HEMOPHILIA
Study Companion

Hemophilia Study Companion

Courtney Thornburg, MD, MS

Overview: In this activity, Dr. Courtney Thornburg of the Hemophilia and Thrombosis Treatment Center at Rady Children's Hospital in San Diego discusses the clinical relevance of hemophilia abstracts presented at the 2018 American Society of Hematology Annual Meeting. Dr. Thornburg will discuss these abstracts in the context of 4 cases of patients with hemophilia A or hemophilia B, and provides her expert opinion of how research in the treatment of hemophilia can guide treatment.

Content Areas

- Hemophilia A
- Hemophilia B
- Extended half-life factor replacement
- Inhibitor formation during treatment for hemophilia
- Factor VIII replacement
- Factor IX replacement

Table of Contents

Target Audience

This educational initiative is intended for a national audience of hematologists, hematology nurse practitioners, physician assistants, nurses and other clinicians who manage patients with hemophilia.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Compare and contrast current treatments, based on the results of recent clinical trials, to select treatments that best match individual patients' needs
- Implement a routine monitoring protocol for bleeding events and inhibitors to guide treatment selection
- Apply the data from current clinical trials to estimate the relative risk of developing inhibitors with approved therapies
- Summarize the safety profile for the extended half-life treatments

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ASH Abstracts

Case 1: Early Prophylaxis Provides Continued Joint Protection in Severe Hemophilia a: Results of the Joint Outcome Continuation Study

Case 2: B-YOND Final Results Confirm Established Safety, Sustained Efficacy, and Extended Dosing Interval for Up to 4 Years of Treatment With rFIXFc in Previously Treated Subjects With Severe Hemophilia B

Real-World Data on the Use of rFIXFc in Subjects With Hemophilia B for Up to 3.7 Years Demonstrates Improved Bleed Control and Adherence With Reduced Treatment Burden

Case 3: Immunogenicity of Two Plasma-Derived FVIII Products and Simoctocog Alfa in Previously Untreated Patients According to *F8* Mutation Type

Emicizumab Prophylaxis Provides Flexible and Effective Bleed Control in Children with Hemophilia A with Inhibitors: Results from the HAVEN 2 Study

The Atlanta Protocol: Immune Tolerance Induction in Pediatric Patients with Hemophilia a and Inhibitors on Emicizumab

Case 4: Real World Use of Extended Half-Life Products and the Impact on Bleeding Events and Joint Health in the United States

Adoption of Prophylaxis in the United States in the Era of Extended Half-Life Factor Concentrates

Personalization of Treatment Regimens for Active Patients: A Comparison of Hemophilia Prophylaxis Treatment Regimens

A New Dosing Model Based on Body Mass Index to Guide Factor VIII Dosing in Patients with Hemophilia A

Case 1: Diagnosis and management of an infant with severe hemophilia A

Primary complaint

The family of a 9-month-old infant with severe hemophilia A is discussing treatment options with their pediatric hematologist.

History of current complaint

Nathan B underwent circumcision after an uneventful pregnancy and spontaneous vaginal delivery. After circumcision, Nathan B developed severe bleeding and was found to have a prolonged activated partial prothrombin time (aPTT). Further evaluation showed he had normal von Willebrand factor activity and antigen, normal factor IX, XI, and XII activities, and factor VIII (FVIII) activity of <1%. He was treated with standard half-life (SHL) recombinant FVIII (rFVIII) with resolution of bleeding.

Since his circumcision, Nathan B has had 2 additional factor exposures: one for a soft-tissue bleed, and one for head trauma. FVIII inhibitor testing was negative after the third exposure day (ED). Genetic testing revealed intron 22 inversion in the *F8* gene. The mother does not recall a family history of hemophilia, and denies a personal history of bleeding, including no history of heavy menstrual bleeding or post-partum hemorrhage. She was referred to genetic counseling for further evaluation.

Nathan B is now 9 months old and he is in clinic for a scheduled follow-up visit. In addition to discussing preventive strategies to reduce bleeding episodes for Nathan B, as he is learning to crawl and walk, you also want to discuss prophylactic treatment with the family.

In the Joint Outcomes Study, children treated with early FVIII prophylaxis (initiation before 30 months and before 3 hemorrhages into any single joint) had which of the following outcomes compared to children who continued episodic (on-demand) FVIII?

A. Reduced risk of abnormal joint disease on MRI at 6 years of age.
B. Reduced risk of intracranial hemorrhage
C. Increased risk of inhibitor development
D. Increased risk of catheter-related infection

Discussion points

Half of infants diagnosed with congenital hemophilia are tested due to bleeding events during circumcision or assisted deliveries, rather than based on family history of hemophilia.[1-4] Infants with hemophilia may also present with intracranial hemorrhage (ICH). Clinicians should have a high index of suspicion for hemophilia and other congenital bleeding disorders in patients with ICH, but fewer than a quarter of newborns with documented ICH are evaluated for congenital hemophilia.[3] In this case, the absence of family history can be explained by an incomplete or insufficient history, or possibly a spontaneous *F8* mutation. Since the patient has already had genetic testing, the mother can have genetic testing for the known variant to determine her carrier status. This information can guide family testing and planning for future pregnancies.[5] If the mother is a hemophilia A carrier, then evaluation by an adult hematologist with expertise in hemophilia is warranted.

For this patient with severe hemophilia, primary prophylaxis (ie, initiation of prophylaxis at a young age and prior to repeated joint hemorrhage) is considered the standard of care.[6] The value of early prophylactic treatment was demonstrated by the 2007 Joint Outcome Study, which showed that patients with hemophilia A

who were randomized to every-other-day FVIII prophylaxis before 30 months of age had better joint outcomes at 6 years of age when compared to patients who only received an enhanced episodic treatment regimen.[7] At the 2018 ASH meeting, results of a long-term follow-up study (JOS-C) were presented, which included data on the primary endpoint of MRI-evidence of osteochondral joint damage.[8] Of the original 65 participants, 18 of those initially randomized to prophylactic treatment were enrolled (early prophylaxis patients), and 19 transitioned from episodic treatment to prophylactic treatment at a mean age of 7.5 years (delayed prophylaxis patients). At 18 years of age, the authors found that patients who received delayed prophylactic treatment were at greater risk of and had more extensive joint damage than those who received early prophylactic treatment. Of patients on early prophylaxis, 67% had no affected joints, compared to only 24% of the delayed prophylaxis group. Patients in the delayed prophylaxis group were also more likely to have multiple joints with evidence of damage. The authors concluded that early initiation of FVIII prophylaxis in the toddler years can prevent later joint damage. The results from the 7-year ESPRIT study also support these findings—patients who were 1-7 years of age when they began treatment had fewer bleeding events and fewer hemarthroses if they received prophylactic treatment.[9] Of 8 patients who started prophylactic treatment before 3 years of age, none had evidence of joint damage, compared to 3 of 10 who were receiving episodic treatment.

Initiating therapy in infants comes with a number of barriers (especially factors that can influence adherence),[10] but should the parents decide to begin prophylaxis with clotting factor, treatment decisions include timing of initiation, dose and frequency, and type of clotting factor (plasma-derived vs recombinant; SHL vs extended half-life [EHL]). The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) recommended that emicizumab-kxwh be considered as a prophylactic treatment for infants any time after birth to reduce the risk of intracranial hemorrhage, while noting that there is limited data on use in infants under 6 months.[11]

Case Review by Dr. Thornburg

Many boys with severe hemophilia are diagnosed within the newborn period related to bleeding with circumcision, heel stick, venipuncture or immunizations. Any bleeding events in infants should prompt investigation for a bleeding disorder, even in the absence of a positive family history.

In this case, we have the patient diagnosed early because of bleeding after circumcision, and we're faced now with a question of how to move forward. The current standard of care treatment for boys with severe hemophilia is primary prophylaxis. We now have a strong evidence base to support the short- and long-term benefits of prophylaxis and rationale to initiate at a young age, and prior to the onset of joint bleeding.

Shared decision making is an important aspect of hemophiliac care, especially when considering prophylaxis. Overall, the goal of shared decision making related to prophylaxis should be to identify the treatment strategy that will work best for the individual patient and family.

The route of administration and dosing frequency of a treatment product may impact decision making. Options for prophylaxis now including clotting factor replacement, including standard half-life and extended half-life products which are administered intravenously 2-4 times per week, and emicizumab, which is administered subcutaneously 1-4 times per month.

Despite the ease of subcutaneous injection, some families may prefer clotting factor treatment, given the long track record and large amount of data from clinical trials and real-world experience. Available data for various treatment options should be reviewed, as well as the gaps in knowledge.

Current gaps in knowledge include inhibitor rates in previously untreated patients treated with extended half-life clotting factor. Also, although emicizumab is approved for all ages, clinical trials have not included previously untreated patients, and there are limited data in children less than 6 months of age. We have no data on inhibitor rates in previously untreated patients who start emicizumab prophylaxis and use factor VIII, as needed, for bleeding.

Case 2: An adolescent with poor adherence to FIX prophylaxis

Primary complaint

A 14-year-old with severe hemophilia B reports several bleeding episodes during his annual comprehensive care clinic visit.

History of current complaint

Darin G has been on prophylactic treatment with standard half-life (SHL) recombinant factor IX (rFIX) 3 times per week since he was 1 year old. He has been self-infusing his factor replacement at home for several years. At his annual comprehensive care clinic visit, you observe a slight reduction in the range of motion in his right elbow. When asked about bleeding events, he describes several spontaneous bleeds in his right elbow and ankles. He admits that some weeks he may only infuse a single dose, but when he has a bleeding event he takes most of his doses in the subsequent weeks. He states that he often ignores reminders (from both his parents and a mobile health app) and puts off infusions because he does not feel like he has the time, and does not remember how important injecting factor on schedule is until he notices a bleed. At the visit you discuss new FIX products, including 3 extended half-life (EHL) products.

Which of the following conclusions is supported by long-term follow-up of patients treated with rFIX-Fc?

A. A similar degree of bleeding control can be achieved with weekly rFIX-Fc infusions and dosing every 8-16 days/twice-monthly dosing
B. The majority of patients who try dosing intervals ≥14 days will have to return to <14-day dosing intervals within 4 years
C. Bleeding control is not adequate in almost half of patients using factor infusions once-weekly, and these patients will require a shorter dosing interval
D. Episodic treatment is an option for some patients, since the bleeding rate in patients using episodic treatment was similar to that of patients on a 7–14-day prophylactic regimen

Discussion points

Adolescents are at high risk for poor adherence, not only because of developmental and social changes but also because the burden of care shifts from their parents.[12] Education for Darin G on the importance of prophylaxis to prevent chronic arthropathy might help to reinforce his belief in the need for treatment, and social initiatives such as the hemophilia summer camp

can provide formal and peer-to-peer educational opportunities.[13]

Extended half-life factor replacement may also be an option for this patient, since EHL FIX can substantially reduce the burden of treatment. Endogenous FIX has a half-life of 18 hours, whereas the half-life reported for EHL FIX is 54-102 hours—patients can transition from 2-3 infusions per week to once-weekly or every-other-week infusions.[14-18] There are currently 3 approved EHL FIX products available: recombinant FIX-Fc (FIX-Fc) is stabilized by fusion to the Fc immunoglobulin domain, recombinant IX-FP (rFIX-FP) by linkage to albumin, and coagulation factor IX (recombinant), glycoPEGylated (nonacog beta pegol) by addition of polyethylene glycol.[19-22] Results for up to 4 years of follow-up for patients treated with rFIX-Fc in an extension of the B-LONG and Kids B-LONG studies (the B-YOND trial) was presented at the 2018 ASH Annual Meeting.[23] Most patients entered the extension study using weekly dosing (n=51/93 from B-LONG) or an individualized, 8–16-day or twice-monthly dosing regimen (n=31, median dosing interval = 13.6 days). These dosing regimens were sufficient for the majority of patients, with only 15.5% changing to a shorter dosing interval. The annual bleeding rate (ABR) was 2.26 (range* 0.40-5.16) in patients treated weekly and 1.85 (range 0.76-4.00) for patients on individualized extended dosing, while patients receiving episodic treatment had an ABR of 11.64 (range 5.12-18.54). During the follow-up period, no inhibitors were detected in any patients. Another recently published analysis of patients in B-LONG focused on 22 patients with dosing intervals of ≥14 days.[24] After a median follow-up of 3.4 years, most patients were on a 14-day dosing interval, but 6 were on >14-day intervals. During the follow-up period, 5 patients returned to shorter dosing intervals—either due to findings from pharmacokinetic studies (n=1), personal reasons (n=2), request due to bleeding (n=1), or repeated bleeding (n=1)—while the remaining 17 continued the ≥14-day dosing schedule; 3 required a temporary reduction in their dosing interval. Medan ABR was 1.6 in these patients, which was similar to the bleeding rates for all patients in B-YOND.

In a separate study, Shapiro and colleagues performed a chart review of patients (N=43) who had received rFIX-Fc outside of a clinical trial.[25] To be included in this retrospective study, patients had to have been treated with rFIX-Fc for at least 6 months (range 0.5-3.7 years), and could not have a history of FIX inhibitor. Patients with mild, moderate, and severe (n=22) hemophilia B were included, and in some cases, the investigators were able to compare bleeding events and factor usage before and after initiation of rFIX-Fc. Of the patients on prophylactic treatment (n=34), 94% were on a 7-, 10-, or 14-day treatment regimen. Adult patients had a decrease in median factor use from 111 IU/kg to 52.5 IU/kg after switching to rFIX-Fc, and in patients with severe hemophilia, there was a reduction in bleeding events: for example, ABRs decreased from 8.2 to 2.3 after patients started prophylaxis with rFIX-Fc.

Case Review by Dr. Thornburg

Any treatment that is prescribed will only work if taken. Based on the history of this patient, it appears that his bleeding is related to lack of adherence rather than too low of a dose or traumatic injuries. An extended half-life factor IX clotting factor may be a good option for him since it would allow for less frequent infusions.

The data presented by Shapiro and colleagues at the 2018 ASH meeting identified reduction in treatment burden as the most common reason for switching to an extended half-life clotting

*ABR reported as median (interquartile range)

factor and demonstrated excellent adherence. However, even with a more convenient product, the patient still needs educational support and strategies to remember his infusions. The HTC can provide education about the impact of recurrent bleeding and joint health, and the benefits of prophylaxis. Having him identify treatment goals, and helping him look at how bleeds may interfere with his short- and long-term goals, could motivate better adherence.

Finally, peer-to-peer approach might help motivate him to stick with the treatment plan. If the patient decides to switch to an extended half-life factor IX clotting factor, then he has 3 options to choose from, including: Fc fusion, albumin fusion and pegylated products. Pharmacokinetic studies can be conducted to determine individual half-life and dosing frequency.

Upon switching, there should be monitoring for inhibitor formation and any adverse events. However, in the BEYOND trial of recombinant factor IX Fc, no patients developed inhibitors during the follow-up period, and there weren't any unexpected adverse events.

Case 3: A toddler with oral bleeding unresponsive to FVIII and antifibrinolytic therapy

Primary complaint

A 14-month-old Hispanic male with severe hemophilia A presents to the emergency department for oral bleeding.

History of current complaint

Gaspar S was tested for hemophilia at birth based on a family history (his maternal uncle had hemophilia). He had normal FIX activity (for age) and FVIII activity <1%. His mother recalls that her uncle was frequently admitted to the hospital because of bleeding episodes and died at 24 years of age. GS is currently treated with on-demand therapy. He has had 6 exposure days (ED) to date—1 ED for bleeding with circumcision prior to diagnosis and most recently 5 ED for management of his first joint bleeding.

He is treated in the emergency department with FVIII replacement and antifibrinolytic therapy without resolution of bleeding, leading you to suspect FVIII inhibitor. An inhibitor assay is drawn and treatment is started with bypassing therapy. Later, you meet with the family to discuss treatment options and preventive measures going forward. The testing done on admission indicated his FVIII inhibitor level was 10 Bethesda units (BU).

Which of the previously-untreated patients in the following scenarios would you expect to have the greatest risk of developing an inhibitor to FVIII?

A. A patient with an F8 null mutation treated with recombinant FVIII
B. A patient with an F8 point mutation treated with recombinant FVIII
C. A patient with an F8 null mutation treated with plasma-derived FVIII
D. A patient with an F8 point mutation treated with plasma-derived FVIII

Discussion points

Inhibitors remain a significant problem in managing hemophilia A, although the factors that lead to inhibitor development in some individuals are not well understood.[26,27] However, as in the case of Gaspar S, individuals with more severe disease or a null mutation, or a family history of inhibitors, appear to have a greater risk of inhibitor development.[28] Recommendations for monitoring patients for inhibitor development have been published by MASAC.[29] Monitoring for inhibitors is important for early initiation of immune tolerance

induction (ITI), and should be done before elective invasive procedures, when the response to factor replacement is inadequate, before and after switching replacement factor, and 2-3 weeks after intensive treatment (≥5 exposure days). When starting treatment, patients should be tested for inhibitor every third exposure day or every 3 months (whichever occurs sooner) until 20 exposure days have elapsed. Testing should continue every 3-6 months until 150 exposure days have been reached, and then testing should be performed 1-2 times per year.

The choice of replacement factor affects the risk of inhibitor development, and this was studied prospectively in the SIPPET trial.[30] In SIPPET, most patients who developed inhibitors did so within the first 15 exposure days, and all developed by exposure day 39. Patients treated with recombinant factor VIII were more likely to develop inhibitor than those who were treated with a plasma-derived factor (37% vs 23%), but none of the EHL products were studied. Liesner et al presented an analysis of data from completed, prospective trials of patients treated with a recombinant or plasma-derived FVIII replacement† to determine the risk of inhibitor formation based on mutation type.[31] None of the previously untreated patients with non-null *F8* mutations developed inhibitors. In contrast, inhibitors were present in 9.8%-12.0% of patients with null *F8* mutations treated with a plasma-derived factor, and in 17% of patients treated with the recombinant factor. Results of the HAVEN 2 study with emicizumab in patients with inhibitors was also presented at the ASH Annual Meeting.[32] Patients <12 years of age (N=88) were enrolled if they had developed inhibitors during episodic or prophylactic treatment, and received emicizumab once-weekly for 4 weeks, followed by a maintenance dose given weekly (qW), every other week (q2W), or every 4 weeks (q4W). Patients in the qW group had an ABR of 0.3, while patients in the q4W group had an ABR of 2.2. No patients developed a new inhibitor. During the study, antidrug antibodies were observed in 4 patients, and in 2 cases these patients exhibited reduced emicizumab levels. Another pilot study addressed emicizumab prophylaxis during immune tolerance induction (ITI).[33] Patients in this study started ITI after 4, once-weekly loading doses of emicizumab. Although this study has only enrolled 8 patients, and results for 4 patients were available, the authors reported a decrease in inhibitor titers since the start of ITI. Treatment for hemarthrosis was required in 1 case, and 3 mild bleeding events were reported in 2 other patients. Two of the 4 patients had no bleeding symptoms.

In December 2018, MASAC published recommendations for the use of emicizumab that partially address both of these uses.[34] The results of HAVEN 2 support the recommendation that emicizumab be considered for any patient with an inhibitor if they are having frequent bleeding episodes during treatment with episodic therapy or a bypassing agent. Patients on an activated prothrombin complex concentrate should discontinue it before starting emicizumab therapy. Finally, MASAC does not currently recommend the use of emicizumab prophylaxis during ITI outside of clinical trials. The full MASAC position statement also addresses a number of other clinical scenarios.

Case Review by Dr. Thornburg

This case gives us the opportunity to discuss inhibitors, specifically for patients with severe hemophilia A.

Inhibitors remain the most significant complication of hemophilia therapy and are associated with increased morbidity and mortality, and resource utilization. The highest

*Octanate®, Wilate®, or Nuwiq®

risk period for inhibitor formation is within the first 50-75 exposure days. Determinants which modify the risk of inhibitor include race and ethnicity, higher in Hispanics and African Americans; genetic variants, higher with large deletions or null mutations; type of factor product, higher with recombinant compared to plasma-derived factor; and presence of immune danger signals at the time of factor exposure; as well as high intensity factor exposure.

At the 2018 ASH meeting, Liesner and colleagues presented data which suggest that the combination of null factor XIII mutation and treatment with recombinant factor XIII is associated with particularly high inhibitor risk. Clinicians might consider treating patients with high risk for inhibitor based on mutation with plasma derived factor VIII vs minimizing factor VIII exposure altogether by starting emicizumab prophylaxis.

The patient in the case scenario has developed a high titer factor VIII inhibitor after 6 exposure days. The patient will require bypassing therapy for management of bleeding. Options for prophylaxis now include bypassing therapy and emicizumab.

Immune tolerance induction may be recommended for inhibitor eradication. The optimal ITI strategy has not been defined. ITI may be prescribed in combination with bypassing therapy prophylaxis. Alternatively, at the 2018 ASH annual meeting, Batsuli and colleagues described their experience with ITI in combination with emicizumab. However, the recently released MASAC position statement on emicizumab supports the use of emicizumab in patients with inhibitors, but has not yet endorsed its use during ITI.

In my experience, I have started patients with inhibitors on emicizumab, and plan to offer ITI through a clinical trial when available. I continue to see value in ITI as successful tolerance allows for treatment of breakthrough bleeding with factor XIII, rather than bypassing therapy, and would potentially allow for enrollment in the gene therapy trial in the future.

Case 4: A patient with several bleeding episodes during episodic treatment with recombinant FVIII

Primary complaint

A 40-year old male with moderate hemophilia A has had several bleeding episodes while on episodic treatment.

History of current complaint

Joey H is a 40-year old, obese (BMI 28) male with moderate hemophilia A (2% FVIII level at diagnosis). He is currently using SHL recombinant FVIII for on-demand treatment. In the last 4 months, he has begun exercising 2-3 times a week for weight management. He has had left knee hemarthrosis and stiffness after spinning classes, and right hip hemarthrosis following an indoor rock-climbing session. He schedules an appointment with you because he is concerned about bleeding events derailing his exercise regimen and weight loss goals. You discuss some guidelines for choosing activities to participate in and refer him to the National Hemophilia Foundation guide to sports and exercise in patients with hemophilia, before discussing some possible treatment modifications.[35]

When outcomes have been compared between patients using different treatment regimens, what outcomes have been demonstrated?

A. A difference in ABR, favoring prophylactic treatment over episodic treatment
B. A difference in measures of joint damage, favoring EHLs over SHLs
C. A difference in measures of joint damage, favoring prophylactic treatment over episodic treatment
D. A difference in ABR, favoring SHLs over EHLs

Discussion points

The introduction of extended half-life (EHL) treatments has changed the therapeutic landscape for hemophilia, and several observational studies presented at ASH looked at the adoption of EHLs and prophylactic treatment, and how EHLs have affected patient outcomes.[36-38] (These studies included results from patients with hemophilia A and hemophilia B, although the number of patients in the hemophilia B cohorts was considerably smaller.) Malec and colleagues presented 2 studies that might offer some insight into how to approach Joey H's case, and the differences in outcomes that might be expected if he were to transition from an episodic to prophylactic regimen. The first study enrolled a younger group of patients with severe hemophilia (N=67, n=58 with hemophilia A; mean age=15), and compared the outcomes between patients on an SHL FVIII replacement and those on an EHL treatment. Most patients were on prophylactic treatment (n=53, 90%).[36] Patients receiving prophylaxis had an ABR of 1.0, compared to 18.6 for those on episodic treatment (P<0.001), and had less evidence of joint damage (although this difference was not statistically significant). Patients using an EHL had a lower ABR than those using an SHL product (ABR 0.5 vs 1.5, respectively; P>0.5), although they had more evidence of joint damage. The authors speculate that patients in this cohort were too young to exhibit a benefit to joint health. In the second study presented by Malec et al, they reported patient characteristics and dosing patterns. For patients with hemophilia A, the most common prophylactic dosing frequency with an EHL was twice weekly, whereas patients using an SHL were infusing factor every other day.[37]

In 2 other studies, the authors reported methods based on pharmacokinetic studies to optimize treatment, although neither have been clinically validated. The study by Watt et al is interesting because they developed tailored treatment regimens to 6 different scenarios representing the patient's risk for bleeding during exercise.[39] Pharmacokinetic data was drawn from published data for a recombinant, standard half-life FVIII (Advate®) and rurioctocog alfa pegol, and National Hemophilia Foundation criteria were the basis for the physical activity profiles.[35] The authors used a mathematical model to identify treatments and regimens that optimized FVIII peak levels and would provide bleeding protection for 6 scenarios (see Table).

Risk[a] during weekday activity[b]	Risk[a] during weekend activity[b]	Optimal treatment
Moderate risk	Moderate risk	SHL every other day
None	Low risk	EHL 2x/week
Low risk	Moderate risk	
Low risk	High risk	
Moderate risk	Low risk	SHL 3x/week
High risk	Low risk	

[a]Risk was defined as published by Anderson and Forsyth, 2017.[35] Briefly, low risk indicates that the activity has a low risk of collisions, collisions might occur in moderate-risk activities, and collisions will occur in high-risk activities.
[b]Weekday activities occurred 5 times per week; weekend activities occurred twice per week.

For Joey H, both indoor cycling and indoor rock climbing are considered low-to-moderate risk activities—a pilot study suggested that a top rope climbing regimen tailored for individuals with hemophilia did not result in increased bleeding episodes, and had a positive impact on joint health.[40,41] One of these prophylactic regimens could, in theory, provide a personalized regimen to minimize his risk for bleeding during exercise. In the second study, a model for dose adjustments based on body-mass index (BMI) was developed by Tiede et al using data from a single-dose pharmacokinetic study of turoctocog alfa.[42] Using the data from this study, the authors concluded that the variation in plasma FVIII activity could be reduced by adjusting the turoctocog alfa dose based on BMI, rather than dosing based on body weight alone. For patients across the spectrum of underweight to obese, the authors suggest a theoretical dose adjustment factor.

Case Review by Dr. Thornburg

Treatment decisions for hemophilia management should be targeted toward the patient's goals, activity level and bleeding history. We are now 5 years into the era of extended half-life factor replacement and at the advent of emicizumab prophylaxis, and these developments have greatly expanded our options for managing hemophilia.

At the 2018 ASH meeting, Dr. Malec's studies described an increase in prophylaxis since the introduction of extended half-life factor products, and quantified real-world use of extended half-life factor products and their impacts on annual bleed rates.

Now, for a patient who participates in low-to-moderate risk activities 2-3 times per week, having more treatment options means that we have greater flexibility to find a regimen that fits his needs. The studies by Maureen Watt and Andreas Tiede give us some insight into the personalization that patients can expect in the future.

The first study suggests treatment regimens based on activity levels and schedules, and the second suggests an approach for optimizing patient dosing.

Our patient should be congratulated for starting to tackle weight management through exercise. Obesity is a risk factor for joint disease, and by addressing overweight or obesity, he should have improved joint outcomes. Based on his bleeding, even with low-to-moderate risk activities, prophylaxis is indicated. Initiation of twice weekly prophylaxis with extended half-life factor is reasonable, and dosing and frequency can then be tailored based on PK studies and clinical response.

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