BCR 24

A Unique Combination of Severe Congenital Factor XIII Deficiency and Type 2M Von Willebrand Disease – A Case Report

Selvaraj, Sundar Rajan; Bockenstedt, Paula; Pipe, Steven

Submission Group

Biomedical/Coagulation Research

Abstract

Factor XIII deficiency is classified under rare bleeding disorders and is in fact, the rarest with an incidence of 1 in 2 to 3 million births and is inherited in an autosomal recessive manner. On the other hand, Von Willebrand Disease (VWD) is the most common bleeding disorder occurring in about 1% of the US population. Type 2M Von Willebrand Disease (Type 2M VWD), a subtype of Type 2 VWD, has an autosomal dominant pattern of inheritance and is characterized by decreased activity of Von Willebrand Factor (VWF) and its failure to interact with platelets. This report describes an interesting case of an individual with a combined severe congenital factor XIII deficiency and a recently diagnosed Type 2M VWD. A 43-year-old male diagnosed with severe congenital factor XIII deficiency at birth following umbilical stump bleeding has been on regular prophylaxis since 2007. Frequent breakthrough bleeds despite receiving prophylactic infusions of Factor XIII concentrate prompted a re-evaluation of the patient’s coagulation profile. Clinical laboratory parameters consistent with a diagnosis of Type 2M VWD were observed in addition to his underlying severe Factor XIII deficiency. DNA sequencing identified a novel missense variant p.Arg1136Trp (c.3406C>T) as the possible causative mutation.

VON WILLEBRAND PANEL RESULTS

VWF Activity (Ristocetin Co-Factor Assay) [Std.Range: 50 - 150%] 10 – 12%
VWF Activity (VWF-GPIbM Activity) [Ref. Interval: 60-184 U/dL] 4 U/dL
VWF Antigen [Std.Range: 50 – 150%] 238 – 269 %
VWF Multimer Assay Normal distribution of multimers
VWF Inhibitor Screen Negative
VWF Activity/Antigen Ratio 0.042 – 0.058
Weekly blood draws overlapping 3 cycles of prophylactic infusions of Tretten (recombinant FXIII-A subunit concentrate) revealed peak and trough factor XIII activity levels of ~80% and ~10% respectively. The subject had a largely sedentary lifestyle over this period of 12 weeks indicating, based on previous experience, that any moderate to vigorous physical activity could necessitate maintenance of a higher trough level. Additionally, the potential utility of VWF concentrates to effectively manage the second hemostatic defect and prevent breakthrough bleeds needs to be explored. To our knowledge, this is the first report describing a unique combination of severe congenital factor XIII deficiency and type 2M VWD.
BCR 26

Optimizing signal strength and suppressive potential of FVIII specific CAR Tregs for tolerance induction in a murine model of hemophilia A

Biswas, Moanaro; Herzog, Roland W; Brusko, Todd M; Rana, Jyoti

Submission Group
Biomedical/Coagulation Research

Abstract

Objective: The development of inhibitory antibodies (inhibitors) against FVIII is a critical complication in the treatment of hemophilia A, as hemostasis can no longer be re-established by FVIII replacement therapy. Immune tolerance induction (ITI) for inhibitor eradication does not always have a successful treatment outcome and bypassing agents or alternatives like emicizumab and fitusiran are associated with their own risks or uncertainty about long-term outcomes. Inhibitor development has been shown to be dependent on CD4 + T cell help, which is in turn modulated by the regulatory T cell (Treg) subset. Cellular therapy with autologous Tregs is therefore a potential approach for tolerance induction to inhibitor development, either as stand-alone therapy or in combination with other established treatments. Engineering FVIII-specific specificity on Tregs can redirect Tregs to the antigen of interest without the risk of generalized immunosuppression. Here we achieved this objective by synthesizing a chimeric antigen receptor (CAR) molecule with specificity to human FVIII. Methods: We generated 2nd and 3rd generation FVIII-specific chimeric antigen receptors (FVIII CAR) with a single chain variable fragment (scFv) specific for the C2 domain of human FVIII fused to murine CD3 z, CD28 and 4-1BB primary and co-stimulatory signaling domains. This was packaged in a retroviral system (pMys-IRES-eGFP, pMys-IRES-mScarlet) and activated polyclonal Tregs were transduced to generate FVIII CAR Tregs. To tackle exhaustion and activation induced cell death (AICD) due to prolonged exposure of CAR T effector cells and CAR Tregs to FVIII, select point mutations were introduced into immunoreceptor tyrosine-based activation motifs in the primary CD3zsignaling domain. For cellular therapy, 1x10^6 GFP + FVIII CAR-Treg sorted cells were adoptively transferred into F8 e16 −/− hemophilia A mice, and recipients were challenged with weekly IV injections of BDD-FVIII for 8 weeks. Plasma was tested for inhibitor formation at 4 and 8 weeks using the Bethesda assay and FVIII IgG1 ELISA. Summary: FVIII CAR expressing murine Tregs were able to bind soluble FVIII as tested by flow cytometry. Antigen recognition via the scFv triggered specific transcription factor upregulation, FVIII CAR-Treg activation, cytokine secretion and cell proliferation independent of the requirement for antigen presenting cells (APC) / MHC restriction. Adoptively transferred FVIII CAR Tregs were able to suppress inhibitor formation against frequent IV injections of BDD-FVIII, while control mice that did not receive cellular therapy developed high titer inhibitors. We are evaluating the suppressive ability of adoptively transferred FVIII CAR Tregs in mice with pre-established inhibitors, either alone or in combination with mouse CD20 antibody. Conclusions: We demonstrate that FVIII CAR Tregs represent an effective way to generate a large pool of antigen-specific cells, with no requirement for MHC restriction, which can effectively suppress an inhibitor response to FVIII in a preclinical model of hemophilia A.
Correcting Bleeding Disorders Using Blood Clotting Factors Produced in vivo by Encapsulated Engineered Allogeneic Human Cells

Introduction: Factor replacement therapy for hemophilia requires frequent intravenous infusions yet are unable to address long-term complications due to suboptimal therapy adherence, non-ideal factor kinetics and generation of inhibitors. To overcome these drawbacks, alternative modalities such as gene and cell therapies are being investigated. Using AfibromerTM spheres made of a blend of alginates and containing a novel antifibrotic component, we have developed several candidate Shielded Living TherapeuticsTM products, in which ex vivo gene modified allogeneic human cells producing high levels of blood clotting factors are shielded from immune rejection by the host, enabling sustained in vivo factor production. Objective: To evaluate in vivo whether sustained delivery of blood clotting factors by implantation of AfibromerTM spheres and containing genetically engineered human cells producing hFVIII, hFIX or hFVII is dose adjustable and durable. Methods: Various doses of AfibromerTM spheres containing engineered human cells were administered intraperitoneally (IP) to murine wild-type (WT) and KO disease models. Factor production was evaluated via a combination of ELISA, activity and bleeding assays. ResultsAfibromerTM spheres containing engineered human cells optimized for hFVIII, hFIX and hFVII protein production were placed IP in WT mice. This resulted in sustained therapeutic levels of the respective blood clotting factors. Spheres producing hFVIII were tested long-term (up to 6 months) and showed stable factor production and good cell viability upon explant analysis of the spheres. Additional studies in hemophilia A KO mice resulted in dose-dependent levels of functional hFVIII in plasma, with a corresponding correction of bleeding time and blood loss in a tail bleeding model. ConclusionsTaken together, these data demonstrate that administration of Afibromer™ spheres containing human cells engineered to express a blood clotting factor can result in sustained factor production and efficacious correction of the bleeding phenotype in murine preclinical models of hemophilia A. The sustained factor secretion achieved after a single IP implantation creates a viable alternative to traditional factor administration or gene therapy, with several important advantages. We aim to develop a new category of medicines for severe chronic diseases including bleeding disorders such as hemophilia A, and to advance its development into clinical testing in this indication.
Development of a plasminogen activator 1 (PAI-1) variant to modulate bleeding

Haynes, Laura; Huttinger, Zachary; Ginsburg, David

Abstract

Objective: PAI-1 is a serine protease inhibitor (SERPIN) whose function in vivo is to downregulate fibrinolysis by inhibiting urokinase- and tissue-type plasminogen activators (uPA and tPA). The goal of this research is to use PAI-1 as a prototypical SERPIN scaffold from which to develop “designer” PAI-1 variants with altered specificity and inhibitory kinetics. Methods: PAI-1 variants of interest were identified using a molecular evolution approach in which traditional phage-display technology was coupled with next generation high throughput DNA sequencing. Filamentous phage displaying PAI-1 fused to the p3 coat protein were randomly mutagenized through error prone PCR, reacted with uPA, and selected with an anti-uPA polyclonal antibody in two sets of complimentary experiments to (1) determine the stable half-life of PAI-1 or (2) the rate at which PAI-1 inhibits uPA. At selected time points in each of the described experiments, the PAI-1 encoding portion of the phage genome was analyzed by next-generation sequencing. Evaluation of 7-10 million sequencing reads per time point facilitated massively parallel kinetic analyses to determine the effect of amino acid substitutions at every residue in PAI-1 simultaneously with respect to both half-life and rate of uPA inhibition. Summary of Results: This analysis generated data for 74% of all possible single amino acid substitutions, identifying 492 mutations that extended the functional half-life of PAI-1, as well as 1509 destabilizing mutations. These results were validated for representative single amino acid substitutions expressed as individual, purified recombinant proteins. Conclusions: These data provide a useful resource for interpreting human mutations identified by future large scale clinical human genome sequencing. In addition, these findings provide new insight into structure-function relationships in PAI-1. Finally, these tools lay the groundwork for future studies aimed at developing novel SERPINs based on the PAI-1 scaffold with altered target protease specific potentially applicable to treatment for a number of disorders of hemostasis and thrombosis, as well as various other SERPIN disorders (eg alpha-1-antitrypsin and C1-inhibitor deficiency).
Bleeding types and treatments in patients with von Willebrand disease before and after diagnosis

Hale, Sarah; Roberts, Jonathan; Malec, Lynn; Halari, Imran; Oladapo, Abiola; Sidonio, Robert

Abstract

Objective: Von Willebrand disease (VWD) is the most common inherited bleeding disorder, however, initial diagnosis and subsequent management of patients after diagnosis remains a challenge. The aim of this study was to characterize the specialists who are treating patients before and after diagnosis of VWD. We also identified the most common bleeding types and the treatments given to these patients. Methods: This retrospective study analysed data from a US medical claims insurance database (IQVIA PharMetrics Plus Database) for patients who had made insurance claims for VWD (International Classification of Diseases, ninth edition [ICD-9] code: 286.4). The claims were made from January 01, 2006 to June 30, 2015. Patients with ≥2 medical claims for VWD and who were continuously enrolled for a 2-year period before and after their 1st VWD claim were included in this study. Descriptive statistics were used to summarize patient demographic and clinical characteristics, which included bleed types, treating physician specialty, and type of VWD treatment, in both the pre- and post-diagnosis periods. Summary: A total of 3,756 patients were included: 73% were female, and the median age at VWD diagnosis was 34 years old (age range 2–82 years). Pre-diagnosis, the top 3 treating physician specialties were hospitalists (22%), primary care physicians (14%) and obstetrician-gynecologists (13%). Post-diagnosis, the top 3 treating physician specialties were hospitalists (14%), primary care physicians (8%) and obstetrician-gynecologists (10%). Only 6% of patients saw a specialist hematologist before VWD diagnosis for a bleeding event and this decreased to 3% after diagnosis. The number of claims made by patients for bleeding events decreased from 45% pre-diagnosis to 34% post-diagnosis. In females, heavy menses were the most common bleed type, representing 29% of pre-diagnosis claims and 21% of post-diagnosis claims. In males, epistaxis was the most common bleed type, representing 13% of pre-diagnosis claims and 8% of all post-diagnosis claims. Overall, insurance claims for medical treatments associated with VWD increased from 19% pre-diagnosis to 27% post-diagnosis. The most prescribed treatments in women were oral contraceptives, desmopressin (DDAVP) and aminocaproic acid (ACA) (pre-diagnosis: 18%, 5% and 2%, respectively; post-diagnosis: 20%, 11% and 5%, respectively). In men, the most prescribed treatments were DDAVP, ACA and von Willebrand factor (VWF) concentrates (pre-diagnosis: 5%, 4% and 2%, respectively; post-diagnosis: 9%, 6% and 4%, respectively). Conclusions: These data show an overall reduction in the frequency of bleeding event insurance claims after VWD diagnosis. This was coupled with an increase in treatment insurance claims for DDAVP, ACA and VWF after diagnosis. These results highlight the importance of diagnosis of VWD and treatment optimization in these patients. Also, only a minority of patients received care from a hematologist, which may impact treatment and care.
No evidence of germline transmission of vector DNA following intravenous administration of AAV5-hFIX to male mice

Spronck, Lisa; de Haan, Martin; Sawyer, Eileen; Heijink, Liesbeth; Twisk, Jaap

Submission Group
Clinical Research/Clinical Trials

Abstract

Background: Recombinant adeno-associated viruses (rAAV) are replication-deficient, non-integrating viruses commonly used as vectors for gene therapies currently in clinical development. Systemic administration of gene therapy raises the possibility of vertical germline transmission of the vector DNA. Aim: Here, we investigated the possibility of germline transmission following IV administration of an AAV serotype 5 vector designed for the liver-directed expression of human Factor IX which is being studied in clinical trials for hemophilia B. Methods: Since hemophilia B predominantly occurs in male patients, paternal germline transmission was investigated in mice in a GLP compliant study, according to current gene therapy guidelines (EMEA/273974/2005). Male C57Bl/6 mice (n=15) each received a single intravenous infusion of 2x10^{14} gc/kg AAV5-hFIX and were mated 6 days later with untreated female mice (n=30). On day 20 post-treatment, males were sacrificed and the seminal vesicle, epididymis, testes and a sperm sample were collected. Successfully mated females were necropsied on day 17 of gestation and the uterus, placenta and fetuses collected for each female. Each fetus was examined for viability and externally visible abnormalities. All samples were analyzed for vector DNA by QPCR. Results: No effect of treatment was observed on male mating performance, fertility indices, maternal body weight, food consumption, pregnancy performance, external fetal abnormalities, or fetal weights. Vector DNA levels of up to 2x10^6 gc/µg gDNA were detected in male reproductive tissues (epididymis, seminal vesicle, sperm, and testes), but not in female uterus, placenta and offspring. Although vector DNA was detected in the reproductive tissues of males, there was no evidence of transmission of vector DNA to female reproductive tissues or to the fetuses. Conclusion: The risk of paternal germline transmission following AAV5-based vector administration is therefore considered to be low.
CRA 22

AMT-061 (AAV5-Padua hFIX variant) an Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-Severe Hemophilia B: Follow-up up to 9 Months in a Phase 2b trial

Giermasz, Adam; von Drygalski, Annette; Castaman, Giancarlo; Key, Nigel; Lattimore, Susan; Leebeek, Frank; Miesbach, Wolfgang; Recht, Michael; Long, Alison; Gut, Robert; Pipe, Steven W

Submission Group
Clinical Research/Clinical Trials

Abstract

Objective: Gene therapy for hemophilia offers the potential for sustained-disease amelioration with a single treatment. AMT-061 is an investigational gene therapy for hemophilia B comprised of an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimized Padua variant human factor IX (FIX) gene with liver-specific promoter. The aim of the study was to confirm that a single dose of AMT-061 will provide a minimum-therapeutic response of FIX activity 6-weeks post-dose in participants with severe or moderate-severe hemophilia B. Methods: Phase 2b, open-label, multi-center trial (NCT03489291) in adult males requiring FIX prophylaxis and without active hepatitis or uncontrolled HIV. Participants were not excluded based on neutralizing antibodies to AAV5. Participants received a single intravenous dose of AMT-061 (2x1013 gc/kg) and will be followed for 5-years. The primary endpoint was FIX activity at Week 6. Secondary endpoints include e-diary recordings of bleeds and FIX concentrate use, laboratory parameters, joint health, patient-reported outcomes, and adverse events (AEs). Summary: All participants had FIX <1% (severe FIX deficiency) and had neutralizing activity to AAV5 at baseline. Following AMT-061 treatment, FIX activity increased rapidly (Figure) to a mean of 31% at Week 6 and increased further to a mean of 47% at Week 26. At Week 26, FIX activity was 51%, 33%, and 57% in participants 1-3, respectively. There were no bleeds post-treatment and no requirement for FIX replacement. No clinically significant liver enzyme elevations above upper limit of normal were observed after dosing in any participant. One participant experienced 2 mild AEs possibly related to treatment (self-limiting headache and slightly elevated CRP). Updated results to 39 weeks of follow-up will be presented. Conclusions: Sustained therapeutic responses of FIX activity were observed 26-weeks after treatment with AMT-061. AMT-061 was well-tolerated with no requirement for immunosuppression. These data support the ongoing Phase 3 study.
Clinical experience with BIVV001, the first investigational factor VIII (FVIII) therapy to break through the von Willebrand factor (VWF) ceiling in hemophilia A

Konkle, Barbara A.; Shapiro, Amy; Quon, Doris V.; Staber, Janice M; Suzuki, Takashi; Kulkarni, Roshni; Ragni, Margaret V.; Lissitchkov, Toshko; Chhabra, Ekta Seth; Poloskey, Stacey; Rice, Kara; Katragadda, Suresh; Fruebis, Joachim

Abstract

Objective: Factor replacement therapy remains the only option for comprehensive care in hemophilia. While extended half-life recombinant FVIII (rFVIII) therapies have reduced the frequency of prophylactic dosing, weekly or greater dosing intervals remain an unmet need because endogenous VWF limits the half-life of current FVIII replacements. BIVV001 (rFVIIIFc-VWF-XTEN) is a novel investigational rFVIII therapy with single-chain FVIII, the Fc domain of human immunoglobulin G1, two XTEN polypeptides, and the FVIII-binding D′D3 domain of VWF, designed to circulate independently of VWF, thereby breaking the VWF half-life ceiling. Higher sustained FVIII levels have demonstrated improved protection from bleeds and preservation of joint health. BIVV001 has the potential to achieve higher sustained FVIII levels, with less frequent administration. Here we present BIVV001 clinical experience to date.

Methods: Males (aged 18−65 years) with severe hemophilia A (<1 IU/dL [<1%] endogenous FVIII) with ≥150 exposure days of prior FVIII treatment were included in two separate open-label studies. In the Phase 1/2a EXTEN-A study (NCT03205163), subjects received a single dose (25 or 65 IU/kg) of rFVIII. After a 3- to 4-day washout period, subjects received a single dose of BIVV001 at the same dose level as rFVIII. In the Phase 1 repeat-dosing study (EudraCT No: 2018-001535-51), subjects received four once-weekly doses of 50 IU/kg or 65 IU/kg of BIVV001. In both studies, safety, tolerability, and pharmacokinetic parameters were assessed, and 28-day safety observation periods followed the last dose of BIVV001. Summary: In EXTEN-A, 7 subjects were enrolled in the 25 IU/kg cohort and 9 subjects in the 65 IU/kg cohort, with 6 and 9 subjects receiving BIVV001, respectively. Geometric mean half-life of BIVV001 was longer than rFVIII for both cohorts (37.6 vs 9.1 hours and 42.5 vs 13.2 hours, respectively; P<0.001). Mean (SD) FVIII activity (one-stage assay) at 5 and 7 days following single-dose 65 IU/kg BIVV001 was 38 (10)% and 17 (5)%, respectively. BIVV001 was well tolerated. No inhibitors were detected through 28 days after BIVV001 dosing. In the repeat-dosing study, an interim analysis was conducted when ≥8 subjects from cohort 1 completed PK assessments. As of February 7, 2019, 10 of 10 subjects enrolled to cohort 1 have received 50 IU/kg BIVV001. Three of 5 subjects enrolled to cohort 2 have received 65 IU/kg BIVV001. Data from the interim analysis will be presented. Conclusions: In EXTEN-A, BIVV001 was well tolerated and no safety concerns were identified. BIVV001 half-life was three- to four-fold higher than rFVIII, demonstrating a breakthrough in the VWF-imposed half-life ceiling. The BIVV001 repeat-dosing study provides an opportunity to assess safety, tolerability, and
pharmacokinetics over multiple infusions. BIVV001 may provide less frequent dosing while maintaining high FVIII levels, resulting in extended protection against bleeds for most individuals with severe hemophilia A.
CRA 46

CLINICAL STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF WILATE DURING PROPHYLAXIS IN PREVIOUSLY TREATED PATIENTS WITH VON WILLEBRAND DISEASE (VWD)

Schwartz, Bruce; Sidonio, Robert

Submission Group

Clinical Research/Clinical Trials

Abstract

Clinical Study to Investigate the Efficacy and Safety of Wilate during Prophylaxis in Previously Treated Patients with von Willebrand Disease (VWD)

Objectives: This study has a primary objective to determine the efficacy of VWF/FVIII concentrate (Wilate) in the prophylactic treatment of previously treated patients with type 3, type 2 (except 2N), or severe type 1 VWD. Secondary objectives of this study will be to collect data to 1) Assess the VWF:Ac and VWF:Ag incremental IVR of VWF/FVIII concentrate over time, 2) Assess the safety and tolerability of VWF/FVIII concentrate in this indication. Also the study will examine, the efficacy of VWF/FVIII concentrate in the treatment of breakthrough bleeding episodes (BEs), and in surgical prophylaxis, as well as the quality of life (QoL) during prophylaxis with VWF/FVIII concentrate.

Methods: The study is planned to enrol 28 PTPs aged ≥6 years and with VWD type 1, 2A, 2B, 2M, or 3. Eligible patients must be receiving on-demand treatment with a VWF-containing product, with at least 1, and an average of ≥2, documented spontaneous BEs per month in the preceding 6 months requiring treatment with a VWF-containing product. This will be assessed as part of a run in observational study to collect bleeding rate prior to the start of prophylaxis. From the beginning of the study, patients will receive prophylactic treatment with VWF/FVIII concentrate for 12 months and record all BEs in a patient diary. Based on these data, the frequency of BEs and the annualized bleeding rate (ABR) under prophylactic treatment will be calculated. Treatment efficacy of BEs will be assessed by the patient (together with the investigator in case of on-site treatment) using a 4-point scale (excellent, good, moderate, none). In case patients undergo surgeries, efficacy of VWF/FVIII concentrate will be assessed at the end of surgery by the surgeon and at the end of the postoperative period by the haematologist. In both cases, predefined assessment criteria will be used. In addition, an overall assessment of efficacy will be made at the end of the postoperative period by the investigator. Summary/conclusions: Prophylactic treatment in other congenital bleeding disorders is widely accepted as the standard of care to prevent bleeding and preserve quality of life in patients. This form of treatment in VWD is not well characterized prospectively as yet. This study will provide data on the efficacy of prophylactic treatment in reducing the rate of bleeding and on the impact of prophylaxis on the quality of life in VWD patients.
CRA 54

Baseline patient characteristics in ReITIrate: A prospective study of rescue ITI with recombinant factor VIII Fc fusion protein (rFVIIIIFc) in patients who have failed previous ITI attempts

Lethagen, Stefan; Königs, Christoph; Meeks, Shannon; Malmström, Håkan; Jain, Nisha

Submission Group

Clinical Research/Clinical Trials

Abstract

Objective: Inhibitor development is the most serious complication of hemophilia A therapy. Immune tolerance induction (ITI) is the gold standard for inhibitor eradication, restoring factor VIII (FVIII) responsiveness. Retrospective data on ITI therapy using rFVIIIIFc have been reported (Carcao et al. Haemophilia. 2018). The ReITIrate study (NCT03103542) was designed to prospectively evaluate success of rescue ITI with rFVIIIIFc. Methods: ReITIrate, a prospective, interventional, multicenter, open-label study, enrolled patients with severe hemophilia A and inhibitors, who failed previous ITI attempts. The primary purpose is to describe the outcome of ITI performed with rFVIIIIFc (200 IU/kg/day) within a maximum of 60 weeks. Here, patient baseline characteristics are reported using descriptive statistics and listings. Summary: Sixteen subjects were included in the study between November 2017 and December 2018. The median (range) age at study enrollment was 7.5 (2–46) years. Seven subjects had a known family history of inhibitors. The median (range) number of prior ITI attempts was 1 (1–3) and the median (range) total ITI duration was 51.5 (12–155) months. All subjects had previously received high-dose ITI, with 3 subjects receiving plasma products, 6 subjects receiving recombinant products, and 7 subjects receiving both recombinant and plasma products for previous courses of ITI. Four subjects received prior immunomodulatory therapy. The median (range) inhibitor titer at screening and historical peak were 11 (0.9–635) BU/mL and 127 (8–3000) BU/mL, respectively. During the 12 months prior to enrollment, the median (range) number of bleeds was 5 (0–24); 11 subjects used activated prothrombin complex concentrate (aPCC) for treatment of bleeds, 5 subjects received recombinant factor VIIa (rFVIIa), and 1 subject each received FVIII/von Willebrand factor, recombinant FVIII, and tranexamic acid. Twelve subjects received prophylaxis with bypassing agents during this period (10 aPCC, 1 rFVIIa, and 1 both products). Conclusions: This is the first prospective study describing rescue ITI with an extended half-life recombinant FVIII product. Enrolled subjects had multiple risk factors for poor ITI outcomes and a long duration of previous ITI. There is an unmet need for successful tolerization in such patients, allowing regular FVIII prophylaxis and potentially leading to improved clinical outcomes and quality of life.
CRA 59

Three-year efficacy and safety results from a phase 1/2 clinical study of AAV5-hFVIII-SQ gene therapy (valoctocogene roxaparvovec) for severe hemophilia A (BMN 270-201 study)

Kim, Benjamin; Rangarajan, Savita; Pasi, John; Mitchell, Nina; Lester, Will; Laffan, Michael; Madan, Bella; Symington, Emily; Yang, Xinquan; Pierce, Glenn; Wong, Wing

Submission Group

Clinical Research/Clinical Trials

Abstract

Objective: Hemophilia A (HA) is an X-linked disorder caused by mutations in the gene encoding Factor VIII protein (FVIII). Gene therapy is increasingly being viewed as a viable treatment option for hemophilia. Herein, long-term clinical safety and efficacy are presented from a Phase 1/2 study of an AAV-mediated gene therapy for severe HA.

Methods: Valoctocogene roxaparvovec is an adeno-associated virus-mediated gene therapy that delivers a functional, codon-optimized, B domain-deleted, human FVIII gene under the control of a liver-specific promoter (AAV5-hFVIII-SQ). An ongoing Phase 1/2 study continues to evaluate the safety and efficacy of valoctocogene roxaparvovec in thirteen males with severe HA. Study participants received a single intravenous injection of valoctocogene roxaparvovec at one of two dose levels (6×10¹³ vg/kg, n=7; 4×10¹³ vg/kg, n=6).

Summary: Participants who received 6×10¹³ vg/kg valoctocogene roxaparvovec showed a reduction in annualized bleeding rate (ABR) of 96%, from a pre-treatment median (mean) of 16.5 (16.3) to 0.0 (0.7) at year three. Participants demonstrated an absence of target joints and target joint bleeds, with 86% experiencing zero bleeds requiring FVIII treatment. ABR diminished by 92% in 4×10¹³ vg/kg participants, from a pre-treatment median (mean) of 8 (12.2) to 0 (1.2) at year two. Sixty-seven percent of 4×10¹³ vg/kg participants experienced zero bleeds requiring FVIII treatment. FVIII usage demonstrated a reduction from pre-treatment median (mean) of 139 (137) infusions to 0 (5.5) at year three in 6×10¹³ vg/kg participants, and from 156 (147) to 0.5 (6.8) at year two in 4×10¹³ vg/kg participants. In 6×10¹³ vg/kg participants, FVIII levels reported by chromogenic assay reached a median (mean) of 60.3 (64.3), 26.2 (36.4), and 19.9 (32.7) IU/dL at the end of one, two, and three years post-infusion, respectively. In 4×10¹³ vg/kg participants, FVIII levels reported by chromogenic assay reached a median (mean) of 22.9 (21.0) IU/dL and 13.1 (14.7) IU/dL at the end of one and two years post-infusion, respectively. Although FVIII levels were measured and will be presented using both the chromogenic substrate assay and the one-stage assay, chromogenic assay results appear to more accurately represent the true level of circulating FVIII. The safety profile of valoctocogene roxaparvovec remains favorable and unchanged, with transient, asymptomatic ALT elevations and no FVIII inhibitor development reported to-date.

Conclusions: Following a single administration of valoctocogene roxaparvovec, participants showed sustained, clinically relevant FVIII activity that reduced self-reported bleeding and exogenous FVIII replacement use at 156 weeks and 104 weeks post-administration in 6×10¹³ vg/kg and 4×10¹³ vg/kg dose cohorts, respectively.
CRA 73

Factor VIII deficiency is associated with abnormal brain volumes

Staber, Janice; Al-Huniti, Ahmad; Novak, Marci; Harshman, Lyndsay; Nopoulos, Peggy

Submission Group
Clinical Research/Clinical Trials

Abstract

Objective: Factor VIII (FVIII) deficiency (hemophilia A) leads to bleedings events requiring prophylactic FVIII replacement therapy. While significant progress has been made in prevention and treatment of hemophilia-related joint and muscle disease with prophylaxis, people with hemophilia (PWH) continue to demonstrate increased rates of anxiety, depression, and executive dysfunction more frequently than the general population. Unfortunately, there is paucity of data to understand, treat or prevent brain disease in PWH. Therefore, our study aims to evaluate brain structure and cognitive function in pediatric patients with severe FVIII deficiency in order to improve outcomes.

Methods: Ten pediatric patients with severe FVIII deficiency were recruited from the Iowa Hemophilia and Thrombosis Center and compared to 23 healthy controls. Inclusion criteria included males aged 6 – 16 years for both groups and confirmed diagnosis of FVIII deficiency for PWH. All subjects with known diagnosis of traumatic brain injury, major chromosomal anomalies, or intellectual disability were excluded. PWH with known diagnosis of intracranial bleed or FVIII inhibitor were excluded. Behavior and cognitive data collected included Behavioral Regulation Index of Executive Function and Wechsler Intelligence Scale for Children. Magnetic resonance imaging sequences were completed and included T1, T2, and diffusion tensor imaging. Freesurfer and BrainTools programs were used to preprocess imaging and generate volumetric data. Summary: Mean age for PWH was 10.2 yrs and 11.8 yrs for controls (p = 0.24). Both groups had similar height, weight, socioeconomic status, and maternal education level. Controls had slightly higher levels of paternal education level compared to PWH; however this was not associated with difference in group IQ scores. Despite normal IQ, PWH demonstrated a worsened behavioral regulation score indicating executive dysfunction. Relative to controls, PWH group had overall lower whole brain volume. Conclusions: PWH demonstrated abnormal brain structure and function compared to healthy controls. Further evaluation is warranted to understand why and how FVIII deficiency and its treatment alter neurological outcomes.
Five-year safety and efficacy of N8-GP (ESPEROCT®) in previously treated children with hemophilia A in the completed pathfinder 5 trial

Raffini, Leslie; Staber, Janice M; Yee, Donald L; Acharya, Suchitra; Clausen, Wan Hui Ong; Cooper, David L; Kearney, Susan

Abstract

Objective: The completed pediatric phase 3 pathfinder 5 trial assessed the safety and efficacy of N8-GP (turoctocog alfa pegol, ESPEROCT®) use for routine prophylaxis and treatment of breakthrough bleeds in previously treated children. Methods pathfinder 5 was a multicenter, multinational, single-arm study evaluating safety, efficacy, and pharmacokinetics. Children (aged <12) with severe hemophilia A were administered prophylaxis (target 60 [50-75] IU/kg twice weekly) in the main phase (26 weeks) followed by an extension phase. Current analysis covers study initiation (February 2013) through completion (September 2018). Summary Of the 68 children (34 aged 0-5, 34 aged 6-11) enrolled, 63 completed the main phase and 62 completed the extension. Most (95%) were previously on prophylaxis. The total study period amounted to 306 patient-years (32,138 exposure days); median (mean) patient exposure was 4.9 (4.5) years. Overall, 838 adverse events (AEs) were reported; 18 serious AEs included 2 possibly/probably related to N8-GP (severe allergic reaction [1] and increasing bleeding symptoms [1]). No inhibitor development was observed in the trial. Two AEs resulted in withdrawal; a third patient with severe allergic reactions (after 4 doses) that resolved after 2 hours without any treatment met preestablished withdrawal criteria. There were no anti-PEG antibodies of clinical significance; however, 21 (31%) patients had anti-PEG antibodies at baseline (prior to exposure), and 1 patient had a single positive measurement after exposure at a titer <1. Overall, 55 patients (81%) reported 330 bleeds during the study; most were traumatic (67%). The success rate for hemostasis was 84% (excellent/good); 71% were treated with 1 injection, and 88% of patients were successfully treated with 1-2 injections. Median (mean) utilization for bleeds was 68 (95) IU/kg. Median ABRs are shown below; estimated mean ABR was 1.1. Forty-seven percent of children had no spontaneous bleeds throughout the trial. Of 13 children with 17 target joints at baseline, 77% (main phase) and 46% (complete trial) reported no bleeds in their target joints. For those previously on prophylaxis, the mean observed ABR was 2.3 compared with the historical ABR of 6.4. The mean prophylaxis dose was 64.7 IU/kg with an interval of 3.5 days. Median ABR Age 0-5 y Age 6-11 y Total Overall 0.6 0.9 0.8 Spontaneous 0.1 0.2 0.2 Traumatic 0.3 0.8 0.5 N8-GP prolonged single dose half-life by 1.9x compared with the child’s prior FVIII product. The mean trough levels on twice-weekly dosing were 0.019 IU/mL (0.016 ages 0-5, 0.024 ages 6-11). Conclusion These data support the safety and efficacy of N8-GP in a controlled phase 3 trial setting in children. Prophylaxis with N8-GP using a consistent dose/interval (65 IU/kg twice weekly) was effective in preventing bleeds. No unexpected safety issues were identified.
Modeling of Daily Administration of N8-GP (ESPEROCT®) vs Standard Half-life FVIII for Patients With Hemophilia A Participating in Sports Activities

Wheeler, Allison P; Wang, Michael; Chrisentery-Singleton, Tammyella; Chitlur, Meera; Kreilgaard, Mads; Cooper, David L; Escobar, Miguel

Abstract

Objective: Daily administrations of FVIII products are considered useful for providing high FVIII coverage for active patients with hemophilia A. This analysis was performed to determine the daily dose levels required of N8-GP (turoctocog alfa pegol, ESPEROCT ®) vs standard half-life (SHL) FVIII (N8, turoctocog alfa, Novoeight ®) to normalize risk of activity-related bleeding for patients with hemophilia participating in daily sports activities (practices, games) of varying risk profiles. Methods: Patients with hemophilia engaging in physical activity have associated increased bleeding risk with sports that have increased potential for contact injuries as classified by Broderick et al (JAMA. 2012): Class 1 - no contact (eg, swimming); Class 2 - contact might occur (eg, basketball); and Class 3 - inevitable contact (eg, American football). To normalize the risk of bleeding, nominal targets of FVIII activity levels for at least 2 h/d based on Broderick et al were chosen: above 30% (Class 1), above 50% (Class 2), and above 70% (Class 3). Pharmacokinetic (PK) simulations were performed using a one-compartment model with first-order elimination. FVIII PK profiles were simulated for the extended half-life (EHL) N8-GP based on the pathfinder 1 PK trial showing 60% prolonged half-life compared with prior SHL FVIII. For PK simulations of an SHL, N8 was used due to 104°F stability with PK based on the guardian clinical trial program. Summary: Daily doses to sustain at least 2 h/d of 30%/50%/70% activity were estimated for N8-GP (9, 15, and 21 IU/kg) and N8 (14, 23, and 33 IU/kg). Steady-state PK profile simulations of once-daily administration are shown in the Figure. Broderick Class 1 (>30%) Broderick Class 2 (>50%) Broderick Class 3 (>70%) N8-GP Daily (weekly), IU/kg 9 (63) 15 (105) 21 (147) Peak/trough activity 32%/13% 54%/21% 76%/29% Difference from 50 IU/kg Q4D -28% 21% 69% N8 Daily (weekly), IU/kg 14 (98) 23 (171) 33 (231) Peak/Trough activity 36%/6% 59%/10% 87%/14% Difference from 25 IU/kg QD 13% 97% 166% N8-GP vs N8 Utilization, IU/kg -36% -39% -36% Conclusion: Experience with routine prophylaxis with EHL/SHL FVIIIs towards guideline recommended >1% activity does not readily translate to HCP understanding of the PK with high daily or much higher every-other-day administration required to minimize risk for the active patient. With a 1.6x (60%) prolongation in half-life for adolescents/adults, this model shows daily N8-GP to be a more efficient strategy compared with daily SHL FVIII (N8) to cover the active patient; N8-GP achieves higher trough levels with a smaller increase in overall factor consumption compared with standard prophylaxis with SHL FVIII.
CRA 79

Five-year safety and efficacy of N9-GP (REBINYN®) in previously treated children with hemophilia B in the ongoing paradigm 5 trial

Kearney, Susan; Zia, Ayesha; Santagostino, Elena; Pietzko, Kerstin; Cooper, David L; Carcao, Manuel

Submission Group
Clinical Research/Clinical Trials

Abstract

Objective: The ongoing pediatric phase 3 paradigm 5 trial is assessing N9-GP (nonacog beta pegol, REBINYN®) use for routine prophylaxis and treatment of breakthrough bleeds in previously treated children with hemophilia B (FIX ≤2%). This analysis presents 5-year safety and efficacy data in a group of children treated with weekly prophylaxis to a higher mean FIX trough (≥15%). Methods: paradigm 5 is a multinational, single-arm study evaluating safety, efficacy, and pharmacokinetics. Children (aged ≤12 years at enrollment) were administered weekly prophylaxis (N9-GP 40 IU/kg) through a 52-week main phase followed by an ongoing extension study. Mild/moderate bleeds were treated with 40 IU/kg. Prophylaxis, bleed treatments, and hemostatic efficacy were captured in electronic diaries. Current analysis extends from May 2012 through October 2018. Summary: Of the 25 children enrolled in the main phase (12 ages 0-6, 13 ages 7-12), 24 completed the main phase and 22 entered the extension (11 per age group). At the time of this analysis, 17 remain in the trial. No patients withdrew due to adverse events. Ten participants remaining in the trial have become adolescents (mean 2.6 adolescent-years of exposure). The cumulative exposure in the study was 116 patient-years (6,194 exposure days). The median (range) time in study was 5.2 (0.2-6.1) years representing 290 (10-325) N9-GP doses per patient. The median/mean prophylactic dose was 43.1 IU/kg/wk. A total of 573 adverse events were reported, including 4 serious adverse events, all of which were considered unlikely related by the investigator. No patients developed anti-FIX inhibitory antibodies (primary endpoint). There were 7 medical events of interest, including 6 allergic reactions (no anaphylaxis). Age-related increase in trough FIX levels was seen; the mean FIX trough levels were 0.179 IU/mL (overall), 0.166 IU/mL (younger), and 0.192 IU/mL (older). Mean PEG plasma concentration reached steady state after ~6 months. Overall, 20 patients (80.0%) experienced 115 bleeds, the majority of which were traumatic (64%) or spontaneous (33%) and in joints (43%). Most (93%) were treated with 1-2 doses with 89% rated as excellent/good. Median individual ABRs are shown in the TABLE; 64% of patients were spontaneous-bleed-free throughout the study. Median ABR Age 0-6 Age 7-12 Total Overall 0.41 0.99 0.66 Spontaneous 0.00 0.00 0.00 Traumatic 0.41 0.50 0.47 Ten minor surgeries and 1 major surgery were performed successfully. Conclusion: These data support the safety and efficacy of N9-GP 40 IU/kg weekly over a median of 5 years in a controlled phase 3 trial setting in children. N9-GP prophylaxis with a trough of ~18% was effective in preventing bleeds with low reported ABR and with 64% of patients reporting no spontaneous bleeds during the entire study period. No unexpected safety issues were identified.
CRA 80

Four-year safety and efficacy of N8-GP (ESPEROCT®) in previously treated adolescents/adults with hemophilia A in the completed pathfinder 2 trial

Escobar, Miguel; Wheeler, Allison P; Geybels, Milan S; Cooper, David L; Lentz, Steven

Submission Group

Clinical Research/Clinical Trials

Abstract

Objective: The adolescent/adult pivotal phase 3 pathfinder 2 trial assessed N8-GP (turoctocog alfa pegol, ESPEROCT®) use for routine prophylaxis and treatment of bleeds in previously treated patients (PTPs). Methods: pathfinder 2 was a multi-center, multi-national, single-arm study evaluating safety, efficacy and pharmacokinetics. Adolescents/adults (aged ≥12 y) with severe hemophilia A were administered prophylaxis (50 IU/kg Q4D) in the main phase with option for eligible patients (0-2 bleeds in prior 6 months) to randomize (2:1) to 75 IU/kg Q7D or 50 IU/kg Q4D during extension 1 (24 weeks) and continue treatment into extension 2. An on-demand group was included throughout. Current analysis covers January 2012 through December 2018. Summary: Of the 186 PTPs (including 46 [25%] from the US) enrolled in the main phase, 150 (81%) started extension 1, 139 (75%) completed extension 1, and 128 (69%) completed the study. Mean age was 31.1 years, weight 75 kg and BMI 24.3. The complete trial covers 785 patient-years of treatment (66,577 exposure days [ED]) during which there were 2,758 bleeds, including 1,807 (66%) spontaneous bleeds and 1,735 (63%) joint bleeds. Twelve patients treated on-demand for a mean 3.1 years reported nearly half of all bleeds (1,270, 46%), including 971 (54%) spontaneous bleeds and 627 (36%) joint bleeds. Hemostatic efficacy was rated excellent/good in 2,470 (90%) episodes; 2,614 bleeds (95%) were treated with 1-2 injections. Of 175 patients on prophylaxis, 55 of 110 eligible were randomized in extension 1. For 177 patients treated with 50 IU/kg Q4D prophylaxis for 613 years (57,723 ED), 126 (71%) experienced 1,312 bleeds. For 61 low-bleed patients with 134 years (7,255 ED) on 75 IU/kg Q7D prophylaxis, 53 (87%) experienced 176 bleeds. Median ABRs are shown in the TABLE . 50 IU/kg Q4D 75 IU/kg Q7D n 177 61 Mean treatment 3.5 years 2.2 years Median ABR 0.8 1.7 N8-GP mean trough levels were 3.1 IU/dL on 50 IU/kg Q4D and 1.0 IU/dL on 75 IU/kg Q7D. A total of 1,827 adverse events were reported over 785 exposure years, including 63 serious adverse events. One patient with an intron 22 inversion developed a low-titer inhibitor at 93 ED and was withdrawn when it progressed to >5 BU. Non-neutralizing anti-PEG antibodies were seen at baseline in 12 patients (6.5%) prior to first N8-GP exposure and 11 (5.9%), who had negative anti-PEG at baseline, had positive antibodies after exposure. Conclusion: These data support the safety and efficacy of N8-GP in a controlled phase 3 trial setting in adolescents/adults. Prophylaxis with N8-GP with a consistent dose/interval (50 IU/kg Q4D) was effective in preventing bleeds; extended dosing was evaluated as successful for a subgroup of low-bleed patients. No significant safety issues were identified.
ONLINE CME AS A TOOL TO INCREASE CLINICIANS’ KNOWLEDGE OF CLINICAL TRIAL DATA FOR GENE THERAPY IN HEMOPHILIA

Hurst, Simi; Warren, Charlotte; Kadkhoda, Haleh; Van Laar, Emily

Abstract

OBJECTIVE: Gene therapy has the potential to be a dramatic paradigm shift in the care of patients with hemophilia. To educate and prepare clinicians for this potential paradigm shift, the National Hemophilia Foundation (NHF), European Haemophilia Consortium (EHC), the World Federation of Hemophilia (WFH), and Medscape Education established a multinational collaboration to develop an online continuing medical education (CME) curriculum. The current study assessed the ability of online CME to improve HCPs’ knowledge regarding the latest data from ongoing trials for gene therapy in hemophilia. METHODSA 15-minute, CME-certified, Expert Video Commentary activity was developed and launched online on 09/25/2018. Educational effectiveness was assessed with a repeated-pairs pre-/post-assessment study design, with each individual serving as his/her own control. Responses to 3 multiple-choice, knowledge questions and 1 self-efficacy confidence question were analyzed. A chi-squared test assessed changes pre- to post-assessment. P values <0.05 are statistically significant. Effect sizes were evaluated using Cramer’s V (<0.05 modest; 0.06-0.15 noticeable effect; 0.16-0.26 considerable effect; >0.26 extensive effect). SUMMARY: To date, 3,028 clinicians, including 2,382 physicians, have participated in this educational activity. This analysis comprises data from the subset of hematologists/oncologists (n=102; hem/oncs) and pediatric hematologists (n=362) who answered all pre-/post-assessment questions during the analysis period of 09/25/18 thru 06/12/19. Both hem/oncs and pediatric hematologists exhibited significant improvements overall and in specific areas of assessment (Table). A notable proportion of providers – 17% of hem/oncs and 34% of pediatric hematologists – expressed increased confidence with regard to their understanding of the latest safety and efficacy data for gene therapy. In addition to the positive impact, these findings also uncovered educational needs, such as the need for additional education regarding vector-related molecular biology, design, and dosing considerations. These topics may be the focus of future CME programs. CONCLUSIONS: Hematologists/oncologists and pediatric hematologists who participated in this online, Expert Video Commentary activity demonstrated significantly improved knowledge of efficacy and safety data from clinical trials in hemophilia.
CRA 89


Hurst, Simi; Warren, Charlotte; Kadkhoda, Haleh; Van Laar, Emily; Pipe, Steven

Submission Group
Clinical Research/Clinical Trials

Abstract

OBJECTIVE: Gene therapy has the potential to be a dramatic paradigm shift in the care of patients with hemophilia.1-4 To educate and prepare clinicians for this potential paradigm shift, the National Hemophilia Foundation (NHF), European Haemophilia Consortium (EHC), the World Federation of Hemophilia (WFH), and Medscape Education established a multinational collaboration to develop an online continuing medical education (CME) curriculum. The current study assessed the ability of online CME to improve healthcare providers’ (HCPs) knowledge regarding how gene therapy is evolving in hemophilia. METHODOLOGY: A 30-minute, CME-certified, panel discussion activity was developed and launched online on 6/18/2018. Educational effectiveness was assessed with a repeated-pairs pre-/post-assessment study design, with each individual serving as his/her own control. Responses to multiple-choice, knowledge questions and 1 self-efficacy confidence question were analyzed. A chi-squared test assessed changes pre- to post-assessment. P values <0.05 are statistically significant. Effect sizes were evaluated using Cramer’s V (<0.05 modest; 0.06-0.15 noticeable effect; 0.16-0.26 considerable effect; >0.26 extensive effect).

SUMMARY: To date, 3,018 HCPs (2,376 physicians) have participated in this education. This analysis comprises data from the subset of hematologists/oncologists (n=66; hem/oncs) who answered all pre-/post-assessment questions during 6/18/18-6/12/19. Significant improvements were observed overall (P<.0011; V=.164) and with respect to: Correctly identifying the nonenveloped parvovirus vector construct (adenovirus-associated virus; AAV) that is currently being studied in gene therapy trials (61% vs 82% [35% relative increase]; P=.0071; V=.234) Recognizing that the University College London/St Jude trial provided the first evidence that therapeutic levels of FIX could be expressed and sustained for several years using an AAV-based system (53% vs 71% [34% relative increase]; P=.03; V=.187) 21% of hem/oncs had increased confidence with regard to how gene therapy could be used to treat hemophilia A. The findings also uncovered educational needs, such as the need for additional education regarding the FVIII expression levels that have been observed within AAV gene therapy trials for hemophilia A.

CONCLUSIONS: Participation in this online educational activity significantly improved hem/oncs’ knowledge with regard to the viral vectors that are currently being studied in hemophilia trials as well as the extent and duration of factor expression that have been observed to date.
**CTM 15**

**Navigating the Emergency Department: A Collaboration Among Hemophilia Treatment Center Staff, Emergency Department Staff & Bleeding Disorder Chapter Staff**

Littner, Lisa; Tanago, Cristina; Otte, Ann; Lamping, Helen; Raterman, Lisa

**Submission Group**

Collaboration/Team Models

**Abstract**

Introduction: Patients with hemophilia often experience delays in the assessment and treatment of a bleeding episode in the emergency department. They also experience challenges with the emergency department staff not knowing treatment protocol or the importance of receiving factor before diagnostic studies. Previous attempts at doing outreach education to the emergency department staff have not been successful due to the large volume of staff and to the frequent staff turnover. A report obtained from our electronic medical record system has confirmed that on average patients experience wait times for treatment in the emergency department that could be reduced.

Long-term Goal: To have patients receive prompt assessment and treatment of a bleeding episode/injury in the emergency department. Objectives: To educate patients and their families on how to prepare for going to the emergency department at Cincinnati Children’s Hospital Medical Center for a bleeding disorder as well as how to prepare for going to the emergency department at an outside hospital while traveling. To educate patients with hemophilia and their family members on how to communicate effectively with the emergency department staff and how to advocate for the prompt assessment and treatment of a bleeding episode.

Methods: A collaborative team, consisting of staff from the Hemophilia Treatment Center at Cincinnati Children’s Hospital and the Emergency Department at Cincinnati Children’s Hospital, worked together to develop an educational card that can be shown by patients/families to the emergency department staff. The hemophilia team developed an educational document for patients and families, entitled “Navigating the Emergency Department: Tips for Bleeding Disorder Patients”. The hemophilia and emergency department teams also collaborated with the Tri-State Bleeding Disorder Foundation to hold an education dinner for patients and families focused on navigating the emergency department.

Summary: The educational card, entitled the “1-2-3 ED card”, includes information about general factor dose information, definition of bleeds, and treatment protocol. The card emphasizes the importance of patients receiving factor before diagnostic studies and also reminds the staff of the internal policy that permits the use of home factor in the emergency department. The educational document, which is written at a lower health literacy level, highlights information on how to prepare for the emergency department and how to communicate with the staff while there. Staff from the hemophilia and emergency department teams comprised a panel for the education dinner and it was well attended by families.

Conclusion: Utilizing an educational card for the emergency department staff and an educational document for patients/families combined with an educational dinner featuring an expert panel has resulted in the patients and families experiencing an increase in knowledge related to preparing for an...
emergency department visit and on communicating effectively with the emergency department staff.
CTM 18

A multidisciplinary approach to the successful transition of a complex patient with severe hemophilia A with inhibitor to Emicizumab (Hemlibra®): A Case Study

Schmidt, Kirstin Schmidt; Haffler, Donna; Busam, Mary

Submission Group

Collaboration/Team Models

Abstract

Objective: Demonstrate the success of collaborative efforts between the specialized multidisciplinary Infusion Pharmacy Provider (IPP), the prescriber, patient and payer, in achieving improved outcomes. Methods: A Case Study including chart review, cost analysis, and interviews with patient and prescriber. Summary: Patient is a 23-year-old male with severe hemophilia A and an inhibitor, followed by a Hemophilia Treatment Center (HTC). Patient developed a high titer inhibitor with a Bethesda Titre of 1000 BU/ml as a child. Several complex treatment plans including: Immune Tolerance Therapy (ITT) utilizing plasma derived and recombinant factor products, immunosuppressive therapy, and prophylaxis with bypassing agents failed. Complications with implanted ports resulted in hospitalizations and replacement of approximately twenty ports. Numerous hospitalizations for uncontrolled bleeding episodes and pain management contributed to a disruptive childhood/adolescence and suboptimal quality of life for the patient and family. Patient was unable to attend school regularly, develop socially, or participate in normal age-appropriate activities. Repeated uncontrollable bleeding episodes led to the development of target joints and hemarthrosis. The complex nature of the patient’s treatment regimen, his psychosocial issues, bleed history, and cost of therapy resulted in frequent communication and collaboration between all stakeholders to maximize therapy outcomes. Inhibitors presents a significant management challenge.² Emicizumab (Hemlibra®) was approved for the treatment of hemophilia A with inhibitors in November 2017. Well in advance of the transition, the IPP and prescriber discussed the benefits with the patient. Although understandably reluctant due to his history of failed therapies, the patient agreed to try Emicizumab. Initial doses were administered at the IPP’s Alternate Infusion Suite (AIS) under clinical observation, per prescriber’s request. The patient and caregiver received extensive education regarding potential adverse events, self-administration, and bleed treatment regimen during these visits. Conclusion: The coordination of care, communication, and goal alignment by all stakeholders resulted in positive outcomes for this patient. Following eighteen months of therapy with Emicizumab, the patient reports improved over-all quality of life as evidenced by his ability to maintain employment, attend college, and engage in social events/activities. Twenty-two hospitalizations in the twelve months prior to changing therapies decreased to one in the eighteen months after transitioning. His bleeding events decreased from six to eight bleeds per month to one bleed in the past eighteen months and this bleed was attributed to a missed dose. Education on the importance of adhering to prescribed dosing schedule was reinforced by both the IPP and HTC. His port has been removed.
Along with his significant increase in quality of life, the dramatic decrease in overall cost of care will be highlighted.
A survey among patients with hemophilia and inhibitors seeking treatment in non-hemophilia treatment centers

Davis, Joanna A.; De Moerloose, Philippe; Benchikh El Fegoun, Soraya; Habis, Richard; Klamroth, Robert

Abstract

Objective: Acute bleeds in patients with rare bleeding disorders (RBDs), including congenital hemophilia with inhibitors (CHwI), acquired hemophilia, congenital factor VII deficiency, and Glanzmann’s thrombasthenia (GT) must be treated as quickly as possible. This study evaluated the obstacles and experiences of patients with CHwI, or their caregivers, for the early treatment of acute bleeds in non-hemophilia treatment centers (HTCs). Methods: Patients in the United States (aged 18–65 years [or caregivers of patients <18 years]) with CHwI, who currently have or have had inhibitors in the last 3–4 years, and who sought treatment in a non-HTC, underwent an interactive online qualitative discussion over 7 days. Summary: The survey was completed by 23 respondents (seven patients and 16 caregivers; all patients with CHwI). Respondents were aware of the need to treat bleeds quickly, which had been taught to them by physicians and learned from experience. Delays in respondents initiating their treatment were typically due to: technical issues (e.g., 7/23 respondents had difficulty gaining access to a vein or port); delay in diagnosis (e.g., 5/23 respondents’ child does not inform caregiver of the bleed); convenience (e.g., 3/23 respondents were unwilling/unable to take treatment out of the home); or financial issues (e.g., one respondent had inadequate insurance). Respondents tended to visit a non-HTC as a last resort, often due to the long distance to an HTC when emergency treatment was needed, unsuccessful pain management, or unsuccessful factor administration at home. Most patients/caregivers (20/23) reported treatment delays in emergency departments (EDs). Delays in EDs were often due to healthcare professional’s (HCP) lack of knowledge (16/23 respondents; 4 hours average wait until treatment) and four reported delays due to lack of available treatment (14 hours average wait for treatment). All patients/caregivers reported that they had dealt with uneducated/unaware HCPs, having to spend significant time educating the ED staff. Three respondents reported not waiting for treatment—partly because they chose hospitals very carefully, and because they had educated their closest hospital prior to needing an emergency service. Patients/caregivers with negative experiences reported that HCPs were unwilling to listen to them, did not seek consultation quickly, dismissed their instructions, and directed care that forced an outcome. When patients had satisfactory experiences, HCPs listened intently, immediately called an HTC/patient’s physician, and provided care in consultation. Respondents highlighted the need for HCPs education on hemophilia. Conclusions: Patients/caregivers are aware of the need to treat an acute bleed fast, but sometimes delay their treatment, and experience delays when attending non-HTCs. The lack of experience of HCPs in managing acute bleeds contributes to these delays. Improved education of HCPs at non-HTCs and provision of protocols or guidelines would be beneficial for patients with CHwI.
rFVIIIFc for first-time immune tolerance induction therapy: interim results from the global, prospective verITI-8 study

Malec, Lynn; Spasova, Mariya; Sharathkumar, Anjali; Chan, Anthony; Wright, Jordan; Reuter, Caroline; Carcao, Manuel; Konstantinov, Dobrin; Rodriguez, Nidra; Wang, Michael; Haya, Saturnino; Lethagen, Stefan; Jain, Nisha; Bhatnagar, Neha; Hwang, Nina; Van Damme, An; Tsao, Elisa; Peyvandi, Flora

Submission Group
Inhibitors

Abstract

OBJECTIVE: Immune tolerance induction (ITI) is the standard of care for inhibitor eradication and restoration of factor VIII (FVIII) responsiveness in subjects with severe hemophilia who develop high-titer inhibitors. Retrospective data support the use of recombinant FVIII Fc fusion protein (rFVIIIFc) in ITI (Carcao et al. Haemophilia. 2018) but this has yet to be confirmed in prospective studies. This study presents preplanned interim results of verITI-8 (NCT03093480).

METHODS: VerITI-8 is a single-arm, nonrandomized, open-label, ethics-approved study of rFVIIIFc (200 IU/kg/day) for first-time ITI. Eligible subjects had a history of high-titer inhibitors (historical peak ≥5 Bethesda units [BU]/mL) and provided informed consent. The primary endpoint is time to tolerization, defined by negative inhibitor titer (<0.6 BU/mL) at two consecutive visits; incremental recovery ≥66% of expected at two consecutive visits; and rFVIIIFc half-life ≥7 hours. ITI failure is defined as not meeting the above criteria by Week 48. This interim analysis was planned when ≥10 subjects had received ≥6 months of rFVIIIFc ITI.

SUMMARY: Fifteen subjects were screened as of the December 5, 2018 cutoff, while 14 subjects enrolled and had received ≥1 dose of rFVIIIFc for ITI. The median (range) age at start of ITI was 2.6 (0.8–16.0) years and historical peak inhibitor titer was 29.6 (6.2–256.0) BU/mL. Six subjects have been successfully tolerized, with a median (range) time to first negative titer, normal incremental recovery, and tolerization of 2.3 (1.7–15.6), 6.0 (4.3–28.1), and 11.7 (8.1–32.0) weeks, respectively. Seven subjects continue to receive rFVIIIFc ITI (median [range] time on ITI: 16.0 [0.1–35.6] weeks) and 1 subject has failed. No adverse events related to rFVIIIFc have been reported.

CONCLUSIONS: Early results from this prospective/ongoing study of first-time ITI indicate that rFVIIIFc may offer rapid time to tolerization in some subjects with severe hemophilia A and high-titer inhibitors. Achieving tolerance faster can improve quality of life and reduce costs.
A Retrospective Study Evaluating Immune Tolerance Induction (ITI) with a Plasma-derived Factor VIII for Patients with Hemophilia A and High Titer Inhibitor

Escobar, Miguel; Amega, Novinyo Serge; Shaffer, Linda; Holguin, Mark; McCavit, Timothy

Inhibitors

Abstract

Objective: The formation of inhibitors to clotting factors is a serious complication in hemophilia A. Immune tolerance induction (ITI) therapy remains the primary method for eradicating inhibitors. This multicenter retrospective data collection project evaluated patient- and treatment-related factors associated with outcomes following primary or rescue ITI with an antihemophilic factor (Human) concentrate in patients with hemophilia A and high titer inhibitors. Methods: Medical records of nine inhibitor patients treated with antihemophilic factor (human) for primary or rescue ITI therapy between January 1, 2012 and July 31, 2017 were evaluated in four US hemophilia treatment centers. Data were de-identified and analyzed descriptively. Outcome measures were defined per the International Immune Tolerance Induction Study: successful (eradication of FVIII inhibitor and normal FVIII recovery), partial success (near normal FVIII recovery), and failure. Results: A total of nine patients between the ages of 10 months and 39 years at time of ITI were evaluated. Six out of nine patients (66.7%) had successful ITI; three with complete success (ages 27, 32, 32 years) and three with partial success (ages 5, 5, 21 years). Three patients failed ITI (ages 1.5, 10.5, 39 years) (Table 1.) Six of the patients had a combined previous ten attempts at ITI with other products (plasma derived and/or recombinant). Of these six rescue patients, ITI with antihemophilic factor (human) was successful in one and partially successful in three. Conclusions: While retrospective data has limitations, real-world evidence demonstrates that ITI with antihemophilic factor (human) concentrate can be successful or partially successful in diverse populations of moderately complex patients with hemophilia A and high titer inhibitor.
Short-term efficacy of recombinant porcine factor VIII in patients with acquired factor VIII inhibitors

Abou-Ismail, Mouhamed Yazan; Vuyyala, Sowjanya; Prunty, Jeremy; Schmaier, Alvin; Nayak, Lalitha

Inhibitors

Abstract

Introduction: Acquired hemophilia A (AHA) is a rare, often severe, bleeding disorder caused by autoantibodies against factor VIII (FVIII) 1. Current first-line treatment includes bypass agents (BPA), which are challenging to dose due to inability to measure activity levels and response to therapy. Furthermore, high dose BPA can be associated with thrombotic events especially in the elderly 2. Recombinant porcine sequence FVIII (rpFVIII) was developed as an alternative to BPA 3. Available data as to its efficacy, safety, and durability of its use has been limited due to the rarity of these patients. One series of seven patients reported good hemostatic efficacy 4. De novo development of anti-porcine FVIII (anti-pFVIII) has been observed in a small subset of patients in another study 5. We describe our institutional experience with rpFVIII in 5 treated patients.

Methods: In a retrospective cohort, we reviewed the medical charts of 5 patients treated with rpFVIII at our institution between 2016 and 2018. Results: We identified 5 patients treated with rpFVIII at our facility, 4 of which had AHA and 1 had congenital hemophilia with acquired high-titer inhibitor. All 5 patients received rpFVIII for indications of acute bleeding, dosed at 100 U/kg daily, or initially every 12 hours tapered to daily. The treatment was well-tolerated in all patients, with no adverse events upon infusion. Initially, all 5 patients exhibited an effective response evidenced by increase in FVIII levels from baseline <1% to 81-170% (peak value obtained within 1 h of infusion), with normalization of the activated partial thromboplastin time (aPTT) and resolution of bleeding symptoms. However, in 4 out of 5 patients (including the congenital hemophilia patient), continued treatment was associated with decreased efficacy of the drug as demonstrated by a lowered peak FVIII value upon infusion and reversion to a prolonged aPTT. The total number of doses given per patient within one treatment course ranged from 3 to 27 doses. Decreased efficacy was noted after an average of 14 doses. Anti-pFVIII levels were measured in 3 patients and found to be elevated (11-20 Bethesda units), consistent with the development of an inhibitor to rpFVIII. Baseline anti-pFVIII were not measured prior to treatment, and it was assumed that none of the patients had pre-treatment porcine inhibitors based on the robust treatment effect observed. Our results are summarized in Table 1.

Conclusion: At our institution, rpFVIII was safe and initially effective in all patients. However, our clinical experience demonstrates rapid and early development of an inhibitor to rpFVIII, which decreases its efficacy and limits its use. Nevertheless, its initial ability to control bleeding remains extremely valuable when embarking on the care of this disorder. A larger study is necessary to appropriately assess the incidence of anti-pFVIII antibody development in this patient population.
Validation of a FVIII Chromogenic Nijmegen Bethesda Assay for the Detection of Inhibitors in the Presence of Emicizumab (ACE-910)

Tiefenbacher, Stefan; Shrotriya, Sangeeta; Robinson, Mary; Adamkewicz, Joanne; Steinbuesch, Diana

Inhibitors

Abstract

Background: The measurement of FVIII inhibitors is important in the management of Hemophilia A patients and is commonly performed using the Classical Bethesda assay based on the one-stage clotting method. It has been reported that FVIII inhibitor measurement in Hemophilia A patients receiving Emicizumab (ACE-910) therapy show drug interference, leading to false negative inhibitor titers when using a one-stage based factor inhibitor assay. Therefore, there is a need to validate a Nijmegen Bethesda method that is not affected by the presence of Emicizumab, a bivalent antibody bridging activated FIX and FX. Objectives: To validate a FVIII Chromogenic Nijmegen Bethesda assay (C-NBA) for measurement of FVIII inhibitors in Hemophilia A patients receiving Emicizumab (ACE-910) therapy. Methods FVIII activity was measured using the Siemens FVIII Chromogenic Assay on the BCS ® XP (Siemens Healthcare Diagnostics Inc.). Dilutions of inhibitor samples were prepared in 50 mM imidazole buffer containing 4% Bovine Serum Albumin (BSA). Sheep anti-human FVIII inhibitor plasma (Affinity Biologicals) was spiked into congenital FVIII deficient plasma to obtain inhibitor validation samples at 40.0, 5.0, 1.0 and 0.25 (negative) CBU/mL. Validation samples were tested in the FVIII Chromogenic Nijmegen Bethesda assay post heat pre-treatment at 56 ± 2°C for 60 minutes. Intra- and inter-assay relative accuracy and precision, as well as dilution integrity, selectivity and sample stabilities were assessed. In addition, a second set of inhibitor validation samples at 10.0, 5.0, 1.0 and 0 CBU/mL, containing either 50 or 100 µg/mL Emicizumab, were prepared and tested. Results Intra- and inter-assay relative accuracy and precision was demonstrated for all levels of positive inhibitor samples. Intra- and inter-assay relative accuracy (RE) ranged between -22.0 to 0.4% and -20.0 to -0.2%, respectively. Intra- and inter-assay precision (CV) for the positive validator samples ranged between 8.8 to 19.6% and 11.4 to 16.1%, respectively. Dilution integrity was demonstrated by testing a high inhibitor sample at four separate pre-dilutions. Selectivity was demonstrated in six congenital FVIII deficient donor plasmas spiked to 1.0 CBU. Sample stability was demonstrated up to 3 hours post heat treatment and 2 hours post incubation, as well as following 3 additional freeze thaw cycles. Emicizumab at 50 or 100 µg/mL did not result in a change to the measured inhibitor titer when compared to a buffer control. Conclusion: The FVIII Chromogenic Nijmegen Bethesda assay (C-NBA) was successfully validated for the measurement of FVIII inhibitors in Hemophilia A patients in the presence of Emicizumab (ACE-910).
NHF’s State Advocacy and the Bleeding Disorders Community

Harp, Dillon; Hayes, Brendan; Robie, Bill; Schaefer, Nathan

Submission Group
Law/Ethics/Health Policy

Abstract

Objective: NHF Chapters must develop, support, and sustain influential advocacy programs to protect and enhance access to health care for the bleeding disorders community. Method: NHF supports the development of state health care policy advocacy programs with in-kind and financial assistance. NHF’s State-Based Advocacy Coalition (SBAC) program and the standard advocacy expectations our Chapters are the pillars of a robust framework of state advocacy programs. The standard advocacy expectations provide clear expectations and identify best practices for advocacy programming. These include: an advocacy committee of staff and volunteer advocates that meets monthly, multi-year strategic planning, clear engagement with legislative and administrative policymakers, an advocacy annual budget, and more. Chapters are also expected to actively engage their network of Hemophilia Treatment Centers, and all Industry partners. The SBAC program provides funding and in-kind support from NHF for chapters to either start an advocacy program or grow and maintain an advanced one, using the standard advocacy expectations as a guide. NHF provides extensive in-kind support for SBAC grantees, as well as assisting all other chapters with their specific advocacy needs. Summary: Since the inception of the SBAC program NHF has seen participation by and enthusiasm among community members in advocacy events and programming grow. Nearly 500 volunteers participated in NHF’s Washington, DC Days in recent years. Chapter run State Advocacy Days are more prevalent and well-attended. At least 1000 advocates now travel to their state Capitol each year to participate in chapter Advocacy Days. There are 15 grantees participating in the SBAC program covering 20 states. Collectively, NHF has trained more than 5,000 volunteer advocates across the country. Increasing numbers of volunteer advocates have turned out in state capitols for several years to make their voices heard and influence health care access. In addition, NHF’s investments in public policy resources have allowed us to encourage and support state regulatory advocacy, e.g. with state Medicaid offices. These new efforts have demonstrated tangible results in the form of protecting and enhancing patients’ access to care. The promotion and support of state chapter advocacy programs by NHF, especially among the SBAC-participating states, has advanced the public policy interests of the bleeding disorders community. Objectively, we’ve seen the increased numbers and enthusiasm of volunteer advocates. Anecdotally, there are many stories of chapters playing a key role in state health care policy, Conclusion: Successful state advocacy work has led to improved access to quality healthcare. Start-up and ongoing support from NHF have played a critical role in that success. The continued refinement of our Chapter standard advocacy expectations and in-kind support of NHF policy staff will continue to be key to advancing state advocacy programs uniformly around the country.
ACUTE LYMPHOBLASTIC LEUKEMIA IN A PEDIATRIC PATIENT WITH HEMOPHILIA B: A RARE CLINICAL CHALLENGE

Abraham, Shirley; Kiser, Riyan

Submission Group
New Products

Abstract

Background: There are no reported cases of acute lymphoblastic leukemia (ALL) in patients with hemophilia B. There is one case report of a young adult with hemophilia B and acute myeloid leukemia (AML). Currently, there is no best practice recommendation for the management of patients with hemophilia B and ALL. Objectives: To report our experience in managing a pediatric patient with congenital hemophilia B and ALL, which presents a rare and unique clinical challenge. Design/Method: Retrospective chart review. Results: This is a 2y/o male with hemophilia B diagnosed at birth from a cord blood sample showing a factor IX level <1%. Mother is a known carrier and maternal grandfather has severe hemophilia B. Patient started prophylaxis with a standard half-life product through central venous access around 8 months of age, following a spontaneous wrist bleed. The schedule was 35 units/kg twice a week. He had no spontaneous joint or soft tissue bleed on this regimen. 3 mo ago he presented with pain and swelling of the right wrist. He fell on an outstretched hand the day before and received 100% factor infusion. X-ray showed metaphyseal lucencies with overlying soft tissue swelling. No evidence of fracture. Due to this finding, additional labs were done: WBC 4.8K, hemoglobin 7.1 g/dL, platelets 18K and 31% blasts. Flow cytometry confirmed the diagnosis of pre-B-ALL. On exam, he had pallor, scattered petechiae and cervical lymphadenopathy. Based on recovery studies and thrombocytopenia, the prophylaxis was changed to 50 units/kg every third day. The platelets are kept above 30K at baseline. For lumbar punctures, he has been corrected to 100% factor level and platelets kept above 50K. However, due to the risk of port infection with frequent accessing, he was switched to long-acting albumin fusion factor IX product on day 22 of induction. The current prophylaxis regimen is 75 units/kg weekly and the schedule is adjusted to coincide with lumbar puncture days whenever needed. He has tolerated all his procedures well without increased bleeding, including end of induction bone marrow aspiration, biopsy and lumbar puncture with intrathecal chemotherapy. He is currently in remission and is in interim maintenance phase of treatment per COG protocol AALL0932. Conclusion: Long-acting factor IX products could potentially decrease the number of infusions and need for frequent central venous access in immunocompromised patients with hemophilia B. In addition, a higher trough level with a weekly schedule could provide better bleed control in patients with severe thrombocytopenia due to underlying malignancy. A baseline platelet count of at least 30K is recommended during treatment. More treatment guidelines need to be established.(1) Clark C et al, Pediatric Blood and Cancer Jan 2011
Tackling a New Era of Treatment in Hemophilia A: One Institution’s Experience of Integrating Emicizumab into Practice

Hallam, Michelle

Abstract

Objective: In October of 2018, emicizumab received FDA approval for prophylaxis in all patients with Hemophilia A. Emicizumab is a novel agent that mimics the activity of Factor VIII by bridging activated Factor IX and Factor X. It is delivered subcutaneously with dosing options of weekly, biweekly, and once monthly (following 4 loading doses). Previous standard of care for patients with a severe bleeding phenotype has been routine infusions of intravenous (IV) Factor VIII. However, given the short half-life of recombinant Factor VIII, and challenges with IV access, these prophylactic treatments carry a high burden of treatment. Therefore, emicizumab has become an attractive alternative for this cohort. The following is an example of how one institution managed the initiation of this novel agent. Methods: The members of the Hemostasis Team at Nationwide Children’s Hospital (NCH) met weekly to create and review an Excel database of all patients interested in emicizumab. Initiation was prioritized for patients with active inhibitors, and patients who were currently not on prophylaxis. The database included a checklist for the following categories: Patient’s homecare company, prescriptions written, insurance approval, dates of loading doses (1-4), completion of education sessions, and follow-up appointments. Additionally, patients starting on emicizumab had baseline joint ultrasondundos of bilateral knees, ankles, and elbows to track long-term joint health on this medication. Screening labs were based on those used in the Haven clinical trials, and included a complete blood count, comprehensive metabolic panel, quantitative D-Dimer, lactate dehydrogenase, and Factor VIII inhibitor titer. There were four education sessions, which corresponded with the loading doses in clinic. Each education session was guided by an education checklist, with the overall goal that patients or caregivers could effectively demonstrate drawing up and administering the medication. Injection site reactions, bleeding, and adverse events were also assessed at each education session. Results: Since FDA approval was granted, through May of 2019, 24 patients with Hemophilia A at NCH have successfully completed the loading process with this agent. Each patient completed screening labs, four loading doses (with corresponding education sessions), and have transitioned to maintenance dosing. The longest delay in the initiation process occurred between prescriptions written and insurance approval, with a median of 29 days (range 2-103 days). Families that were unable to demonstrate competence with administration (n=2) were placed on a biweekly regimen, and connected with home nursing services for administration. Twenty-two of the 24 patients have completed baseline joint ultrasondundos. Conclusions: Emicizumab is a novel therapy for the treatment of Hemophilia A. Therefore, initiation of this medication should be carefully planned and closely monitored by trained HTC staff. Above is an example of how one institution managed this process.
Use of Return to Sport Testing for Prevention of Bleeding Episodes Following an Acute Injury in the Hemophilia Patient

Horton, Rachel

Submission Group

Orthopedic and Physical Therapy

Abstract

Use of Return to Sport Testing for Prevention of Bleeding Episodes Following an Acute Injury in the Hemophilia Patient. Rachel Horton, PT, DPT, CSPS. Objective: Return to sport testing, specifically hop and drop vertical tests, have been utilized in the general athletic population following ACL tear or other injury in determination of readiness to return to high level activities and sports with minimized risks of re-injury. This case study looked at the ability to utilize these same tests for a hemophilia patient recovering from femoral nerve damage and resultant quad atrophy due to a prolonged iliopsoas bleed to return to activity without reinjury or rebleeding into the involved muscles. Methods: A 10 year old moderate FVIII patient recovering from muscle damage related to a severe iliopsoas bleed completed the Y-balance test, single leg broad jump on one foot, triple broad jump on one foot, the single leg triple crossover hop test and drop vertical jump over 4 time points, starting at approximately 12 months post injury and ending at 18 months post injury. Objective measurements were collected for each task in addition to video analysis using Hudl Technique. In addition, the Patient Specific Function Scale (PSFS) and Tampa Scale-11 (TSK-11) were completed at time points 1 (12 months post injury) and time point 4 (18 months post injury). Summary: There was a decrease in distance hopped on the injured lower extremity from time point 1 to time point 2 on the single hop test by 1.8cm and on the triple hop test by 12.1cm. Injured v. non-injured leg comparisons at time point 1 was 81% for single hop and 87% for triple hop. At time point 2, comparisons were 80.1% for single hop and 78% for triple hop. There was no appreciable difference in distance hopped in braced v. non-braced conditions at time point 2. Despite decreases in measured hop distance, video analysis demonstrated an improvement in mechanics during both hop tests and also drop vertical test. No collapse of the injured leg was noted during time point 2. Conclusion: Return to sport testing was successfully utilized in this patient’s physical therapy program to provide valuable information on creating appropriate return to activity timelines and demonstrating remaining limitations which allowed for his program to be more tailored to him. However, with decreased performance demonstrated at time point 2, return to sport testing was utilized as just one component in a full physical exam and discussion with the patient’s HTC care team. Additionally, use of video analysis proved to be beneficial in demonstrating improvement in form when improvement in measured distance was not present. Age is an important factor to consider when selecting return to sport tests.
Abstract

Physical therapy and Extensions for Community Healthcare Outcomes (ECHO): Western States Hemophilia Regional Project Objective: Report on the utilization of a multi-point videoconferencing platform, Extensions for Community Healthcare Outcomes (ECHO), in providing a clinical learning opportunity to physical therapists (PTs) involved with people with bleeding disorders (PWBD) within Western States Region Hemophilia Treatment Centers (WSR HTC). Methods: WSR HTC includes thirteen HTC’s located in California, Nevada, Hawaii, and Guam. Monthly one-hour evidence based case presentations with a facilitated discussion were conducted using the ECHO platform. Each session was recorded, so all the therapists invited to participate have access to the information. Data were collected from the WSR participating PTs by using anonymous on-line surveys, Qualtrics software (Qualtrics, Provo, UT), and prior to the start of the physical therapy ECHO session and upon completion of each session. Descriptive statistics were calculated to evaluate the educational value of presentations. Results: Thirteen PTs, surveyed prior to the first PT ECHO session had reported > 6 years of experience as a PT. Twenty-three percent reported < 5 years of experience working with PWBD and over half of PT surveyed had > 16 years of experience working with PWBD. Eight topics were presented in 2018 included musculoskeletal ultrasound imaging, invasive surgery rehab outcomes for patients with inhibitors, kinesiology taping, knee arthroplasty and stiffness, iliopsoas bleeding, myofascial decompression, chronic pain, knee bleed, and ankle joint impact from bleeding. An average of nine HTC PTs attended each session (range 4 to 18). Ten (11.2%) non-HTC PTs (outpatient PTs, HTC nurse, HTC Nurse Practitioner) attended some of the PT ECHO sessions. Table 1. Ninety-five percent of respondents reported strong agreement with the program’s educational value and appropriateness for a practicing PT. Thirty-seven (94.9%) of responses reported agreement that the PT ECHO program improved their knowledge of physical therapy and bleeding disorders. Table 2. Conclusion: Videoconferencing platforms such as ECHO allows PTs in the WSR HTC, who are geographically separated to successfully share clinical knowledge to facilitate best practice in the area of specialty care for PWBD. Please see files attached for tables and figures.
ORT 65

EVALUATION OF JOINT BLEEDS USING PORTABLE ULTRASOUND AND ITS IMPACT ON TREATMENT OF PERSONS WITH HEMOPHILIA IN A RESOURCE LIMITED SETTING

Wanjiku, Christopher Mwaniki; Isaji, Samuel; Kaltenmark, Tiffany; Akins, Stacie

Submission Group
Orthopedic and Physical Therapy

Abstract

BACKGROUND: Hemophilia is a bleeding disorder that can adversely affect the joints of Persons With Hemophilia (PWH) if not appropriately managed. Recurrent bleeding into a joint causes synovial hyperplasia, chronic inflammation, fibrosis and haemosiderosis resulting in arthropathy. Timely infusion of Clotting Factor Concentrate (CFC) may help prevent this sequel. The joints frequently affected include the knee, ankle, and elbow as a result of direct trauma or spontaneous bleeding. Detailed evaluation of joint swelling may help distinguish acute and sub-acute bleeds from joint symptoms as a result of chronic arthropathy thus guiding appropriate treatment and improving both outcomes and conservation of resources. OBJECTIVES: To assess the impact of ultrasound evaluation of joint bleeds on the choice of treatment selected for PWH. METHODOLOGY: In April 2018, 5 patients who presented with self-reported symptoms of bleeding into their joints (increased pain, swelling or decreased range of motion) to Moi Teaching and Referral Hospital in Eldoret, Kenya had their joints assessed using a broadband linear array transducer connected to a monitor display. Of these patients reporting symptoms of an acute bleeding event; two had symptoms in the knee, two in the elbow, and one in the ankle. The initial plan from physician’s physical examination assessment was to infuse all of them with CFC. After scanning them with the ultrasound probe it was revealed that one ankle, one knee, and one elbow did not have an effusion suggestive of an acute or subacute joint hemarthrosis and symptoms were consistent with exacerbation of pain associated with chronic arthropathy. For these cases conservative management was used rather than infusing CFC and they proceeded to full symptomatic improvement. DISCUSSION: Three out of five PWH proceeded to recovery from their self-reported symptoms of acute joint bleeding events without CFC infusion. It is likely that the clinical presentation mimicking an acute or a subacute joint bleed may have been pain from a joint with hemophilic arthropathy that is best managed by physiotherapy. The use of ultrasound to confirm presence or absence of an active bleeding event may assist in conserving factor for potential life-saving cases. This may also help in preventing misdiagnosis of chronic arthropathy in a patient with active bleeding. CONCLUSION: Assessment of joint bleeds using ultrasound has the potential to impact the administration of CFC to PWH with chronic arthropathy, and also to prevent missing an acute bleed. A study on a large number of PWH with joint pain and, swelling or decreased range of motion needs to be undertaken to demonstrate the relevance of ultrasound assessment of bleeds in PWH.
PI 12

Depression in hemophilia and von Willebrand using the Beck Depression Inventory

ABREU BASTAR, ANA PAOLA; ABREU BASTAR, ANA LAURA; ESCOBAR RUIZ, VALERIA

Submission Group

Psychosocial Issues

Abstract

It is widely known that patients with a chronic disease have a high risk of depression (Fleiz and Zambrano, 2004). Depression is a common illness worldwide, with more than 300 million people affected. Depression is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. Especially when long-lasting and with moderate or severe intensity, depression may become a serious health condition. It can cause the affected person to suffer greatly and function poorly at work, at school and in the family. At its worst, depression can lead to suicide. Close to 800 000 people die due to suicide every year (WHO, 2018). According to data from INEGI (2017) in Mexico, the number of suicides is increasing, the annual rate among young people is 7.9 per 100 thousand inhabitants, while the total population is 5.3. Particularly Tabasco occupies the first place in young suicide and the ninth in the rest of the population. Objective: To estimate the prevalence of clinically depression in adults with Hemophilia and von Willebrand resident in Tabasco, Mexico. Method: 81 patients with Hemophilia and von Willebrand and 36 apparently healthy people (control group). The presence of depression was determined using BDI-II (Beck’s Depression Inventory). All of the findings were assessed by SPSS 21. Data were analysed using descriptive statistics, the chi – square test and p –values. Summary: 54.44% of the patients with a bleeding disorder presented depressive symptoms, 45.67% did not present depressive symptoms, 28.39% had mild depressive symptoms, 16.04% had moderate depressive symptoms, 9.87% severe depressive symptoms. In the case of the control group 80.55% did not have depressive symptoms. Statistically significant differences were found only in apparently healthy people compared to patients with a bleeding disorder (p=0.03). Conclusions: Comparing to the control group, patients with a bleeding disorder obtained an elevated score in the BDI-II. More than half of the patients presented depressive symptoms. Once the patients who had high scores on the test were detected, cognitive behavioral therapy was used to treat depression; the therapist helped the patients to identify and break down your thought patterns and reactions into different categories of negative thought, including: overgeneralization, all–or–nothing thinking, rejecting the positive, records of thoughts through cognitive restructuring, monitoring of daily activities. As patients perceived that they have control and control over the activities they performed and enjoyed them, they regained their self-confidence. In this way, they began to resume activities or habits that had been suspended, thus favoring their moods. Key Words: Bleeding disorders, Depression, Psychology.
Behavioral Health and Substance Use Screening Practices among Hemophilia Treatment Centers

Pfost, Gretchen Pfost; Robinson, Jordan; Jarvis, Aerial; Stevenson, Angela; Karim, Rania

Submission Group

Psychosocial Issues

Abstract

Objective: To examine the frequency and methods used to screen patients for substance use and behavioral health disorders in Hemophilia Treatment Centers (HTC). We hypothesized that inconsistencies in methods utilized and frequency of utilization exist. Methods: Marshall University (MU) Physical Therapy faculty along with MU addiction education staff developed a 26-question survey using Qualtrics. The survey included questions on demographics, validated screening tools utilized, screening frequency, and team member responsible for screening. The HTC email addresses were obtained from the Hemophilia Treatment Center Directory on the CDC’s website. Following approval from MU IRB, the survey was disseminated via an online link. Descriptive analysis was performed on the data. Summary: Health professionals from 19 HTCs, representing 8 different regions, completed the survey. The overall response rate was 13.6%. Social workers (12, 63.2%), nurses (6, 31.6%) and counselors/psychologists (1, 0.05%) submitted responses. On average HTCs reported 34.5% (0-92%) of their patients experience chronic pain with an average 22.4% (0-56%) receiving prescription opioids for pain management. Adverse consequences related to opioid use existed in all of the HTCs including overdose (31.5%), withdrawal symptoms (42.1%), increased dose due to tolerance (63.2%), and increased bleeding episodes (26.3%). The majority of HTCs (57.9%) reported being the primary provider of pain management for people with hemophilia (PWH). Standardized screening for substance use disorders is occurring 31.6% of the time with marijuana and illicit drugs (100%) being most commonly screened followed by alcohol and prescription drugs (83%) and tobacco at 33%. Frequency of screening for substance use varied widely from every comprehensive visit to initiation of an opiate contract to suspicion of misuse. Screening for behavioral health is more common (81.3%) with a variety of validated screening tools being utilized. Over 60% of the time, screening for anxiety and depression occurs either annually or every visit. Conclusions: PWH often develop chronic pain related to joint arthropathy. Based on our findings, the incidence of chronic pain in PWH is relatively equal to the national average. HTCs are often the primary provider of pain management and are challenged to find safe treatment methods. PWH are often prescribed opioids which may place them at increased risk for potentially developing an opioid use disorder. The presence of a behavioral health disorder may further enhance one’s risk. Although behavioral health screenings appear to be more consistently utilized in HTCs, substance use screenings are rare. Our research suggests that universal screening for substance use and behavioral health conditions should be considered, as a standard of care in HTCs, to better inform healthcare providers of patient risk, need for referral and to guide prescriber’s decision making with regard to pain management options.
Parents Empowering Parents (PEP) Community Survey: How does the community want to stay engaged, communicate, and receive information?

Nguyen-Driver, Mina

Submission Group
Psychosocial Issues

Abstract

Introduction: Parents Empowering Parents (PEP) is a program designed for parents of children with a bleeding disorder (BD). With multi-dimensional content and exercises, PEP provides educational material and tools to strengthen parenting skills focusing on children to becoming independent, capable adults. PEP reduces isolation and feelings of hopelessness and helplessness. While most parents seek books or talk with friends for parenting advice, PEP offers a support network for parents who not only have difficulty trouble shooting parenting skills, but also has a child with a bleeding disorder. The PEP program, administered by Energizing and Empowering Minds (EEMinds), have been launched in over 13 different countries since 1996. To ensure that PEP remains relevant and meaningful, EEMinds launched a survey to capture data about how the PEP Community wants to stay engaged, communicate, and their technology preferences.

Method: The PEP Community Survey is a 24-question survey of quantitative or qualitative questions. Data was captured electronically via Survey Monkey using multiple choice, Likert scales, and comment functionality. The request to complete the survey was sent out to community members via email on May 2, 2018. The survey included questions regarding community member’s demographics, number of PEPs participated in, and technology and communication preferences. Results: Forty-one (N=41) community members responded to the survey request. Most of the respondents were either parents of children with BDs or professionals that work at the Hemophilia Treatment Center (HTC). Sixty-seven (67%) percent of the respondents use Facebook daily. Over 87% of respondents would like to receive PEP information via email and over 73% would like to be more involved with PEP. The key PEP program aspects that were most recognized by respondents is 1. having a safe place to share personal stories, 2. connecting/bonding with other parents, and 3. learning new and effective parenting skills. One-hundred percent of respondents have recommended PEP to other parents. Conclusion: The Community has spoken. EEMinds is not only listening, it is taking action. PEP helps parents of children with BDs to develop skills that directly influence their ability to parent. The survey results show that the PEP program is valued by the community. The results also provide specific guidance and direction on how EEMinds needs to invest its resources in relevant and meaningful ways. There are several workstreams that have been triggered based on the survey, which is to be more active emailing newsletters, posting on our Facebook page, and connecting families.
PI 57

Gender Differences in Parenting Stress and Social Support Among Hemophilia Families

Gates, Carletha

Submission Group
Psychosocial Issues

Abstract

Objective: This research study examined gender differences in parenting stress and social support perceptions in families of children with hemophilia. This study sought to raise awareness of gender differences related to hemophilia parents’ stress and impact how they can better utilize social support networks as they raise their chronically ill child. Understanding the link among gender, stress, and perceptions of social support is important to help parents develop coping strategies to meet the unique challenges of caring for their child with hemophilia. Methods: A quantitative, online survey design was used for this study. Two instruments measured the data: the Parenting Stress Index-Short Form (PSI-SF) measured parenting stress, and the Medical Outcome Study Social Support Survey (MOS-SSS) measured social support. A demographic questionnaire developed by the researcher was also used. Using a purposive sampling technique, mothers and fathers, over the age of 18, who have children with hemophilia, and reside in Maryland, Washington, DC, or Northern Virginia were recruited for the study. Two research questions and related hypotheses were developed for the study. MANOVA was used to determine whether mothers and fathers of children with hemophilia differ with regard to level of perceived parenting stress and level of perceived social support. Summary: The study revealed that mothers expressed significantly higher levels of parenting stress than did fathers. The findings also indicated that mothers’ perception of social support was significantly higher than that of fathers. No significant difference in parenting stress in the severity of the child’s hemophilia was found. The total sample consisted of 62 participants; 59.7% (n = 37) were mothers and 40.3% (n=25) fathers. Univariate testing found that mothers (M = 140.05) had a significantly higher level of perceived parenting stress than fathers (M = 121.08). Univariate testing found that mothers (M = 68.46) had a significantly higher level of perceived social support than fathers (M = 56.32). Parenting stress did not significantly differ for parents with children with mild to moderate hemophilia (M = 134) and parents with children with severe hemophilia (M = 131.64). Conclusion: The findings from this study support the need for hemophilia advocates to have a more in-depth dialogue about parenting stress. No matter the severity of the child’s hemophilia, all hemophilia parents experience stress and are in need of gender-specific social support. Study results should equip hemophilia advocates with information that will add clarity to the implications of gender differences and how to relate these differences to understanding stress and providing gender-specific social support. The information from this study can be used to engage parents through programs and services that would help decrease stress and increase social support use to improve the health, wellness, and overall quality of life of the hemophilia family.
PI 60

Pain assessment and treatment in bleeding disorder care: The need for social work specific education

King, Jennifer

Submission Group

Psychosocial Issues

Abstract

Objective: Persons with bleeding disorders experience pain in association with needle pokes, joint and muscle bleeds and permanent tissue damage. The impact of this pain on patients can include time off school or work, a change in career, income, stress, mental health concerns and change in relationships. Comprehensive pain management includes strategies from the “Four P’s of Pain Management” which include pharmacological, physical, psychological and prevention. The aim of the project was to examine current psychological knowledge and management of pain within our patient population. This study asked the following research questions: 1) What is currently understood about pain and bleeding disorder care among social workers (CSWHC)? 2) What specific pain knowledge and training is prioritized by social workers in Hemophilia Treatment Centres? A scoping review was conducted concurrently with the qualitative study. Medline and SocIndex were searched with the terms “social work” and “pain management” and a second search was conducted with the term “social work and hemophilia/von willebrand’s or platelet disorders”. A total of 105 articles were examined by three independent reviewers. Eleven articles have been included for the purpose of examining the role of social work in pain management. Methods: Qualitative interviews were conducted and recorded with 12 social workers from the CSWHC between September 2018 and February 2019. Five provinces were represented. Social work participants were deployed within paediatric, adult or within combined clinics. The interviews were approximately 20-45 minutes. Transcribed interviews were coded with NVivo by two independent reviewers with Thematic Analysis. Summary: Social workers identified the roles of social work to include completion of psychosocial assessments and meeting the practical needs of patients, while supporting patients in medical decisions. Barriers to pain management and the impact of pain on patients were described as having an impact on individuals and families. Social workers also discussed their understanding of acute and chronic pain in patients, which has indicated an increase of knowledge is required. Skills development in multi-dimensional nature of pain and pain assessment were determined to be most likely to produce positive impact on practice outcomes. Initial themes include hope, relationship of trust, stigma (diagnosis vs. pain), defining multidisciplinary roles. Conclusion: Study results, first, will contribute to the literature supporting the need for social work education for those practicing in bleeding disorder care. Secondly, they will provide recommendations for an educational pain curriculum for social workers in bleeding disorder care. This education will reflect the need for pain knowledge in acute and chronic pain dimensions which will facilitate dialog with other professionals in pain management. Pain assessment will also be a focus in order for social workers to be able to support and provide appropriate referrals for pain management.
HemoFOCUS Screener for Inattention, Hyperactivity and Impulsivity: A Quality Improvement Intervention for Children with Severe Hemophilia

Pullen, Amanda

Submission Group
Psychosocial Issues

Abstract

Objectives: Psychosocial professionals within the St. Jude Children’s Research Hospital’s Hematology Clinic observed trends of inattention (IN) and hyperactivity/impulsivity (HI) concerns reported by teachers and parents of children with severe hemophilia. Although these observations are anecdotally shared by members of the bleeding disorder community on a frequent basis, this concern has not been well documented in the literature. Traditional community-based avenues of intervention are not consistent, leaving this population largely unserved. Children with severe bleeding disorders coupled with IN and/or HI are at high risk for school and family dysfunction. The main objective of this QI is to initiate early identification of children with severe hemophilia at-risk for IN and/or HI and to establish a feasible, systematic process for screening patients in a fast-paced outpatient hemophilia clinic for medical management.

Methods: Hematology educator and social worker targeted a population of patients aged (3-16) with severe hemophilia and utilized the following assessment tools: open ended questions about academic or behavioral concerns, neuropsychological assessment referral if history of brain hemorrhage, and the Conners 3 assessment as a main tool to assess risk for ADHD and common comorbid problems and disorders in children. Psychosocial professionals approached caregivers with open-ended questions about IN and HI to triage the testing tool to be administered. As needed, psychological or neuropsychological testing was referred to Psychology clinic and the results were evaluated in conjunction with Hematology staff. Summary: In this cohort of 28 patients with Severe Hemophilia, the risk of ADHD was identified and diagnosis confirmed in 50% (n=14) of children evaluated. 21.4% (n=6) of patients were identified at risk for ADHD but require additional testing for diagnosis. The number of patients identified with no risk for ADHD was 28.6% (n=8). Conclusions: The Conners 3 is a useful tool for psychosocial providers to use with caregivers in the outpatient hemophilia clinic and effectively identified children with needs. This Quality Improvement (QI) project increases awareness among staff and community providers regarding how IN and/or HI can directly impact patient outcomes, validates caregiver concerns, and eases the course of action to get support. Within this cohort, 50% of severe hemophiliaics presented with elevated IN and HI with a formal diagnosis of ADHD, which is significantly higher than that reported in the general population of 3-7% (Mash & Barkley, 2014). These results are being used to facilitate interventions in the school setting via providing staff education, establishing behavioral plans, and advocating for classroom accommodations through The Individuals with Disabilities Education Act (IDEA) or Section 504. Overall, the QI project provides preliminary results and confirms the need for additional research required to assess the potential link between inattention and hyperactivity/impulsivity and severe hemophilia.
The impact of face-to-face social work meetings in bleeding disorder care

King, Jennifer

Submission Group

Psychosocial Issues

Abstract

Objective: Specialized knowledge is required to assess, treat and to support patients with bleeding disorders and their families. Social workers working in this unique clinical area, often do so in isolation with a lack of onsite discipline-specific mentorship. National meetings which provide face-to-face contact with other social workers counters this and provides imperative opportunity for collaboration and education. This promotes significant learning and professional growth; enhancing patient care. Conversely, securing funding for our meetings is becoming increasingly difficult, therefore, tangible and stated benefits need to be voiced. Method: Ten CSWHC members attended their annual general meeting in May 2019. Canadian Social Workers in Hemophilia Care (CSWHC) are registered with provincial regulatory bodies and are integral members of the comprehensive care team within Hemophilia Treatment Centres (HTC). The social work role focuses upon psychosocial assessment and treatment with the goal of optimizing Quality of Life (QoL). These social workers have worked within bleeding disorders care between 2 weeks to 25 years. Each social worker attending this meeting, shared their personal experience and the impact of attending this face-to-face meeting. Summary: Social workers emphasized three main areas of impact from face-to-face meetings: Skills and Knowledge Development Listening to the new language/acronyms expands knowledge base Increased awareness and understanding of bleeding disorders which increases patient support Encourages acquisition and maintenance of practice wisdom Support and Affirmation Gain support from experienced CSWHC social workers Fuels the passion for the work Enhanced connections/relationships Heightened awareness of regional differences and disparity in healthcare Promotion of networking, innovation, engagement and mentorship Affirmation of skills and services provided; support around challenges Program Development Recruitment and retention of committee members Succession planning Collaboration around the development, planned implication and evaluation of patient/family services/programs Conclusion: Technology can be seen as a cost effective and reliable replacement for face-to-face meetings and in many ways, it can facilitate the work being completed between meetings. However, research shows the impact that in-person communication has on relationship and program development. Social workers know the necessity of face-to-face interactions for the advancement of social connections given the unique opportunity afforded through this more personal meeting method for the use of non-verbal body language, nuances, efficiency, engagement, development of trust. The CSWHC state that there is a need to maintain face-to-face meetings at a minimum of one time a year. Acknowledgements: Stefan Branov, Claude Bartholomew, Patty Phrakonkham-Ali, Hulda Niv, Doug Campbell, Lezley Ireland, Mirelle LeClaire, Natalie Benson
Quality Improvement: An Initiative to Foster Mental Health Wellness among a Hemophilia Treatment Center Patient Population

Farina, Sabrina

Submission Group

Psychosocial Issues

Abstract

Objective: The goal of this program was to engage attendees of a Community Wellness Fair program in personal wellness methods. Attendees came from Houston and the surrounding metropolitan area. The program was designed to raise awareness of mental health issues, to identify reputable mental health care resources, and to normalize the topics of depression and suicidal ideation. Because the time interval between comprehensive hemophilia clinic appointments is 6 to 12 months, patients benefit by having personal coping skills available whenever needed, should they experience overwhelming life stressors and attempt to cope with these experiences on their own. Offering educational programs on emotional self-care and mental health care resources helps provide patients with effective tools to cope with personal life experiences when most needed. Methods: Gulf States Hemophilia and Thrombophilia Center (GSHTC) hosted a “Community Wellness Fair” for patients and their families in May 2019. A variety of mental health vendors and demonstrations were available, including tai chi, mini massages and modified seated chair yoga. Two on-site counselors were available to meet with participants after completion of a depression screening form. The fair also featured a presentation by a staff member of the UTH Department of Psychiatry on the psychological impact of living with a chronic condition. A community member then described his struggles with depression. The movie “Inside Out” was screened for youth and reviewed by a professional psychiatrist. A peer-reviewed mental health resource booklet, compiled and distributed nationally among hemophilia treatment center (HTC) social workers, was distributed to attendees. Summary: The Wellness Fair was attended by 27 participants who were invited to complete a post-event survey for evaluation of the program and planning for future events. The 20 (74%) respondents were nearly evenly divided between patients and parents/family members; 30% were male and 55% female; 15% did not provide their gender. Evaluations completed by attendees demonstrated a high level of satisfaction with the program content and a desire for practical information about mental health wellness. Responses included the comment “This is the first event I have attended and will be attending more. Thank you . . . for caring about your patients and their families.” Suggestions for future programs included information about children with Von Willebrand disease, substance abuse issues, and more activities for entire families. Conclusions: In addition to providing practical help and advice for dealing with stress, demonstrating to patients and their families that the HTC supports them, may, in the long term, be helpful in unforeseen areas such as medication compliance, reduction of clinic no-shows and completion of treatment logs. Currently GSHTC plans to further develop and enhance programs on personal wellness for the community at large and for specific gender and diagnosis needs.
PSO 17

Using Photovoice with the Bleeding Disorder Population: A Pilot Project

Littner, Lisa; Schulte, Christine; Lamping, Helen; Raterman, Lisa

Submission Group

Peer Support/Outreach/Integration Models

Abstract

Introduction: Photovoice is a qualitative research method that has been used for communities to share pictures as a tool for discussion that is often used at a grassroots advocacy level. Photovoice can show both strengths about a topic or concerns. Photovoice can create empowerment by sharing perspectives and can also create a foundation to advocate for awareness and change. Long-term Goal: To create more awareness surrounding bleeding disorders during the month of March, which is bleeding disorders awareness month. Objectives: To apply Photovoice methodology to the use of social media among the hemophilia population in the Cincinnati, Ohio geographical area. To engage people with hemophilia and their families in sharing their stories related to their bleeding disorder by sharing photographic images on social media during bleeding disorders awareness month. Methods: People that follow the Tri-State Bleeding Disorder Foundation on social media as well as members of a closed social media group that consist of parents of children who are patients at Cincinnati Children’s Hospital were asked to participate in the pilot Photovoice project. Participants were asked to share pictures on their own social media pages and to use hashtags to link the photos to the Tri-State Bleeding Disorder Foundation’s page. The project was promoted by sharing an infographic that explained Photovoice and the details of the project. Several community stakeholders were identified as people active on social media and they were personally asked to participate so that examples of the project could be shared with others. There were weekly themes and a weekly contest for pictures that best exemplified that week’s theme with the winners winning a small gift card. Summary: This innovative pilot project applied the methodology of Photovoice to social media to generate awareness and advocacy during bleeding disorders awareness month. The theme of this Photovoice project was “Living with Hemophilia”. Weekly themes consisted of: living with a new diagnosis, living with treatment, living and learning about a bleeding disorder, and living with health and being physically active. Conclusion: Utilizing Photovoice and applying this methodology to social media as a pilot project with the bleeding disorder population is an innovative idea. This grass roots level movement is a modern way for people to share their story of living with a bleeding disorder. To date, the use of this methodology with the bleeding disorder population has not been documented in the literature. Participants in this project reported satisfaction with being a part of the project. The project’s authors reported that it was a positive and creative way to create more awareness on a personal level about bleeding disorders and they plan to repeat the project in the future.
Objective: To investigate how bleeding disorder characteristics influence patient perceived challenges and management strategies. Methods: This is a mixed-method, retrospective, cross-sectional continuation of a pilot study identifying themes of self-perceived challenges and management strategies for persons with bleeding disorders. Sixty-one participants with a bleeding disorder (BD), either hemophilia (PWH) or Von Willebrand disease (PWVWD), were asked what their most significant challenge was in managing their BD and how they managed that challenge. Data were collected from March, 2017 through December, 2018, coded for themes and uploaded to NVivo. Similar themes were grouped for analysis. Subject-level data was extracted from the electronic medical record including demographics, disease type, severity and presence of joint disease (JD). Pain interference was determined from participant response to the Brief Pain Inventory (BPI). Results: The mean age of the cohort was 31.4 years, with a median of 25 years, and range of 7 to 75 years. 87% were PWH, 13% PWVWD. There were 26% mild, 25% moderate, and 49% severe PWH. 54% had JD. Identified challenges included: participation restriction (24%), acute bleeding (22%), infusion (19%), bleeding sequelae (10%), other’s unfamiliarity with bleeding disorder (other’s unfamiliarity) (10%), no challenges (10%), and other (6%). Management strategies reported were: acceptance (37%), learning through experience (25%), education/advocacy (11%), seeking help (9%), other (9%), and no challenges (9%). Severe PWH greatest reported challenges were participation restriction (27%) and infusion (27%). Management strategies were acceptance (41%) and experiential learning (31%). Mild-moderate PWH greatest reported challenges were acute bleeding (35%), infusion and no challenge (17% each). Management strategies were acceptance (30%) and seeks help (26%). Seek help was not identified as a strategy among severe PWH. Reports of no challenges was higher among those <18 years than those ≥ 18 years. Mean pain interference was 13.2 out of 70 based on the composite score of BPI measures. As age increased, the likelihood of JD and interference increased. Regardless of challenge, people with JD reported interference averaging 18% (range 0-27%). Conclusions: Gaining insight to patient-perceived challenges and management strategies is important to be able to tailor an effective treatment approach that is individualized and meets the changing needs of PWBD across circumstance and life-course.
PSO 71

Optimizing language for effective communication of gene therapy concepts: A qualitative study

Arcé, Claire; Branchford, Brian; Hart, Daniel; Hendry, Sarah; Kelleher, Maria; Kim, Michelle; Ledniczky, Robert; Lee, Mimi; Lee, Sharon; Minshall, Matthew; Negrier, Claude; Prince, Steve; Rice, Michelle; Sidonio, Robert

Submission Group

Peer Support/Outreach/Integration Models

Abstract

Objective: For communities of persons living with hemophilia and other genetic conditions, gene therapy could represent a paradigm shift in treatment strategies. As therapeutic modalities become increasingly complex, there is a critical need for all stakeholders (patients, physicians, patient advocates, nurses, caregivers, reimbursement agencies, drug developers, and regulators) to communicate with a lexicon that is intelligible, accurate, and consistent. In doing so, expectations can be more carefully managed and potential risks, benefits, and limitations can be better understood. In recognition of this need, a first-ever study of gene therapy lexicon was conducted. Here, we report findings that identify a recommended language set for effectively communicating information about adeno-associated virus (AAV)-based gene therapy for hemophilia, between and among stakeholders.

Methods: Structured screener interviews were used to identify a total of 84 suitable participants representing five individual countries (US, UK, Spain, France, Germany, Italy) and audiences (hematologists, nurses, caregivers, patients, and patient advocates). Then, a series of in-depth interviews, face-to-face focus groups, advisory board meetings, and online group interviews were held to collect, refine, and test language and image concepts. Sessions were conducted in local languages with detailed discussion guides. Across multiple topics, preferred words, phrases, and pictorial representations were developed and agreed upon through an iterative and adaptive process. Undesirable, disagreeable, or confusing language was identified. Preferences were largely consistent across audiences and countries; however, where differences existed, country-specific recommendations were made.

Summary: Study results show that the hemophilia community has preferences around consistent lexicon used to describe hemophilia and its therapeutic approaches. Further, outcomes suggest that the use of preferred language can increase understanding and comfort during discussions of novel and complex therapeutic modalities such as gene therapy. Conclusions: This study suggests that consistent use of community-informed lexicon can minimize miscommunication and facilitate informed decision-making regarding potential future treatment opportunities. *Authors listed alphabetically
PSO 86

Identification of Orthopedic and Genetic Needs Reported by Persons with Type 3/Severe Von Willebrand Disease

Cesta, Jeanette; Geary, Margaret; Kuebler, Edward

Submission Group

Peer Support/Outreach/Integration Models

Abstract

Identification of Orthopedic and Genetic Needs Reported by Persons with Type 3/Severe Von Willebrand Disease

Objective: To determine the medical and educational needs reported by persons with Type 3 and other severe types of Von Willebrand Disease (VWD) who attended the second USA National Type 3/Severe VWD Conference held in Florida in June 2018. Little research has been done concerning medical issues and education in Type 3/Severe VWD. As patient identification increases, it is vital that education, support and resources are available for these patients.

Methods: A survey of 48 questions was developed and administered to 74 vetted patient attendees. Responses for any individual question varied between 62-66. The survey was administered through an Audience Response System (ARS) utilizing handheld clickers. The responses were compiled and immediately visually available to the respondents via a projector screen. The multiple-choice questions were used to identify basic demographics, medical and psychosocial concerns, and educational needs.

Summary: In this self-reported ARS survey, basic demographic data was obtained. This sample of VWD patients reported a need for more education on several issues related to their medical and psychosocial issues including depression/mental health issues, lab results and product choices. In addition, subjects reported significant needs for care, treatment and education in the fields of orthopedic services and genetic counseling. Respondents' answers expressed a lack of orthopedic care despite a need for it. Only 8 (13%) patients reported having an orthopedic surgeon attend his/her bleeding disorder clinic. Forty-two (67%) did not know of any orthopedic resources. However, 18 (28%) reported that he/she had already had at least one joint surgery/procedure due to VWD and 5 (8%) plan to have surgery in the future. Eight (12%) had had joint replacements. Only 25 (40%) of respondents knew that they had undergone genetic testing related to their bleeding disorder, 30 (48%) have not had genetic testing, 8 (13%) were unsure. When asked, “Were your parents diagnosed with a bleeding disorder before your birth?” of the 63 who answered, 51 (81%) stated “no, neither parent”. When asked if a parent was diagnosed with a bleeding disorder after the respondent’s birth, 24 (38%) responded “yes” to one or both parents. Twelve (19%) respondents have had their diagnosis change since first being identified with a bleeding disorder.

Conclusion: Orthopedic care, genetic testing and education are vital services wanted by Type 3/Severe VWD patients. The community should further evaluate these needs and take action to respond. These results may also empower persons with Type 3/Severe VWD to seek support from professional and social members of their community.
PSO 87

A look from within: a needs assessment of educational support for the Rare Bleeding Disorders Community

Waite-Ardini, Sarah; Nammacher, Kate; Abruzzo, Gianna

Submission Group

Peer Support/Outreach/Integration Models

Abstract

Objective: The National Hemophilia Foundation Education team partnered with an evaluator to conduct a needs assessment of the rare bleeding disorder (RBD) community to help inform the development of programming tailored to the community’s unique experiences and needs. Methods: A guided discussion with the attendees of a Bleeding Disorder Conference (BDC) session titled, “The Lonely Island: Dealing with Being Rare” in 2018 as well as brief surveys at the end of the session were compiled as part of the needs assessment. Additionally, 12 one on one interviews of those part of the RBD community (either affected themselves or a close relative to someone that is affected) were conducted. Summary: Various challenges for this population were identified, including: connecting with others who have the same RBD; healthcare providers’ lack of knowledge/understanding of specific RBDs; accessing knowledgeable hematologists and RBD experts; accessing the latest science specific to their RBD; scarcity of treatment resources; difficulty getting diagnosed. Other secondary challenges were also expressed. While challenges were identified, those that participated in the needs assessment also highlighted the ways in which they see the RBD community can best be served. Common suggestions included: the addition of RBD-specific programming at NHF’s Bleeding Disorder Conference (BDC); continuing to make NHF and Chapters inclusive; creating more opportunities for the RBD community to connect with others with the same RBD (at NHF’s BDC and other events); creating targeted educational materials and opportunities for the RBD community; creating opportunities for members of the RBD community to identify and engage with the medical community. Conclusions: By conducting this needs assessment, NHF took an important step in asking the RBD community directly how they can best be supported given their unique experiences and needs. While challenges for the RBD community were identified, several opportunities to support the RBD community were also identified.
Quality of life and health in patients with Haemophilia in Mexico

ABREU BASTAR, ANA PAOLA; ABREU BASTAR, ANA LAURA; ESCOBAR RUIZ, VALERIA

Submission Group

Quality of Life/Outcomes Research

Abstract

Introduction and Objectives: Hemophilia is a congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) (in hemophilia A) or factor IX (FIX) (in hemophilia B). The deficiency is the result of mutations of the respective clotting factor genes (World Federation of Hemophilia, 2012). Through its associated symptoms, functional limitations and treatment burden, directly impacts the health-related quality of life (HRQoL) of both patients and their families (Von Mackensen, 2007). In Mexico there is little research that contributes to the quality of life (QoL) in patients with Hemophilia. This study aimed to describe and analyze the health-related quality of life (HRQoL) of patients with Hemophilia according to the severity of the illness.

Materials and methods: A sample of 56 patients with Hemophilia. Quality of life and health conditions were evaluated with the inventory INCAVISA created by Riveros, A., Sánchez, J., and Del Águila, M. (2009). The study design was quantitative, non-experimental, descriptive and transactional. Data were analysed using descriptive statistics using SPSS 21 for Windows. Levene test was used for equality of variances. Tukey test was conducted to found which specific group’s means (compared with each other) are different.

Summary: 27 patients with moderate Hemophilia, 21 patients with severe Hemophilia and 8 patients with mild Hemophilia. Deterioration in QoL appeared in the following areas: 50% in cognitive functions, 46.5% in attitudes to treatment, 37.5% in isolation and medically dependent individuals, 30.4% in physical performance, daily life and relationship with the health care, 28.5% in self-concept, 26.8% in relationship with family, 16.1% in free time and 10.7% in social and family networks. Significant differences according to the severity of the illness were found only in physical performance and medically dependent individuals. Using the analysis of variances, a significance was found between patients with severe and mild hemophilia (p=0.005 and p=0.037 in physical performance and medically dependent individuals respectively) and severe patients comparing with moderate patients (p=0.005 and p=0.057 respectively).

Conclusions: Physical activity in patients with severe hemophilia is limited in relation to patients with mild and moderate hemophilia. Also, patients with severe hemophilia may maintain a passive attitude about their health care and feel uninterested in their illness. Psychological attention should focus on using informational and motivational techniques, social - emotional skill development, rehab, problem solving skills and cognitive restructuring.
QOL 29
An evaluation of health utility and quality-of-life in hemophilia: a systematic literature review

Martin, Antony; Shaikh, Anum; Asghar, Sohaib; Evans, Jonathan; O'Hara, Jamie; Sawyer, Eileen K; Li, Nanxin (Nick)

Submission Group
Quality of Life/Outcomes Research

Abstract
Objective: Hemophilia may negatively impact a patient’s health utility and quality of life (QoL). Health state utility values (HSUVs) and QoL are important inputs to the evaluation of novel treatment being developed in hemophilia, including gene therapies. This systematic literature review identified and evaluated HSUVs and QoL for people with hemophilia (PWH) type A and/or type B, as well as utility decrements relevant to the experience of PWH, by treatment and health state. Methods: Building on a review undertaken in 2014 (Grosse et al. 2015), we conducted a systematic literature review to March 2019 through a search of electronic medical databases, including MEDLINE®, Web of Science, Cochrane Library databases and the School of Health and Related Research Health Utilities Database (SCHARRHUD). Major clinical, patient, and pharmacoeconomic conferences in 2016-2019 were also queried. Studies were independently double screened by independent reviewers, after which data extraction was performed. The information extracted included study design, description of treatment and health state, respondent details, instrument and tariff, HSUV and QoL estimates, quality of study, and appropriateness for use in economic evaluations of novel treatment. Summary: Of 1,511 titles and abstracts screened, 20 studies and 12 conference abstracts were included. The studies identified applied a mix of direct and indirect health utility elicitation techniques. Two studies applied direct time trade-off (TTO) methodology and the remaining 30 studies adopted indirect valuation methodologies. HSUVs were found to decrease with increasing disease severity. For example, in Hoxer et al. (2018), mean (standard deviation) HSUV were 0.80 (0.21), 0.73 (0.22) and 0.67 (0.25) in people with mild, moderate, and severe hemophilia, respectively. Utility values were also found to vary by severity of musculoskeletal damage, frequency of bleed episodes, inhibitors, hemophilia subtype, treatment regimen, treatment adherence and other disease-related complications. Interestingly, HSUVs derived from valuations from the general public were found to be valued lower than those derived from PWH for similar health states. For example, in Carlsson et al. (2017), general population participants consistently rated significantly lower HSUVs for hemophilia disease states compared to PWH (range: 0.54-0.60 vs. 0.67-0.73). Several hemophilia-specific QoL instruments were used alongside HSUV evaluations. These QoL findings further contribute to improving the understanding of the impact of hemophilia on PWH. Conclusions: This systematic review shows significant impact of hemophilia on health utilities and QoL among PWH. The substantial humanistic burden experienced by PWH highlights unmet needs remaining in hemophilia. Our review findings also suggest potential disease state adaptation among PWH, which warrants further research using robust patient preference studies.
Satisfaction with Teen Transition Services at US Hemophilia Treatment Centers by Center – Variation by Pediatric and Lifespan Centers 2014 and 2017

Baker, Judith; Lattimore, Susan; Shearer, Rick; Ashton, Merilee; Riske, Brenda

Submission Group
Quality of Life/Outcomes Research

Abstract

Background: Helping teens with bleeding disorders prepare to manage their care as they transition to adulthood is a national priority for US Hemophilia Treatment Centers (HTC). The National HTC Patient Satisfaction Surveys (PSS) reveal high satisfaction with HTC teen transition services. Yet how satisfaction differs comparing HTCs that primarily care for children to HTCs that care for patients throughout the lifespan is unknown. Objective: To assess variation in patient satisfaction with US HTC teen transition services by HTC type. Methods: The US HTC Network conducted nationally uniform patient satisfaction surveys in 2015 and 2018 on care received, respectively, in 2014 and 2017. A Regional workgroup devised, piloted, and finalized an electronic, two-page survey for self-administration at clinic, or at home, in English or Spanish. Participation was voluntary. Respondents were anonymous but identified their HTC. Parents completed surveys for children under age 18. The PSS included two teen transition questions for respondents age 12-17 to complete. HTC type was categorized as ‘pediatric’ if >80% of responses were from patients/caregivers of individuals under age 18, and ‘adult’ if >80% were from patients over age 24. All other HTCs were categorized as ‘lifespan’. For both years, approximately 26% of HTCs were classified as pediatric, 52% as life-span, and 22% as adult. Results: Over 700 teens age 12-17 (or their parents/guardians) from an average of 130 HTCs (94.0%) from all US regions participated in 2015 and 2018. Approximately 96.5% of teens at pediatric HTCs (96.4% - 96.5%) and 96.2% at lifespan HTCs (95.9% - 96.5%) reported being ‘always’ or ‘usually’ (A/U) satisfied with HTC services overall. On average, 90.4% of teens at pediatric HTCs (90.1% - 90.7%) and 91.0% at lifespan HTCs (90.3% - 91.6%) reported being A/U satisfied with how HTC clinic staff talked about how to care for the bleeding disorder as they became an adult. Similarly, 92.5% (92.0% - 92.9%) of teens at pediatric HTCs and 92.5% (92.3% - 92.7%) reported being A/U satisfied with how the HTC clinic staff encouraged them to become more independent in managing their bleeding disorder. Conclusions: HTC patients age 12-17 years consistently report very high levels of satisfaction with HTC teen transition services, regardless if the HTC primarily cares for patients up to age 17, or throughout the life-span. This suggests teens receive support and tools to successfully transition to adult care across the US HTC Network. A national uniform HTC Patient Satisfaction Survey provides vital information, is feasible to conduct using a regional structure, and well received nationwide.
QOL 33


Lattimore, Susan; Baker, Judith; Riske, Brenda; Shearer, Rick; Ashton, Merilee

Submission Group

Quality of Life/Outcomes Research

Abstract

Background: US Hemophilia Treatment Center (HTC) care reduces mortality and hospitalizations, and guidelines recommend this care model. Yet national data that uniformly and longitudinally monitors patient experience with HTC care is limited. Objective: To assess patient satisfaction with HTC services and clinicians over time. Methods: The US HTC Network conducted the first ever nationally uniform patient satisfaction surveys on care received in 2014 and 2017. A Regional workgroup devised, piloted, and finalized an electronic, two-page survey for self-administration at clinic, or at home, in English or Spanish. Content was based on national instruments to enhance comparability and scientific robustness. Questions assessed demographics; satisfaction with HTC team members and services; insurance and language barriers. Respondents were anonymous but identified their HTC. Participation was voluntary. Patients with HTC contact in 2014 and 2017 were eligible. Data were collected for 4 months in 2015 and 6 in 2018; on average 130 HTCs (94%) from all US regions participated. Parents completed surveys for children under age 18. Data were entered, analyzed and aggregated at national, regional and HTC levels at a central site. Results: 5006 and 4767 persons participated, respectively, in 2015 and 2018. In both years, over 1400 (30%) respondents were female, nearly 80% were White, and 10% Hispanic. On average, 3038 had Factor 8 or 9, 1280 Von Willebrand, 186 other factor deficiencies and 369 other bleeding disorders. Respondents reported being ‘always’ or ‘usually’ (A/U) satisfied with HTC staff and services from 90%-97% of the time in both 2014 and 2017. In both years, >4400 gave these highest A/U ratings for HTC Hematologists and Nurses; 3300 for Social Workers; >2600 for Physical Therapists; 1400 for Genetic Counselors, and >1100 for Psychologists. In both years, 96% were A/U satisfied overall with HTC services. Over 95% gave the A/U satisfaction ratings both years for these services: getting needed care and information, being treated respectfully, spending sufficient time with staff, and involved in shared decision making. 82% and 91% of respondents, respectively, gave the A/U satisfaction ratings for care coordination with primary care providers and other specialists. Over 90% of >700 youth age 12-17 gave HTC teen transition services the A/U satisfaction ratings both years. 96% of >2760 respondents reported A/U satisfaction with their HTC Pharmacy (340B) Factor Program in 2017. Insurance and language barriers to HTC care posed problems A/U for 27% and 15%, respectively both years. Conclusions: Patients consistently report high levels of satisfaction with HTCs, documenting HTC value over time. Patient satisfaction influences treatment adherence, can influence reimbursement, and is increasingly required by payers. A national uniform survey is feasible to conduct using a regional structure to implement, is well received by patients, and provides critical information to stakeholders.
Increasing Medical Alert Devices (MAD) Compliance in School Age Children with Hemophilia: A Quality Improvement Project

Burge, Kara; Wilkerson, Brittany; Crary, Shelley

Submission Group
Quality of Life/Outcomes Research

Abstract

Background: Medical Alert Devices (MAD) are an integral method of alerting first responders of pertinent medical information. It is recommended that persons with bleeding disorders wear MAD to communicate life-saving information. School age children with Hemophilia can be at risk for developing life-threatening bleeding. These bleeds may occur while the child is away from home or from those who are familiar with their bleeding disorder. It was reported that many school age children do not wear MAD for various reasons, including financial barriers and dislike of appearance. Through routine patient follow-up, it was determined that most school age children with Hemophilia at the AR Hemophilia Treatment Center (HTC) were not wearing some form of MAD. Objective: Increase compliance with MAD in school age children with Hemophilia to improve safety. Methods: This study was conducted through qualitative interviewing during comprehensive visits. The HTC social worker met with school age patients with Hemophilia to determine: 1.) Ownership of a MAD, 2.) Compliance with wearing a MAD, and 3.) If not worn/owned, what barriers were present. During the first phase of data gathering that took place over 3 months, of the 13 boys interviewed, 100% of the patients screened did not wear MAD. Through this data we determined primary reasons for poor compliance included financial barriers and dislike of MAD aesthetics. The second phase consisted of developing a plan to address identified barriers. This involved purchasing and distributing personalized MAD for identified patients. Patients were integrated in decision making by selecting their MAD color. During the final phase of this project, we will make 2 follow-up phone calls, 6 and 12 months from the date of MAD distribution to determine if compliance has increased and is maintained. Summary: MAD have life-saving potential and are especially important for school age children with Hemophilia. Compliance with MAD has been poor at the Arkansas HTC for various reasons including cost burden and dislike of aesthetics. Through qualitative interviewing we were able to identify primary barriers for non-compliance and proactively intervene. We anticipate that compliance will improve by decreasing financial barriers and by having a more active role in the distribution of the MAD. Conclusion: Many school age children with Hemophilia do not wear MAD due to barriers including cost and dislike of aesthetics. Although this QI project is still ongoing, it has improved the HTC’s understanding of the relationship between those barriers and MAD compliance. By addressing these barriers, we expect to increase MAD compliance by the following year.
QOL 38

EVALUATION OF PATIENT AND PHYSICIAN REPORTED REASONS FOR SWITCHING FVIII REPLACEMENT THERAPIES AMONG PATIENTS WITH HEMOPHILIA A

Afonja, Olubunmi; Carpinella, Colleen M.; Aubert, Ronald; Farej, Ryan; Mulvihill, Emily; King-Concialdi, Kristen

Submission Group
Quality of Life/Outcomes Research

Abstract

OBJECTIVE: While a new generation of therapies for patients with Hemophilia A are available, it is unclear what patient characteristics, perceptions, and barriers are associated with the decision to switch FVIII replacement therapies. This study assessed patient characteristics, health history, and reasons for switching from a FVIII product with more frequent dosing (³3x infusions/week) to a product with less frequent dosing (≤2x infusions/week) from patient/caregiver and physician perspectives. METHODS: Data collection was a mix of qualitative and quantitative procedures. The qualitative portion consisted of two online discussion forums: patients (n=17) and caregivers of patients (n=11) receiving a FVIII product dosed ³3x/week, and patients (n=22) and caregivers of patients (n=5) who switched to a product dosed ≤2x/week. The quantitative portion was a retrospective medical chart review (n=207) which captured variables (e.g., bleed rate, treatment history) 6 months pre- and 6 months post-switching to a product with less frequent dosing. SUMMARY: Prominent drivers among patients for starting a FVIII product with less frequent dosing included: 1) experiencing diminished effectiveness while on a product dosed ³3x/week resulting in increased breakthrough bleeding, 2) experiencing vein access issues, and 3) beginning prophylaxis as opposed to on-demand infusions after a bleed. Key barriers to changing included: 1) fears regarding the process of switching being complicated, time consuming, and costly, 2) perceived risks associated with switching, and 3) possible lack of healthcare provider support. Physicians were most likely to report that patients switched products because they sought a newer product with twice weekly dosing or less per FDA-approved dosing recommendations (35.3%), followed by patient requested the switch (30.4%), and patient sought a reduction in infusion frequency to improve adherence (27.5%). Switching to a product with less frequent dosing was associated with improvements in patient-reported bleeding-related outcomes. Patients were more likely to self-administer the treatment post-switch (63.8%) compared with pre-switch (48.8%; p<0.001) and had fewer infusions per week post-switch (2.8 vs. 3.3; p<0.001). Patients’ annualized bleed rate was lower (5.9) post-switch compared with pre-switch (7.7; p<0.001). Both the number of spontaneous joint bleeds and joint bleeds after trauma or injury were lower (3.2 and 2.7) post-switch (3.6 and 4.3; p=0.044 and p<0.001). The bleeding event was less likely to be classified as moderate or severe (34.5% and 5.9%) post-switch compared with pre-switch (55.0% and 10.0%; p<0.001 and p=0.049). Fewer infusions were required to resolve the bleeding event post-switch (2.6 vs. 3.2; p<0.001). CONCLUSION: A prominent reason why patients switch treatment is to improve bleeding-related outcomes. Indeed, we found that switching to a
FVIII product with less frequent dosing was associated with improved patient-reported bleeding-related outcomes. These findings are critical for improving patient outcomes and support the FDA mandate to incorporate patient perspectives in the regulatory process.
QOL 53

Patient Perspectives on the Impact of Severe or Moderate Hemophilia on Physical Activity: HemACTIVE Survey Findings from the US and Canada

Blamey, Greig; LeCleir, Gregory; Khair, Kate

Submission Group

Quality of Life/Outcomes Research

Abstract

Objectives: The HemACTIVE survey assesses patient perspectives on the effects of hemophilia and treatment on physical activity. It was previously shown that in the US, most survey participants wished for greater activity, believing that less pain and better protection would enable their aspirations. Whereas the majority of US participants had severe hemophilia, most Canadian participants had moderate hemophilia. The objective of this study was to evaluate findings from the US and Canada, focusing on key similarities/differences between countries and between severity levels. Methods: A 25-minute web-based survey was conducted on patient perception of impact of hemophilia on daily activities. Patients with moderate or severe hemophilia A (PwH), ages 2–65, from North America and EU were enrolled. Patients <18 years required caregiver involvement. Surveys were administered after screening phone interviews. No statistical analyses were included; findings are descriptive only. Summary: 110 participants from the US (64 PwH, 46 caregivers) and 41 from Canada (23 PwH, 18 caregivers) were analyzed. Importantly, 88% of US participants had severe hemophilia and 12% moderate, compared with 22% severe and 78% moderate in Canada. Despite these differences, prophylaxis use was similar between countries (88% US vs. 83% Canada, and 93% of participants from either country expressed the desire to be more active. The following differences were observed: 70% of US PwH considered themselves to be currently active/highly active vs. 83% in Canada. US PwH were less likely than Canadian PwH to participate in indoor/gym activities (66% US vs. 76% Canada), outdoor activities (65% vs. 80%), non-contact sports (55% vs. 71%), and contact sports (25% vs. 32%), and more likely to feel extremely/very limited in spontaneous activities (15% vs. 0 in Canada). While more US PwH adjust activities due to hemophilia (73% US vs. 66% Canada), rates of stopping activities were similar between countries (34%-35%). However, the top reason for stopping activities differed between countries: existing joint damage restrictions for US PwH vs. fear of future joint damage in Canada. More US PwH than Canadian PwH believe that greater bleed protection, less pain, and fewer bleeds would enable greater activity (85%-90% US vs. ~30%-40% Canada). Compliance to prescribed treatment regimens also differed, with 54% of US PwH occasionally or frequently missing infusions vs. 38% in Canada. US PwH were more likely than those in Canada to indicate that having hemophilia has made them into a stronger person (85% vs. 76%). Conclusions: Despite differences in baseline characteristics, with most US participants having severe hemophilia, and most Canadian participants having moderate hemophilia, >80% from either country were on prophylaxis, and >90% wished to be more active.
QOL 55

The WFH World Bleeding Disorders Registry – 16-month update

Naccache, Mayss; Coffin, Donna; Youttanakorn, Toong; Toootoonchian, Ellia; Byams, Vanessa; Diop, Saliou; Hermans, Cedric; Noone, Declan; O'Hara, Jamie; Pierce, Glenn F; van den Berg, Marijke; Iorio, Alfonso; Konkle, Barbara

Submission Group
Quality of Life/Outcomes Research

Abstract

Objective: The World Federation of Hemophilia (WFH) World Bleeding Disorders Registry (WBDR) is the only global registry collecting standardized clinical data on a large population of people with hemophilia (PWH). By collecting real-world data, which can be used to address important clinical questions and support advocacy initiatives, the WBDR aims to improve the quality of care for PWH around the world. The goals of the WBDR are to enroll at least 10,000 PWH from more than 50 countries, aiming for representation of patients from around the world. Methods: The WBDR is a prospective, longitudinal, observational registry of patients diagnosed with hemophilia A and B. HTC participation steps include: 1) registration with the WBDR; 2) approval from their Institutional Review Board; 3) obtaining patient consent; and 4) contribution of data on an ongoing basis. All HTCs contribute data on basic demographics, diagnostics, and clinical variables included in the Minimal Data Set (MDS). HTCs may also choose to contribute to the Extended Data Set (EDS) to obtain more complete patient data. Summary of results: Since January 2018, 52 HTCs from 32 countries have received ethics approval and have enrolled > 2100 PWH (Figure 1, 2). Patients registered with the WBDR represent all regions of the world and all World Bank gross national income categories. Most patients enrolled are male (99%), with hemophilia A (86%) and severe disease (52%). The most frequent severity category among hemophilia A patients was severe (54%), while severe and moderate category have the same frequency among hemophilia B patients (41%) (Figure 3). The median age of patients in the registry is 17 years, with a ratio of children to adult participants of 51% : 49%. Median age at diagnosis is 20 months. Age at diagnosis decreased as GNI increased, from 37 months in low income countries, to 9 months in high income countries for all PWH, with a similar pattern among PWH with severe disease. Conclusions: The successful first year of the WBDR laid a solid foundation on which the registry will continue to expand. This global network of HTCs and patients has started providing real-world data, on which evidence to improve the quality of care worldwide will be generated. Further aggregate data is presented in the first WBDR Data Report, available online at: https://www.wfh.org/en/our-work/wbdr/2018-data-report. The WFH thanks the many dedicated health care providers and patients who are part of this important initiative. The WBDR is supported by our Visionary Partners: SOBI and Takeda; and our Collaborating Partners: Bayer, CSL Behring, Grifols, Pfizer, and Roche.
Objectives: The quality of life in people with hemophilia (PWH) varies greatly according to socioeconomic status as well as demographic characteristics such as age. Over the past 50 years, there have been substantial improvements in hemophilia care resulting in increased quality of life and a higher life expectancy for those affected by this inherited condition. In this report, we will describe the age distribution of PWH regionally, and by gross national income (GNI), as reported in the Report on the Annual Global Survey (AGS) 2017. The AGS data including the age information can be a useful tool for advocacy in the care of PWH. Methods Data on age distribution of hemophilia patients from the AGS published by the World Federation of Hemophilia was analyzed. This is an annual cross-sectional survey. The AGS 2017 report included responses on age breakdown of PWH from 93 countries. This report uses five age categories: 0-4, 5-13, 14-18, 19-44, 45+. These age categories included 122,336 people with hemophilia A (PWHA) and 24,895 people with hemophilia B (PWHB) worldwide. Gross national income (GNI) per capita categories from the World Bank Group were used. Summary The 2017 AGS report revealed that 31% of PWHA in European countries fall into the 45+ age category, compared to only 14% in Africa, 7% in South East Asia and 8% in the Eastern Mediterranean (Figure 1). For PWHB, the trends were similar, with 32% of patients above 45 years of age in European countries. This ratio was 11% in Africa, 10% in South East Asia and 7% in the Eastern Mediterranean region (Figure 1). When comparing pediatrics to adults by GNI, the ratio of adults increased as GNI increased (Figure 2). In the lower income level countries, there were 56% of PWH under 19 and 40% over the age of 19 whereas in high income countries, the proportions were 31% and 68% respectively. The percentage of PWH over the age of 45 is higher in countries with higher income (29%), than those with lower income (4%) (Figure 3). Conclusions: The analysis of age in PWH can have great indications about the quality and access to care within a country. Increased access to treatment and comprehensive health care services, can lead to better patient outcomes, and PWH can come close to achieving normal life expectancy. As quality and access to care improve, the percentage of PWH in older age categories is expected to increase. Analysis of the AGS data indicates that, despite the continuous improvement in quality of care, the developing regions continue to have additional need for adequate resources when compared to the developed regions.
Objective: Over the past 20 years, the Annual Global Survey (AGS) has provided an international snapshot of the progress in hemophilia patient identification and access to care. This survey was designed to give the national member organizations (NMOs) affiliated with World Federation of Hemophilia (WFH), healthcare providers and policy makers an overview of the patterns and trends in treatment, and to determine the gaps and areas where improvements are necessary. The annual report monitors hemophilia care using demographic information on patients as well as information on the level of care. Methods: The Report on the Annual Global Survey is an annual cross-sectional survey. Each year in April the questionnaire is sent out to NMOs to complete the survey. The questions are organized in different sections including Data Source, Identified Patients, Hemophilia Care and Factor Use. The survey includes patients with hemophilia A, B, type unknown, and those with von Willebrand disease and other bleeding disorders. Surveys can be filled out online or on paper in English, Spanish or French. Between May and October data is received and reviewed. The review process includes individual follow up with the NMOs. Once the review process is complete, the Report on the Annual Global Survey is published. In 2018, the survey was sent to 140 NMOs. Summary: Response Rate: In 2018, a record of 116 countries responded to the survey, a significant increase since the report first started 19 years ago when only 77 countries were included in the report. The countries included in the 2018 report were representative of 91% of the entire world population (Figure 1). Patient identification Since the start of the survey there has been an increase of 184% in reported number of identified patients. In its first year, the AGS identified 111,203 and has since increased to 315,423 (Figure 1). This can be attributed to progress through the WFH Comprehensive Development Model including improvements in the WFH data collection efforts. Factor use Looking at the World Bank’s gross national income per capita categories, there is a vast difference between the factor usage of the lower income and higher income countries. Since 2002, the increase in factor use in high income countries has been more significant than the increase in low income countries (Figure 2). Conclusions: The findings of the AGS offer insight into hemophilia care management. On the verge of its 20 th anniversary, the AGS report has shown continuous improvement with support of the NMOs. Improved data collection, and analysis of this data has allowed for better advocacy and healthcare planning, to further diagnose patients with bleeding disorders and to continue to work towards the WFH mission of treatment for all.
Data is the new currency: The World Bleeding Disorders Registry Data Quality Accreditation Program

Youttanankorn, Worachanok Toong; Coffin, Donna; Naccache, Mayss; Tootoonchian, Ellia; Byams, Vanessa; Hermans, Cedric; Diop, Saliou; Noone, Declan; O'Hara, Jamie; Pierce, Glenn F; van den Berg, Marijke; Iorio, Alfonso; Konkle, Barbara

Submission Group
Quality of Life/Outcomes Research

Abstract

Objective: The World Bleeding Disorders Registry (WBDR) has been designed to collect real world and patient level data from Hemophilia Treatment Centers (HTCs) globally. Data are a powerful tool that can be used to generate evidence for better care and treatment; and to build advocacy initiatives aimed at policy decision makers. While the World Federation of Hemophilia (WFH) encourages patient enrollment, we do not want a silo of poor-quality data. Instead of benefiting from them, we could be drowned in the data pool. Hence, the WFH has implemented the WBDR Data Quality Accreditation (DQA) Program. The objective of the DQA Program is to raise awareness of quality data, and to ensure that the data in the WBDR are of high quality. The term ‘quality’ is complex but for the WBDR, all data are evaluated on two dimensions, which are ‘completeness’ where all data fields are completed; and ‘accuracy’ where data are accurate and valid. By implementing the DQA Program, we also expect ‘consistency’ in both ‘complete’ and ‘accurate’ data. We assessed the impact of the DQA Program on the quality of data at each HTC. Methodology: At site level, standardized data collection procedures have been encouraged and employed among the HTCs. They have access to tools (i.e. User Handbook), individual training sessions, and technical assistance in data quality. At the WFH, we conduct a robust data validation process for all patients and all data fields. Regular feedback using data clarification forms is provided to each HTC. Improvement of data quality of each HTC before and after implementing the DQA Program was assessed. HTCs are classified according to the WBDR Data Quality Rating, which consists of Basic (0%-49%); Developed (50%-74%); Intermediate (75%-84%); Advanced (85%-94%); and Leaders (95%-100%) (Figure 1). Summary: In 2018, the WFH worked with 29 HTCs that entered data into the WBDR. Prior to implementing the DQA Program, only five (17%) of 29 HTCs were classified as ‘Leaders’ level and one HTC (3%) was considered ‘Advanced’. After employing the DQA Program, 24 (83%) of the 29 HTCs achieved the highest level of data quality rating and were classified as ‘Leaders’. Three HTCs (10%) achieved the level of ‘Advanced’ (Figure 2). Conclusion: According to World Health Organization, "Sound decisions are based on sound data". The value in good quality data is immense, so awareness in data quality should always be promoted. Compromising on data quality could cause serious consequences that impact the usefulness of the data. The phrase ‘Data is the new currency’ should be applied in all steps of data management, especially in the medical registries. For the WFH, the DQA Program not only promotes a sense of ownership of quality data but also maintains the overall quality of the WBDR in the long run. The WBDR is supported by our Visionary
Partners: SOBI and Takeda; and our Collaborating Partners: Bayer, CSL Behring, Grifols, Pfizer, and Roche.
Combining Data from Hemophilia Registries with the World Bleeding Disorders Registry: A Proof of Concept Study with the Czech National Haemophilia Programme Registry

Naccache, Mayss Naccache; Engren, Johan; Blatny, Jan; Ovesna, Petra; Pierce, Glenn F; Coffin, Donna

Abstract

Objective: Registries, with international collaboration between countries, are the best way to pool sufficient data to increase knowledge and evidence in rare disorders. The World Federation of Hemophilia (WFH) World Bleeding Disorders Registry (WBDR) provides a platform for a network of hemophilia treatment centers (HTCs) around the world to collect uniform and standardized patient data and guide clinical practice. As a global organization with access to a network of 140 national member organizations (NMO), more than 1,000 HTCs, and numerous patients in countries with varying levels of access to care, the WFH is uniquely positioned to develop such a registry. In an effort to combine resources from existing hemophilia registries, and maximize the utility of data that currently exist, the development of the WBDR includes an international data integration component with the aim of facilitating data transfer from existing patient registries to the WBDR. Methods: As part of a proof-of-concept study, de-identified data from the 2018 Czech National Haemophilia Programme Registry (CNHPR) is being imported into the WBDR. This import is based on a minimal set of data common to both registries. Data fields in both registries were examined to assess their interoperability. Common data elements were further analyzed for data compatibility and standardization of terms, before being mapped from the CNHPR to the WBDR (Figure 1). In addition to the procedural step required, legal, regulatory and technical issues, will also inform a standard protocol which will be developed to import data from other existing patient registries into the WBDR. Summary of results: Data on 775 patients are being imported from the CNHPR to the WBDR. The data reported in the CNHPR represent 100% of identified patients in the Czech Republic. Further results will be communicated in a manuscript in 2019. Conclusions A protocol to import data from other existing patient registries into the WBDR is currently in development, based on the proof-of-concept study. The program is available to interested countries who want to set up an import process to combine their national data with the WBDR. Interested individuals are encouraged to contact the WFH at wbdr@wfh.org. The WBDR is supported by our Visionary Partners: SOBI and Takeda; and our Collaborating Partners: Bayer, CSL Behring, Grifols, Pfizer, and Roche.
QOL 90

The Patient Reported Outcomes Burdens and Experiences (PROBE) Study Questionnaire Development and Validation


Submission Group
Quality of Life/Outcomes Research

Abstract

Objectives: The health status of people living with hemophilia (PWH) has not been systematically investigated globally. There is a substantial need to improve capacity to collect and interpret relevant patient-reported outcomes (PRO) data to support patient-centered research and optimal care of PWH. PROBE aimed to: 1) implement a structured data collection of PRO across countries to build a robust evidence base for comparative effectiveness research, evidence-based decision making, and advocacy, 2) explore the measurement properties of the PROBE questionnaire and 3) assess the feasibility of PROBE for assessing health status among PWH and participants without bleeding disorders across regions. Three intermediate objectives were identified: develop a patient-led research network; develop a standardized questionnaire to gather PRO; and perform a feasibility study of implementing the PROBE questionnaire. Methods: Data collection from April 2015 to February 2017. 2,101 surveys were collected through all study phases across 24 countries. 1,541 met study criteria for analysis. Clinical Trial registration: NCT02439710. Summary: The PROBE questionnaire consists of four major sections: demographic data, general health problems, hemophilia-related health problems and health-related quality of life. Outcomes of importance to PWH and metrics to consider for measurement were determined. Domains for outcomes of importance to measure reduced burden of living with hemophilia include (metrics): Life and Family (family life, marital status, children, current health status); Education/School and Employment (attendance, educational attainment, employment duration, underemployment) and Activities (impact on activities of daily living, mobility impairment, assistance required). Domains for reduced complications associated with hemophilia and treatment (metrics): Joint Disease (joint status); Pain, Depression/Anxiety (chronic/acute pain, pain interference, pain occurrence, pain medication, depression); and Other Comorbidities (HIV/HCV, obesity, resource utilization, mortality, longevity). PROBE questionnaire validation studies established face validity, relevance, clarity and completeness (Skinner, Pilot and Feasibility Studies 2018); test-retest reliability (reproducibility) (Chai-Adisaksopha, Haemophilia 2019); a core analytic framework (psychometric properties) (Chai-Adisaksopha BMJ Open 2018); and cross-cultural validation (Chai-Adisaksopha, Haemophilia 2019). Conclusions: The PROBE questionnaire established and assessed patient-important outcomes in PWH and control participants, with a demonstrated short completion time using both paper and electronic versions. PROBE proved the feasibility to engage diverse patient communities in the structured generation of real-world outcome research at all stages. Results demonstrate that the PROBE questionnaire is valid for assessing PROs and health status among PWH and participants without bleeding disorders across regions. The known group property of PROBE will allow its
use in future clinical trials, longitudinal studies, health technology assessment studies, routine clinical care or registries. Longitudinal PRO data collection using an instrument such as PROBE will be useful within clinical development programs, clinical management settings and to support access to care initiatives.
**QOL 91**

**Von Willebrand Disease: An international Survey to Inform Priorities for New Guidelines**

Kalot, Mohamad; Al-Khatib, Mohammed; Connell, Nathan; Flood, Veronica; Brignardello-Petersen, Romina; Clark, Cary; Castano, Jenny; Riker, Ellen; Robinson, Fiona; Skinner, Mark; James, Paula; Mustafa, Reem

**Submission Group**

Quality of Life/Outcomes Research

**Abstract**

Background: Von Willebrand disease (VWD) is an inherited bleeding disorder caused by a quantitative or qualitative deficiency of the protein, von Willebrand factor (VWF). There is a lack of clear guidance on best practices to inform the care of people with VWD.

Objectives: Identify and prioritize the main topics of a collaborative guideline development effort. Methods: A scoping survey to prioritize topics to be addressed in a collaborative guideline for VWD was distributed to international stakeholders including patients, caregivers, clinicians, and allied healthcare professionals. The distribution strategy was coordinated by the guideline chairs and representatives of the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH). The survey was conducted in English, French, and Spanish. The survey focused on both diagnosis and management of VWD, using 7-point Likert-scale response options and open ended comments. Descriptive analysis of participants and comparative analysis of results by stakeholder subtype (patients/caregivers versus healthcare providers [HCP]), gender, and income setting was performed. Qualitative conventional content data was analyzed utilizing both deductive and inductive coding processes.

Results: 601 participants responded to the survey (49% patients/caregivers, and 51% HCPs). The highest priority topics identified were diagnostic criteria/classification, bleeding assessment tools, treatment options for women, and surgical patients. In contrast, screening for anemia and plasma-derived therapy versus recombinant therapies were rated the lowest priority topics (figures 1 – 2). Conclusion: The survey results highlighted areas of importance in the diagnosis and management of VWD across diverse groups of stakeholders and will direct future guideline efforts. The large number responses (601) and discrete comments (9,500) attest to the interest and involvement of the VWD community in this effort.
Female Patients with Hemophilia A: A Claims-Linked Chart Review

Afonja, Olubunmi; Farej, Ryan; Batt, Katharine; Martin, Carolyn; Aubert, Ronald; Carlyle, Maureen; White, John; Sidonio, Robert

Submission Group
Women’s Research Group

Abstract

Objective: Hemophilia A is a male-predominant disorder because of its inheritance pattern, yet many females have Factor VIII deficiency with bleeding events requiring similar treatment.[1] However, data about female patients remains scarce due to the rarity of diagnoses. Healthcare claims yield sufficient research sample size, yet lack important clinical data. This study was performed to characterize female patients with HA or HA-related symptoms using a claims identification approach, validated with medical chart abstraction. Methods: Administrative claims dated 01 January 2012—31 July 2016 were accessed for patients with commercial and Medicare Advantage with Part D insurance and 18 months’ continuous health plan coverage from the Optum Research Database. To maximize selection of patients with potential HA, expansive inclusion criteria were implemented. These included stated diagnosis or treatments commonly used for HA (i.e., Factor VIII, desmopressin), and/or bleeding event diagnoses (i.e., heavy menstrual bleeding, dental extraction, post-partum bleeding) combined with treatment for bleeding disorders. Patients with hemophilia B or qualitative platelet disorder diagnoses were excluded. A sample of patients was selected for medical chart abstraction for information on bleeding history, traditional HA therapies, and other treatments for bleeding (i.e., hysterectomy, transfusions, surgical cauterization, or iron supplementation). Summary: From >1 million female patients meeting broad HA or bleeding-event criteria, 323 had evidence of Factor VIII or desmopressin use. The abstraction sample included 150 patients; 86 providers participated. Upon review, 56 patients had no evidence of a bleeding disorder (unanticipated desmopressin use) and were excluded. The remaining 30 had evidence of a bleeding disorder, Factor VIII concentrate use, and/or Von Willebrand disease. Upon medical chart review by clinician experts, 8 patients were identified as having probable or possible HA. Their mean age was 60 ± 17 years, and most were Medicare-insured, with broad distribution across the US. The mean Charlson comorbidity score was 2.50 ± 2.56; the most prevalent comorbidities were coagulation/hemorrhagic, fluid/electrolyte, and non-traumatic joint disorders. Conclusions: Because HA diagnoses among females are rare, bleeding events or treatments coded for reimbursement rarely reflect the most accurate diagnosis. The broad inclusion criteria used for initial claims identification in this study unintentionally selected patients with desmopressin use unrelated to bleeding (e.g., diabetes insipidus) suggesting identification of female HA patients with severe symptoms is difficult even with broad criteria in a large data source. Accurate use of diagnostic codes to characterize female patients will be key to successful treatment and future claims-based research for this population. Disclosures: This study was funded by Bayer. [1] Byams VR, Kouides PA, Kulkarni R, et al.; Haemophilia Treatment Centres Network Investigators. Surveillance of female patients with inherited bleeding disorders...
**WR 50**

**A retrospective chart review to assess clinical characteristics of women and girls with factor VIII and IX deficiency**

Chaudhury, Ateefa; Tsao, Elisa; Kulkarni, Roshni; Sidonio, Robert; Tymoszczuk, Justyna; Jain, Nisha; Oviedo Ovando, Mariana

**Submission Group**

Women’s Research

**Abstract**

Objective: Evaluate clinical characteristics, hemostasis management, and clinical outcomes regarding menstruation, child birth, surgical procedures, dental care, and spontaneous and traumatic bleeds of women and girls with factor VIII (FVIII; hemophilia A) or factor IX (FIX; hemophilia B) deficiency (WGFD). Methods: A retrospective chart review is ongoing at three US hemophilia treatment centers (HTC) to collect data on WGFD (obligate or potential carriers of FVIII or FIX deficiency, with or without genetic confirmation). Data are collected on patients who had at least two HTC visits and underwent medical or surgical interventions for hemostasis management between April 2012 and November 2018, with the outcome available in medical charts. Summary: Interim results as of April 5, 2019 include charts from two HTCs on 26 (89.7%) patients with FVIII deficiency and 3 (10.3%) patients with FIX deficiency. The median (range) age at factor deficiency diagnosis was 18.5 (0.1–72.0) years. Twenty-four (82.8%) and 8 (27.6%) patients had a family history of hemophilia and other bleeding disorders, respectively. A total of 17 (58.6%) patients initially visited the HTC due to family history/genetic counseling. Other reasons for visiting an HTC were heavy menstrual bleeding (n=12 [41.4%]) or spontaneous or traumatic bleeds (n=12 [41.4%]), including 7 (24.1%) patients reporting both heavy menstrual bleeding and spontaneous or traumatic bleeds. Of the 12 patients with spontaneous or traumatic bleeds, 4 (33.3%) patients had joint bleeds, 6 (50.0%) patients had excessive nose bleeds, and 9 (75.0%) patients had easy bruising. For those with FVIII deficiency, the median (range) FVIII level at diagnosis was 32.5 (2.0–101.1) IU/dL (n=24), median (range) baseline hemoglobin was 12.9 (5.4–14.8) g/dL (n=19), and median (range) baseline von Willebrand factor ristocetin cofactor was 70 (40–150) IU/mL (n=16). The median (range) number of documented bleeds was 1.0 (0.0–24.0) in the first year at the HTC. Final results of this chart review, including data from those with FIX deficiency, HTC interventions, and outcomes for hemostasis management, will be presented. Conclusions: This chart review provides further insights into the clinical presentation and hemostasis management of WGFD evaluated at HTCs in the US. Results may contribute to the design of future prospective studies evaluating treatment options for this patient group.
Specific guidance is lacking for delivery planning in terms of how high a factor level should be achieved for pregnant women with von Willebrand disease (VWD) who, by the third trimester, do not have von Willebrand factor (VWF) (or factor VIII) levels greater than 50-100%. Specifically, guidance is lacking on whether replacement therapy should target a VWF minimum level in the 100–150% range, i.e., a range closer to the 200–250% levels observed in normal pregnancy.

Objectives: The primary objective is to document the rate of primary postpartum hemorrhage (PPH) and thereby the effectiveness of targeting minimum VWF levels of 100–150% for delivery. The secondary objective is to document further effectiveness outcomes and safety.

Patient VWF levels will be maintained at 100-150% for the immediate 72-hour postpartum period, and thereafter maintained at 50-100% target VWF levels through days 5-7 postpartum after normal vaginal delivery or days 7–10 postpartum after caesarean section.

Methods: This is a prospective, open-label, cohort study of the dosing of Wilate in pregnant patients with VWD to achieve minimum VWF levels of 100–150% for delivery. Outcome parameters will be assessed among patients termed non-correctors and correctors. Patients with a third trimester (gestational week 34–38) VWF level <100% will be enrolled in the non-corrector group. Patients with VWF levels ≥100% at gestational weeks 34–38 will be enrolled in the corrector group. Sample size is based on 65 pregnant VWD non-corrector patients and up to 30 corrector patients. Both correctors and non-correctors will be given tranexamic acid post-partum for 14 days.

Inclusion Criteria: includes VWD patients diagnosed prepartum as type 1 per NHLBI criterion of VWF level <30%, or type 2, or type 3. Exclusion Criteria includes age <18 years, presence of other concurrent disorder of hemostasis, platelet dysfunction, or collagen disorders; presence of liver disease or renal disease, clinical suspicion or diagnosis of preeclampsia or eclampsia, HELLP syndrome, TTP, DIC, or other acquired vasculopathy or coagulopathy, or inability to perform local laboratory monitoring.

Primary outcome parameter will be the rate of primary PPH, defined as estimated blood loss ≥1000 mL, or severe PPH defined as estimated blood loss >2000 mL within 24 hours postpartum. Other outcomes are secondary PPH, laboratory measures, and safety.

Screening will begin in Q3 2019 and end in Q2 2023, with recruitment ending 6 months before (i.e., Q4 2022).

Summary: This planned study aims to determine in VWD if VWF levels postpartum should be attained at levels closer to levels achieved physiologically in a normal pregnancy. Conclusions: Results from this study will hopefully lead to reduction of the relatively high rate of PPH in VWD women with levels <50-100% in the third trimester.
**WR 81**

**Women and girls with hemophilia: Gender-based differences in comprehensive care**

Fox, Laura

**Submission Group**

Women’s Research

**Abstract**

Women and girls with hemophilia: Gender-based differences in comprehensive care  
Objectives: The majority of studies of hemophilia have focused on males, leaving a gap in our knowledge of patient characteristics and care provided to females with hemophilia. This study aimed to systematically investigate whether gender-based differences in care exist and to describe the level of care females with hemophilia receive. This study utilized retrospective data analyses to investigate the effect of gender on comprehensive care in the US Hemophilia Treatment Center (HTC) Network, including enrollment as patients and participation in comprehensive care visits.  
Method: This is a retrospective cross-sectional study utilizing the American Thrombosis and Hemostasis Network’s (ATHN) dataset. The sample included patients enrolled in ATHN during a two-year period from April 2016 to April 2018. Inclusion criteria were factor VIII (FVIII) or factor IX (FIX) deficiency (defined as FVIII or FIX level < 50%) of all ages and severities. Descriptive statistics were performed for the entire sample, but direct comparisons were limited to patients with mild hemophilia due to the low number of females with moderate or severe hemophilia.  
Results: Females made up 7% of the overall sample, 19% of mild FVIII deficient patients, and 24% of mild FIX deficient patients. Females with mild hemophilia had higher factor levels than males with mild hemophilia (P<0.001), older age at diagnosis (P<0.001), and a shorter duration of enrollment in the ATHN database (P<0.001). Females were less likely to have a comprehensive care visit (P<0.001), and more likely to have an unknown treatment type (P<0.001) or an unknown factor type (P<0.001). Males were significantly more likely to have a comprehensive care visit even when controlling for factor level, inhibitor status, HIV status, hepatitis status, and ATHN enrollment duration (OR: 1.53; CI: 1.29-1.85; P<0.001).  
Conclusions: The proportion of patients at all HTC’s who are female is significantly lower than expected based on estimated population prevalence of 0.3 to 1 female with FVIII or FIX < 40% for every male with hemophilia (Hermans and Kulkarni, Haemophilia, April 2018). This study provides evidence that the care of females with hemophilia differs from that of males with hemophilia. Determining the precise way in which gender impacts care warrants further discussion and investigation. These differences may reflect variability of practices of care team members, of patient self-perceptions and behaviors, of surveillance practices, or even differences in the rate at which data is being entered into the ATHN dataset for female patients. However, it is clear that at some level of the patient care paradigm gender is making an impact. The authors acknowledge The American Thrombosis and Hemostasis Network, ATHN-affiliated US HTC’s, and their 38,000+ patients who have contributed their demographic, clinical, and genetic information to the ATHN dataset.