hepatitis (71% vs. 53%) and HIV/AIDS (30% vs. 9%) than those in the hemophilia B sample (all p<0.009). The prevalence of overweight/obesity (59% vs. 60%), arthritis (55% vs. 42%), and hypertension (22% vs. 24%) were not significantly different between hemophilia A and hemophilia B samples (all p>0.05). Prevalence of comorbidities was greater among individuals with severe than mild/moderate hemophilia for most conditions: liver disease/hepatitis (79% vs. 48%), arthritis (61% vs. 38%), HIV/AIDS (37% vs. 6%), and stroke/brain hemorrhage (11% vs. 2%) (all p<0.02), the exception being overweight/obesity (52% vs. 70%, p=0.007). The individuals with hemophilia A had a significantly greater number of comorbidities than those with hemophilia B (mean±standard deviation: 2.5±1.9 vs. 1.6±1.1; p<0.0001); 85% of the hemophilia A sample reported having more than one comorbidity compared to 61% of those with hemophilia B (p<0.0001). The number of comorbidities increased significantly with advancing age (p<0.0001).

Conclusions: As one of the largest prospective studies of persons with hemophilia, the HUGS sample is representative of the US hemophilia A and B populations. Except for overweight/obesity, the most prevalent comorbidities reported in HUGS related to their hemophilia complications, and were significantly associated with hemophilic severity. As the life expectancy of persons with hemophilia increases, the need for studies focusing on the health care needs of individuals with hemophilia and comorbid conditions will increase.
Haemophilia A Carriers Experience Reduced Health-Related Quality of Life

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Objective: Haemophilia A is an X-linked recessive bleeding disorder that affects males. Emerging data support evidence for increased bleeding in female haemophilia A carriers, and more haemophilia carriers are seeking care in Haemophilia Treatment Centers. Given that data regarding the effect of increased bleeding on health related quality of life (HR-QOL) in haemophilia A carriers is sparse, we tested the hypothesis that haemophilia A carriers have reduced HR-QOL related to bleeding symptoms.

Methods: We conducted a cross-sectional, case-control study at Vanderbilt University in Nashville, Tennessee. Case subjects were obligate or genetically verified haemophilia A carriers age 18 to 60 years. Control subjects were recruited from mothers of children with cancer who receive care at the Vanderbilt pediatric hematology oncology clinic. Trained interviewers administered the Rand 36-Item Health Survey 1.0, a validated questionnaire evaluating eight health concepts that may affect HR-QOL, to each study participant. The score for each of the eight health domains ranges from 0 to 100 with a lower score indicating poorer HR-QOL. Mann-Whitney U tests were used to compare median scores for the eight health domains between the case and control groups.

Summary: Forty-two haemophilia A carriers and 36 control subjects completed the Rand 36-Item Health Survey 1.0 and were included in analyses. All but one participant had normal factor VIII activity. Haemophilia A carriers had significantly lower median factor VIII activity (75% versus 138.5%, p-value <0.001 by Mann-Whitney U test) and significantly higher Tosetto bleeding scores (5 versus 1, p<0.001 by Mann-Whitney U test) compared with controls. Haemophilia A carriers had a significantly lower median score for the domain of “Pain” compared to control subjects (73.75 versus 90; p= 0.02). In the domain of “General health”, haemophilia A carriers had a significantly lower median score compared to the control group (75 versus 85; p= 0.01).

Conclusion: Haemophilia A carriers in our study demonstrated significantly lower median scores on the Rand 36-item Health Survey in the domains of “Pain” and “General Health” compared to women in the control group. Our findings highlight the need for further investigation of bleeding in haemophilia A carriers and the effect of bleeding on HR-QOL in this population.
Hemophilia Genotyping Results from the My Life, Our Future Project

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Objective: My Life, Our Future (MLOF) is a national project directed by a partnership formed to: 1) conduct wide-scale genetic testing of the U.S. hemophilia community, thereby increasing the rate of patient testing above the currently estimated 20% and allowing carrier detection; 2) establish a repository of associated samples and data to support scientific discovery and treatment advances including informing inhibitor risk and disease severity.

Methods: A multi-sector partnership was formed to make hemophilia genotype analysis available to the U.S. community. The National Hemophilia Foundation (NHF) educates consumers and supports recruitment. The American Thrombosis and Hemostasis Network (ATHN) provides hemophilia treatment center (HTC) provider education, a secure infrastructure for data collection, and point of access for research proposals. HTCs enroll patients, obtain samples and provide clinical results to patients. Puget Sound Blood Center (PSBC) serves as the central genotyping laboratory and sample repository. Biogen Idec provides scientific collaboration and initiative support.

A pilot study involving 11 HTCs was successfully completed in 2013, and patients continue to be enrolled at those and additional sites. Genotyping is performed through an initial screen by Next Generation sequencing of extracted DNA using a molecular inversion probe-based capture strategy. FVIII and FIX mutations are confirmed in the CLIA-certified PSBC hemophilia genomics laboratory using a separate DNA sample. A clinical laboratory report is returned to the HTC and results transmitted into the ATHN Clinical Manager database accessible only to the patient’s HTC providers. For patients who give informed consent, coded data and samples are stored in a research repository, which can be linked to coded clinical data from the ATHN dataset for future research applications. NHF’s national and local chapter educational programs increased awareness and educated families about MLOF.

Summary: As of June 13, 2014, 25 HTCs were enrolling patients and 865 patients were enrolled. Of those patients, 168 opted for clinical genotyping only and 697 also gave informed consent to have data and samples entered into the research repository. Mutation analysis has been completed in 707 patients, including 354, 151 and 202 with severe, moderate and mild haemophilia respectively. By comparison to available hemophilia A and B databases, 61 novel mutations have been identified in 68 patients. Lessons learned from the initial stages of the program’s rollout helped us to improve our approach to recruitment and education about the importance of genotyping and research in hemophilia.

Conclusions: My Life, Our Future is a novel partnership to address unmet needs for hemophilia genotyping services and research. Expanding participation in the program will increase clinical genotyping for patients with hemophilia, increase knowledge of FVIII and FIX mutations present in the U.S. hemophilia population, and provide a robust research repository for future scientific discovery.