Hemophilia A: Strategies for Improving Long-Term Holistic Management, Adherence, and Quality of Life

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Abstract

Hemophilia A is a rare inherited bleeding disorder characterized by a deficiency in factor VIII. The evolution of currently approved prophylaxis therapy in hemophilia A will be reviewed, including the clinical value of prophylaxis, real-world experience with prophylaxis, and patient quality-of-life factors that must be considered when choosing treatment options for these patients.

With the discovery of the anti-hemophilic globulin in the middle of the 20th century, a variety of therapeutic options became available, including cryoprecipitate, factor VIII, and factor IX concentrates. In the late 1970s and early 1980s, the transmission of HIV and hepatitis wreaked havoc among the hemophilia population. This led to the development of high-purity plasma concentrates as well as recombinant products, which in turn revolutionized the treatment of hemophilia, giving rise to home therapy as well as hemophilia prophylaxis. As a result, quality of life and life expectancy has improved dramatically for people with hemophilia. Recent advances in technology have created new therapeutics with extended half-lives and nonfactor replacement products, while gene therapy has opened the door to curing hemophilia. The World Federation of Hemophilia (WFH) published new guidelines for management of hemophilia in 2020 (Srivastava et al., 2020).

DEFINITION OF PROPHYLAXIS

Prophylaxis is standard of care for patients with severe phenotype hemophilia. Prophylaxis is defined as the regular administration of therapeutic products to prevent bleeding (Berntorp, 2003; Carcao et al., 2018; Srivastava et al., 2020; Table 1). This includes the administration of clotting factors and nonfactor replacement therapy. Prophylaxis should also enable people with hemophilia to lead healthy and active lives, in-

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Table 1. Definition of Prophylaxis

Primary prophylaxis	Regular continuous prophylaxis **in the absence of documented joint disease**, determined by physical examination and/or imaging studies and started before the second clinically evident joint bleed and before 3 years of age
Secondary prophylaxis	Regular continuous **prophylaxis initiated after 2 or more joint bleeds** but before the onset of joint disease at 3 or more years of age
Tertiary prophylaxis	Regular continuous prophylaxis **initiated after the onset of documented joint disease**, typically initiated in adulthood

Note. Information from Srivastava et al., 2020.

cluding participation in most physical activities similar to those without hemophilia.

FACTOR VIII CONCENTRATES AND EXTENDED HALF-LIFE FVIII

There are many factor VIII concentrates available to patients with hemophilia A (Croteau, 2018; Peyvandi et al., 2013), including standard half-life products and the more recently developed extended half-life products. Different cell lines are used to create these concentrates, and these concentrates vary in terms of their amino acid composition or constructs. Most of these constructs are either full-length or B-domain deleted/truncated (Table 2).

A number of different strategies have been employed in extending the half-life of the recombinant clotting factors. This includes the production of single-chain products, albumin fusion, Fc fusion through the immunoglobulin, or the utilization of a polyethylene glycol (PEG) molecule attached to factor VIII (Pipe, 2016).

The half-life prolongation of factor VIII is limited by the dependence of factor VIII on von Willebrand factor. The pharmacokinetics of these products, including area under the curve, half-life, and clearance vary greatly among the different products (Coyle et al., 2014; Mahlangu et al., 2014, 2016; Octapharma, 2019; Pipe et al., 2016; Powell et al., 2012; Tiede et al., 2013).

Table 2. Factor VIII Concentrates

Product	Cell line	FVIII construct	Additional features	Mean adult half-life ± SD, hr
Turoctocog alfa	CHO	B-domain truncated		10.8 ± 4.9
Ionoctocog alfa	CHO	B-domain truncated	Single-chain, FVIII activity by 1-stage clotting assay, multiply by 2x conversion factor	14.2 ± 3.7
Octocog alfa	BHK	Full-length	Includes human chaperone protein HSP70 to assist protein folding	14.3 ± 3.7
Rurioctocog alfa pegol	CHO	Full-length	Random pegylation with branched 20kDa PEG, most covalently bind to B-domain	14.7 ± 3.8
Simoctocog alfa	HEK-293	B-domain deleted		17.1 ± 11.2
Damoctocog alfa pegol	BHK	B-domain deleted	Site-directed pegylation with 60kDa PEG, linked to introduced cysteine residue	18.7
Efmoroctocog alfa	HEK-293	B-domain deleted	Fusion with IgG1 Fc at carboxy-terminus	19.7 ± 2.3
Turoctocog alfa pegol	CHO	B-domain truncated	Site-directed pegylation with 40kDa PEG, conjugated to 21 amino acid B-domain sequence	19

Note. FVIII = factor VIII; HSP = heat shock protein; IgG = immunoglobulin G; PEG = polyethylene glycol. Information from Croteau (2018); Peyvandi et al. (2013).

Table 3. World Federation of Hemophilia Prophylaxis Recommendations

Pediatric patients	For pediatric patients with severe haemophilia A or B, the WFH recommends early initiation of prophylaxis with clotting factor concentrates (standard or extended half-life) or other haemostatic agent(s) prior to the onset of joint disease and ideally before age 3.
Adolescents and adults	For adolescents and adults with haemophilia who show evidence of joint damage and have not as yet been on prophylaxis, the WFH recommends commencing tertiary prophylaxis in order to reduce the number of hemarthroses, spontaneous and breakthrough bleeding, and slow down the progression of haemophilic arthropathy.

Note. Information from Srivastava et al. (2020).

Products with extended half-lives are as effective as the standard half-life products. The annualized spontaneous bleeding rates in trials involving pediatric, adolescent, and adult populations are actually quite low, ranging from 0 to 2 episodes (Fischer et al., 2017; Nolan et al., 2016; Pasi et al., 2017).

An area of considerable controversy that has been debated for many years is what minimal level of factor VIII is needed to prevent bleeding. It was originally thought that increasing the factor VIII level to 1% in patients with severe hemophilia was enough to prevent bleeds (Collins et al., 2009; den Uijl et al., 2011). It turns out that this is not true since many of these individuals continue to bleed spontaneously. Current WFH guidelines suggest that maintaining levels above 3%, and perhaps in the 3% to 5% range, should be the goal for prophylaxis (Srivastava et al., 2020). There are also data suggesting that maintaining factor VIII levels above 12% should be the goal for patients with severe phenotypes of hemophilia A.

WORLD FEDERATION OF HEMOPHILIA PROPHYLAXIS RECOMMENDATIONS

The WFH guidelines now recommend that pediatric patients with severe hemophilia A or B should initiate prophylaxis with either standard or an extended half-life clotting factors, or other hemostatic agents before the onset of joint disease, ideally before the age of 3 years (Srivastava et al., 2020). They also recommend that tertiary prophylaxis be initiated for adolescents and adults with hemophilia who already have joint damage in order to reduce the number of hemarthroses and breakthrough bleeding episodes to slow down the progression of hemophilic arthropathy (Table 3).

DOSING AND PERSONALIZED PROPHYLAXIS

There is high interpatient variability in selecting and dosing factor VIII products (Bjorkman, 2010). Many studies have shown that when patients are matched for a number of variables, including height, weight, and age, the pharmacokinetics (PK) of a product given at the same dose varies substantially. This is why individualizing treatment is so critical for management of patients with hemophilia. When considering prophylaxis, three major variables should be taken into account. One is certainly the hemophilia phenotype and bleeding history. The second is the PK of the specific product being considered. And the third is the anticipated physical activity and baseline joint status of each patient (Ar et al., 2016; Figure 1).

In the PROPEL study of PK-guided prophylaxis with an extended half-life product in 115 patients with severe hemophilia A, researchers targeted two different factor VIII trough levels (Klamroth et al., 2021). The low trough level kept

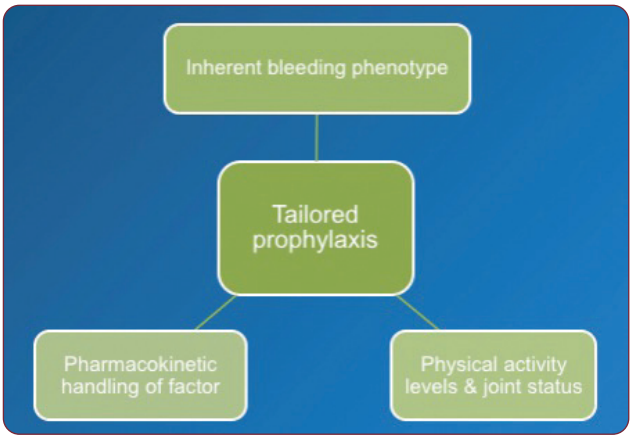

Figure 1. Personalized prophylaxis. Information from Carcao & Iorio (2015).

factor VIII levels between 1% and 3% while the high trough level kept levels between 8% and 12%. Researchers found that the cohort of individuals maintained at the high trough level had a much higher percentage of zero bleeds compared to those maintained at the low trough level (62% vs. 42%). Individuals in the high trough level had a lower mean total annualized bleeding rate (ABR) compared with those in the low trough level (1.6 vs. 3.6). Not surprisingly, the spontaneous joint ABR was also decreased in the high trough cohort.

A post-hoc analysis from this same study was presented at the International Society on Thrombosis and Haemostasis (ISTH) in 2021 (Escuriola-Ettingshausen et al., 2021). The investigators found that total spontaneous joint ABRs were lower in the high trough arm vs. the low trough arm, regardless of the specific prophylactic treatment regimen and regardless of the ABR prior to study initiation. The researchers also found that there were more zero bleeds in the high trough cohort, regardless of treatment prior to study entry. In other words, no matter what regimen individuals took before study enrollment, the high trough arm continued to show better results regarding zero bleeds and spontaneous joint ABRs.

NONFACTOR THERAPY: EMICIZUMAB

Emicizumab is a monoclonal antibody that mimics the function of factor VIII. It was approved by the U.S. Food and Drug Administration for treatment of hemophilia A, regardless of inhibitor status, in October 2018. Emicizumab binds factor X with factor IXa, thereby mimicking the function of factor VIII (Figure 2). It can be administered subcutaneously, and it can be given once weekly, once every 2 weeks, or once every 4 weeks.

Four different HAVEN (Emicizumab Versus No prophylaxis in Hemophilia A) studies have been conducted in the pediatric population up to the age of 1 and in the adult population up to the age of 77 (Kruse-Jarres et al., 2019; Mahlangu et al., 2018; Oldenburg et al., 2017; Pipe et al., 2019; Young et al., 2019), including patients with and without inhibitors. When PK profiles were analyzed in the pediatric, adolescent, and adult cohorts, emicizumab trough concentrations increased with loading doses until about week 5. Emicizumab levels were then maintained between 38 and 50 µg/mL with once weekly, once every 2 weeks, or once every 4 weeks, depending on the patient's PK (Young et al., 2018). A total

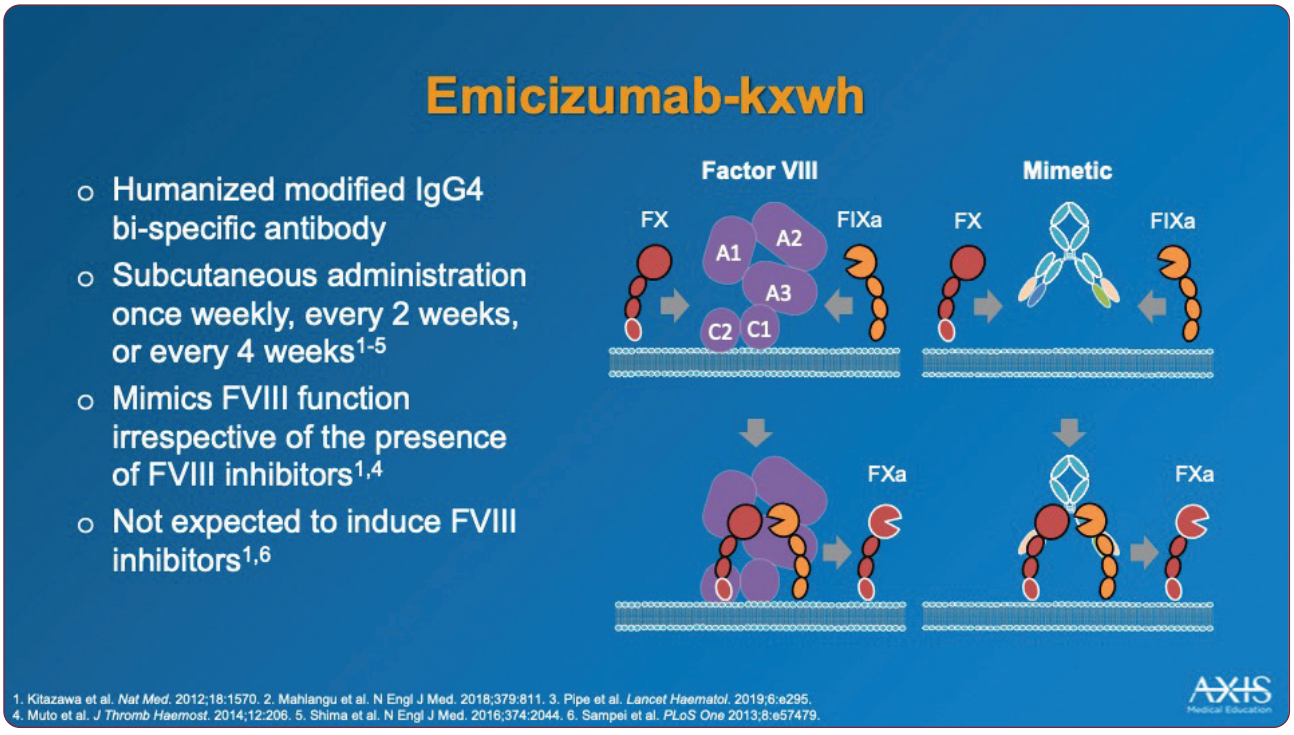

Figure 2. Emicizumab-kxwh.

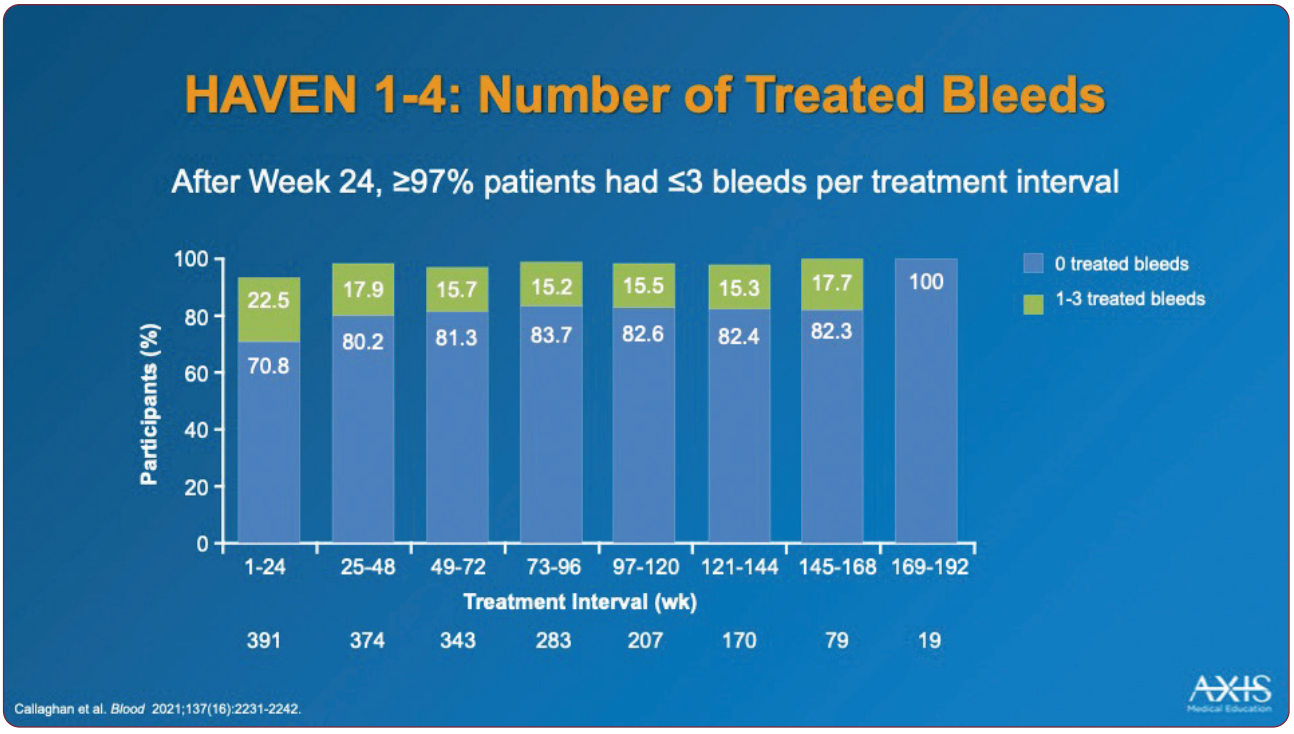

Figure 3. HAVEN 1–4: Number of treated bleeds.

of 399 patients were treated with emicizumab, and the median age was 28 years (Callaghan et al., 2021).

After week 24, more than 97% of patients experienced three or fewer bleeds per treatment interval (Figure 3). The ABR across all the HAVEN studies was quite low (1.4 for the entire study period; see Figure 4). A total of 226 evaluable patients were found to have more than one target joint at baseline and completed at least 52 weeks of treatment with emicizumab. There were 530 target joints in 226 patients at baseline (61% of the patient population). After receiving at least 52 weeks of emicizumab, there was target joint resolution in 95% of those patients, defined as fewer than two spontaneous or traumatic bleeding events in a 12-month period. Approximately 89% of patients had zero target joint bleeds. Thromboembolic events were the chief concern for investigators in HAVEN 1 to 4. However, thrombotic microangiopathy was recognized early and associated with use of activated prothrombic complex for more than 24 hours at high doses. Subsequently, changes to the protocols banned the use of prothrombic complexes, and no further thromboembolic events were observed.

CONCLUSIONS

Prophylaxis should be the standard of care for patients with a severe phenotype hemophilia A. Extended half-life factor VIII products and non-replacement products are as effective as standard half-life products and are associated with fewer adverse risks. Personalized treatment plans should be developed for every patient, addressing variations in dosing and factor half-lives.

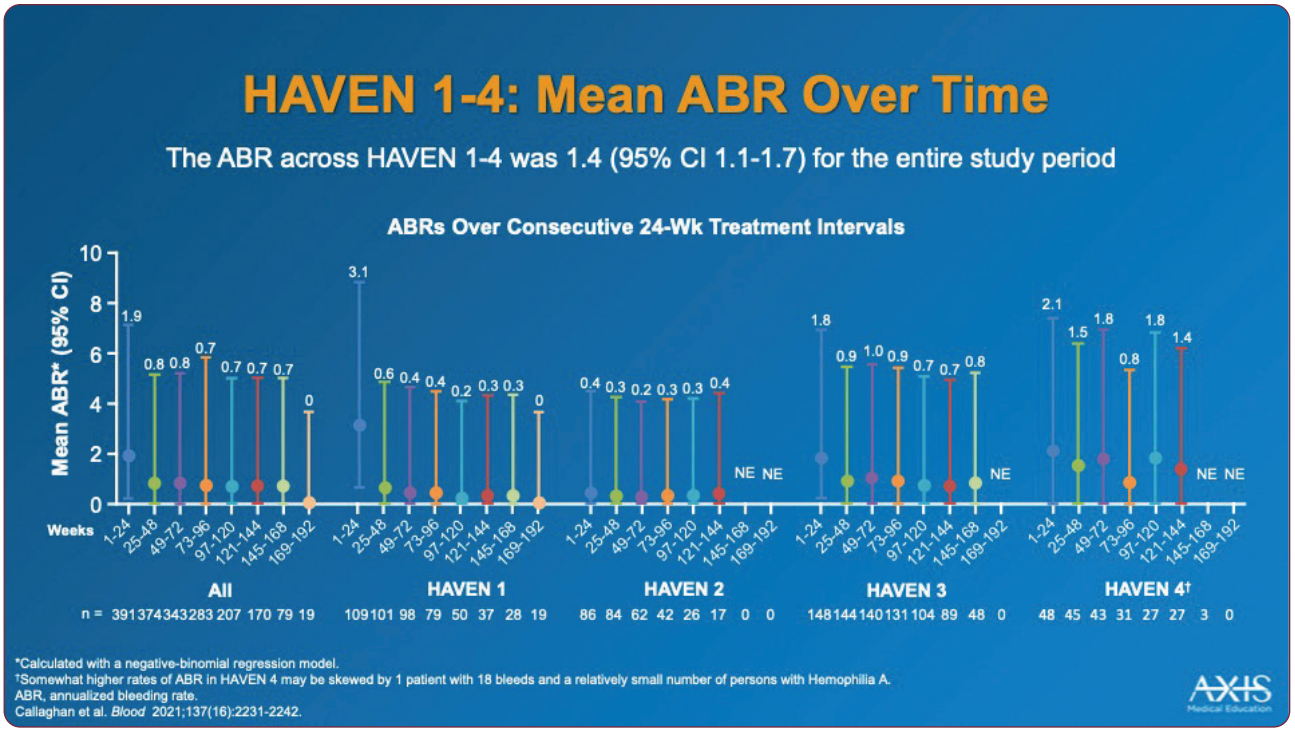

Figure 4. HAVEN 1–4: Mean ABR over time.

HIGHLIGHTS FROM AN EXPERT FACULTY PANEL DISCUSSION

An Expert Panel Discussion was held in December 2021 for a video-based CME activity. Topics included optimizing prophylaxis, improving quality of life, and maximizing compliance to long-term therapy for patients with hemophilia A: https://bit.ly/V2_1787. The following sections present expert perspectives from this discussion.

TREATMENT PLANNING

Miguel Escobar, MD: *In your clinical practice, how do you currently differentiate among available agents in creating treatment plans that include the patient and the caregiver?*

Dr. Young, let's say a 3-year-old comes into your clinic with severe hemophilia A. He is receiving standard half-life factor VIII two times per week but still has had three bleeds in the last 6 months. Will you change the management of this patient and how will you discuss changes with the parents?

Guy Young, MD: Any time I see a new patient, it's always important to review the current treatment regimen and how is it working. As a rule, I adhere to shared decision-making when speaking to the patient or parents about treatment options. One option is to continue current therapy. However, it's important to discuss other options, even if the current treatment is working. I usually say something like "Here are the benefits of this therapy and here are the risks," and then I compare the risks and benefits of the new vs. the old therapy. In this way, both patients and parents can make the best choice to suit their individual needs. The best choice for somebody on twice-a-week extended half-life factor VIII without much bleeding could be just to continue that same drug. In the scenario that you presented with the patient that has had three bleeds in the past 6 months, that number is too high. More than one bleed per year is unacceptable and I would recommend considering other treatment options.

Miguel Escobar, MD: You bring up an important point: How much bleeding are we willing to tolerate? This might be different for an adult who has a lot of arthropathy vs. a child. And it seems like you are saying that your ideal goal is to have zero bleeds.

Guy Young, MD: Absolutely there is going to be a difference between children and adults. Since I treat children, I'm going to defer to Dr. Leissinger about the adults. With young children like a 3-year-old, our goal is really zero bleeds. That's because obvious bleeds are really just the tip of the iceberg. Subclinical bleeding, or so-called microbleeding, does occur. If a patient has one bleed in a year, that patient probably has had at least one or two or more subclinical bleeds, although it's hard to know really. So even if the goal is zero bleeds, that doesn't necessarily mean zero subclinical bleeds. This is what we saw in the Joint Outcome Continuation study. Even for those patients on really effective prophylaxis, there was some deterioration in their joint disease, even in those patients who started early. We have to really have a very low threshold for tolerance of any kind of bleeding in the young age group.

Miguel Escobar, MD: Dr. Leissinger, let's say that you have a 22-year-old who comes to your center with severe hemophilia A. He has mild arthropathy in two joints and is on prophylaxis with an extended half-life factor VIII that he takes intermittently. He tells you that he has bled three times in the last 6 months. How would you approach this type of patient?

Cindy Leissinger, MD: The way I would approach the patient is similar to what Dr. Young has said. I want to find out what the patient is taking, how he has been doing, and then walk through different treatment options with him.

It is especially important in this age group (i.e., late teens or early twenties) when they are just beginning to make their own medical decisions. For various reasons, including going off to college, getting busy doing other things, and no longer being supervised by mom and dad, they may veer off strict prophylaxis.

So we really have to figure out what are their personal goals, their beliefs, and what is most important to them. This is where shared decision-making comes into play, and we really need to sit down with them and have that conversation.

Obviously, I will discuss various treatment options, and I will make recommendations and prioritize the recommendations that I think would be of greatest benefit. I also have to keep in mind that they need to buy into this. They need to agree. They need to feel like this is something that matches up with their lifestyle.

And activity level definitely comes into play. Maybe the patient is just starting college, has access to a regular gym, and wants to start working out? On the other hand, some college guys might want to spend more time in the library instead of pursuing sports. So we have look at where they are in their life journey and assess what's going to be most appropriate for them.

Certainly, if someone has had three bleeds in the last 6 months, even if it's a young adult, that's too many bleeds, particularly if they are joint bleeds. We will need to talk about what we can do better. Maybe it's an adherence problem. If I review their infusion logs or their records, maybe I see that these bleeds are due to a missed dose. Or maybe these breakthrough bleeds are occurring despite good adherence. If their adherence has not been very good, we're going to talk about strategies that might improve their adherence.

QUALITY OF LIFE

Miguel Escobar, MD: *How do you include quality of life into your decision-making?*

Cindy Leissinger, MD: I think this has become extremely important. I really like that the new World Federation guidelines incorporate quality-of-life goals into prophylaxis recommendations. This has really become a team event. Social workers, nurses, physicians, even physical therapists—we all talk about current practices, goals, and expectations.

Maybe a patient wants to join a soccer league on the weekends. The key is to identify what

is important in the patient's life. And for older patients, we have to consider that they may be developing comorbidities that require other medications and therapies. It all comes back to listening to what our patients are telling us.

Guy Young, MD: It is critical to acknowledge that we rely greatly upon our multidisciplinary colleagues. Physical therapists are really good at telling us about our patients' physical quality of life, including mobility and activity. Our social workers are really good at assessing the dynamics associated with school and home life. We have families in which multiple children are affected by hemophilia. Other families have children with and without hemophilia. Both situations are challenging. We have a psychologist on our team who can delve into matters beyond the scope of a social worker. In our practices, we must consider the whole patient, and in the world of pediatrics, the whole family.

There are a lot of quality-of-life tools used to measure secondary outcomes in clinical trials, and lots of quality-of-life papers have and continue to be published in association with therapeutic trials. The question is, do we want to incorporate these tools into our practice?

Some people are reluctant because it represents more work and involves administering lots of questionnaires. I remember when the HJHS (Hemophilia Joint Health Score) was first introduced. There was a little bit of pushback from clinicians who said "That's pretty detailed," or "It's going to take a lot of time." But now, this has become standard practice for assessing joint health.

As a community, we need to decide whether or not we want to incorporate such tools into our practices. We also need to determine who would administer these questionaries, whether it be a social worker, a nurse, a psychologist, a physician, or someone else, and who will follow up on the results.

In my pediatric practice, it's critical that every patient sees the social worker and the psychologist separately during comprehensive visits. To avoid pushback, we just tell patients and parents that they are going to see the entire team, including the doctor, the nurse, the physical therapist, the social worker, and the psychologist without emphasizing any particular clinician. By doing it that way, we are able to address complex quality-of-life issues.

Miguel Escobar, MD: Quality of life has certainly become part of our standard of care. Even the drug regulatory agencies mandate that quality-of-life studies be done at the same time the efficacy and side effects of drugs are being tested.

As you mentioned, there are many different quality-of-life assessment tools out there. Some of them have been standardized while other have not. Some are appropriate for select patient populations and others can be used more generally. Examples of instruments most used for the measurement of health-related quality of life include EQ-5D, SF-36, PROBE questionnaire, CHO-KLAT, Hemophilia Well-Being Index, and HAEMO-QoL-A (Srivastava et al., 2020).

ADHERENCE

Miguel Escobar, MD: We know that hemophilia is a chronic disease, and like any chronic disease, it is burdensome for patients to be treated all of their lives. With diabetes, patients can achieve satisfactory symptom control, even though adherence is maybe 40% to 60%. The same is not true for hemophilia. There's probably no evidence-based threshold that defines adequate adherence for hemophilia prophylaxis. If our patients do not receive treatment, they bleed. So there is a much higher threshold of adherence required among hemophiliacs. And at least in my practice, this is difficult to achieve, especially in certain populations.

So, I'd like to discuss how we deal with these individuals in our practices. I know that we all attempt to educate our patients as soon as they come to us, but despite all of our efforts, there is always going to be issues with some of our patients. The issue of adherence may be very different in the pediatric vs. adolescent vs. adult vs. older populations, and the barriers to adherence may relate in part to those age differences. So how do you approach the problem of adherence?

Guy Young, MD: My experience is that the issues of adherence reflect what has been published. In the younger years, adherence is very good. Most

parents are very diligent about ensuring that their young children receive whatever treatment we prescribe. However, as children reach school age, they can start to resist as time constraints arise and adherence becomes more problematic. Once they become teenagers, we expect patients to assume independence and responsibility for their own care. During these years, adherence decreases even more. And then in young adulthood, adherence gets even more difficult, especially when patients are moving out of the house, going to college, or getting jobs. During this time, treatment is often no longer home based.

We all have patients in our practice who are exceptionally adherent, including teenagers, so we don't spend a lot of energy on them. We really focus our energy on the 20% in the younger age group and the 50% to 60% in the teenage and young adult groups, where adherence is an issue. Our nursing staff, our social worker, and our psychologist focus a lot of energy here and try to identify the barrier(s) to adherence. Is the barrier venous access? Is the barrier lack of time or forgetfulness? It is important to dig in and find out what is the real barrier for each of our patients. And we must remember that the barrier for one patient is different than the barrier for another. Only by identifying the barrier can a strategy be devised to improve compliance.

It's challenging, no matter what. We've had some successes. Oftentimes, even if we can identify the barrier and devise a strategy to overcome it, things don't necessarily get better. The best we can do is try.

Cindy Leissinger, MD: I completely agree with Dr. Young. Adherence is perhaps the most challenging aspect of what we do in comprehensive care. We can take the time and effort to plan the best treatment course and make these decisions with buy-in from both patients and parents, but without adherence, our efforts are all for naught. We know that one or two joint bleeds can trigger a progressive joint disease pattern that leads to irreversible joint damage, and we know that it doesn't take many prophylaxis failures to set this into motion. For some patients and parents, no amount of education will affect compliance. Some patients will just have lapses where they will be nonadherent for a period of time because they just get tired. Others will miss doses periodically for one reason or another, and getting to the bottom of this may change adherence for the better. Others will reach a point where they just stop and no amount of counseling or accommodating will make a difference. The questions of adherence can be really trying.

On a somber note, I will add that studies on adherence in chronic illness indicate that the best predictor of future adherence is past adherence. As Dr. Young said, some teenagers are really very adherent because they recognize the benefit that they get from adherence. These individuals tend to have good self-esteem, self-confidence, self-reliance, and resilience.

These are people with a purpose. They want to play sports. They are very forward-looking and they incorporate adherence into their daily routine. It's just rolled into their lifestyle. We don't have to spend a whole lot of time motivating them because they are self-motivated. The real challenge is the patient who lacks self-confidence or maybe has some underlying mental health issues. These patients may feel overwhelmed and struggle with anxiety or depression. These are perhaps the hardest patients to help.

Involving a psychologist and social workers is really key. We've also incorporated a clinical pharmacologist who can sit with patients and discuss treatment-related issues. We show them PK modeling so that they understand what happens with their factor VIII levels over time. Our physical therapist does ultrasounds of their joints and shows them what a joint looks like during a major bleed. We have found that all of these things can improve patient adherence, although none of them can guarantee it.

Miguel Escobar, MD: Those are very important points. Adherence certainly needs to be addressed early in the course of care. And we must be vigilant for opportunities to improve adherence. I remember asking one patient what he really wanted in his life. He told me that his wife was expecting and said that he really wanted to be able to play with his kids when they get older. I said that

the only way to do this is to remain adherent to his treatment regimen because in 5 or 8 years, his joints might not be in as great a shape as they are now.

I think that the issue of mental health is an important one. In our practice, we use a questionnaire to screen for depression. We found that a couple of our patients who were not adherent were severely depressed. Now we use one of these scoring systems as a routine part of our clinical history.

Guy Young, MD: I'd like to expand this discussion and talk about newer treatments, specifically nonfactor therapies like the FDA-approved emicizumab, as well as emerging treatments like gene therapy. I had one case where venous access was identified as the barrier to adherence. One of my teenage patients said to me "I just don't like poking my veins. I don't even let my mom do it because it's painful. And half the time, we miss the veins anyway." And so when emicizumab became available, I asked him about trying something a little bit different. I told him that there was no vein to hit, although there was still a needle stick. He said that he was open to trying it. When he finally started emicizumab, he did great for a while. And then, to Dr. Leissinger's point about predicting adherence, he did so well clinically that he stopped injecting emicizumab because he "didn't need it." He eventually showed up with a large joint bleed. Ultimately, this was a good lesson for him because he finally realized that he needed to use emicizumab every week. After a long discussion, it's been about almost a year now and he has been completely adherent. To begin with, we addressed the barrier of venous sticks. And subsequently, we addressed the issue of overconfident nonadherence in a discussion with the psychologist. And now, this patient is doing much better.

For those patients who are going to be nonadherent, no matter what we do, I'm banking on gene therapy to fix the problem once and for all. As new treatments emerge, we really have to think how they will impact the nonadherent patient. One nonadherent group may do well with gene therapy. Another risk-averse, nonadherent group may do better with nonfactor therapy that is given infrequently.

Miguel Escobar, MD: That's a great point. I've had similar experiences with emicizumab when patients think that it's so effective, they just stop taking it because they believe that it will just stay in their body for a long time. A lot of nonadherence has to do with patient misperceptions, which is why ongoing education is so important.

CHOICE OF PROPHYLAXIS

Miguel Escobar, MD: *How do you decide between extended half-life factor concentrates and nonfactor replacement therapy such as emicizumab?*

Cindy Leissinger, MD: I'll let Dr. Young speak about this with children and infants. My adult patients all come to me on some type of therapy and many of them have set ideas about what they like and what they don't like. Nevertheless, for every new adult we see, we review all treatment options and even discuss what's in the pipeline, just to make them aware. In discussing emicizumab, I review the advantages and disadvantages with both factor replacement vs. nonfactor therapy and then I listen to what the patients are saying. So many of them are very eager to try a nonfactor therapy in order to avoid IV infusions and IV sticks. These individuals like the convenience of emicizumab and they like the fact that this drug provides them with a steady state of protection.

Others are very happy with factor replacement and skittish about trying something new. Some just want to wait awhile and consider emicizumab later.

In general, patients who are very, very active or participate in activities that involve some risk of injury tend to be most comfortable with the protection associated with factor VIII. For these patients, we offer products that help them to achieve peak levels of factor VIII that emicizumab cannot provide. Others are comfortable with these products because they know their factor VIII levels can be monitored. Still, others are looking more for steady-state levels of protection or convenience of administration. These decisions are not all that difficult for patients to make once they are informed.

Guy Young, MD: I'm going to focus on the really young children, since children 6 years and older are treated as Dr. Leissinger describes.

What Dr. Leissinger said definitely applies to most of my previously treated patients who are school age or older.

I have seen a lot of change in my practice in the youngest patient group. These 1- to 2-year-old pups (or maybe not pure pups, but rather patients who've had very limited exposure to factor replacement therapy) are the ideal candidates for initiation of primary or secondary prophylaxis. Typically, prophylaxis is started at an early age, and the World Federation of Hemophilia guidelines typically recommended initiating prophylactic treatment around the age of 1 or 1.5 years.

Our choices for factor therapy include standard or extended half-life concentrates, both given IV and both given multiple times per week vs. initiation of nonfactor therapy. With IV concentrates, I explain that most patients will require placement of a central venous catheter/port in order to bypass the difficulty of accessing veins. I explain that ports are placed by surgeons under anesthesia, and factor concentrates need to be infused 2 or 3 times per week. I also explain that a needle is used each time to access the port.

Conversely, I explain that emicizumab is a newer treatment for which we don't have a lot of data, especially in children younger than 2 years of age. I also explain that there are trials going on currently in that age group, although the data have not been reported. However, the current FDA indication for emicizumab includes newborn children and older, so treatment is not off-label. I also describe the injections as subcutaneous so that a port does not have to be placed. And emphasize that treatments are often given every 2 weeks after the first 4 doses. When this is explained, many parents look at me as if to say, "Dr. Young, I don't understand. Obviously, we are going to choose the option that does not require our son to have surgery for port placement and avoids the insertion of needles into the port that could increase his risk of infection. For many parents, it's a no-brainer. You can't even compare the two. Fully 80% to 90% of parents choose emicizumab, even if their child received a dose or two of factor concentrate for bleeding prevention with circumcision. My children are older, but my son with growth hormone deficiency required subcutaneous injections. I have thought to myself that if IV treatments every day or every other day were required, I wouldn't have been able to do it.

So I have seen a definite shift in favor of an easier and more convenient treatment option that doesn't involve surgery or incur the risks associated with an indwelling port. Yes, most parents are choosing to go the emicizumab route, and I think it's very understandable.

In the next few years as I pass patients on to adult hematologists, there are going to be a whole lot more people on nonfactor therapy. What will you do at that point? Will you keep your patients on emicizumab or the next best thing that comes along?

Miguel Escobar, MD: In the youngest population, the choice of emicizumab is very understandable. Dr. Leissinger and I certainly see a little bit of everything in our adult patients. Some patients are very receptive to trying emicizumab while others are not because they are fine with their current treatment. For those patients who choose to take emicizumab, not too many choose to resume their previous treatment.

We will see what happens in the coming years, because more nonfactor therapies are going to be approved. Many of them will be given subQ at different intervals, and these agents will likely change the management of hemophilia as we know it.

SUPPLEMENTAL EDUCATIONAL RESOURCE

A Patient/Clinician Decision Support Pocket Reference Guide that can serve as a point-of-care teaching and counseling resource is available at https://cdn.reachmd.com/uploads/1787_pocketreference_guide_v13_digital.pdf

Disclosure

The faculty reported the following relevant financial relationships or relationships they have with ineligible companies of any amount during the past 24 months: **Miguel A. Escobar, MD,** reported a financial interest/relationship or affiliation in the form of *Consultant*: Biomarin; Kedrion Bio-

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