Advances in Hemophilia and the Role of Current and Emerging Prophylaxis

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Abstract

The primary goal of hemophilia treatment and management is the prevention of painful, disabling, and costly joint arthropathy that results from its characteristic bleeding into joints and muscles. Prophylactic treatment with clotting-factor concentrates has been shown to prevent hemophilic arthropathy and is, therefore, the standard of care for hemophilia A and B.

Data has demonstrated the clinical efficacy and overall benefits of prophylaxis in young children, adolescents, and adults. Early initiation with primary prophylaxis is ideal, but secondary prophylaxis in adolescents and adults has also demonstrated significant success. Because the standard of care includes prophylaxis with factor-concentrate replacement in order to prevent joint damage in patients with hemophilia, prophylaxis is now more common and needs to be addressed in all clinical settings, including managed care. However, further research is needed to help clinicians develop individualized factor-replacement protocols and understand the impact of long-term use into adulthood.

World Federation of Hemophilia guidelines do not have definitive recommendations on continuation of prophylaxis into adulthood. The optimal regimen for initiating prophylaxis, duration of treatment, and dosing regimens continue to be studied.

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Hemophilia is a rare X-linked inherited bleeding disorder, usually manifesting in males (**Figure 1**[1,2]), with bleeding into joints and muscles.[1,3] Hemophilia A accounts for 80% to 85% of patients with hemophilia; it is caused by a defect in the gene coding for coagulation factor VIII (FVIII).[1-3] Hemophilia B, also known as Christmas disease, results from a mutation in the gene responsible for the synthesis of coagulation factor IX (FIX).[1,2] These gene defects impair an individual's ability to produce these clotting proteins, which play a major role in the process to stop bleeding.

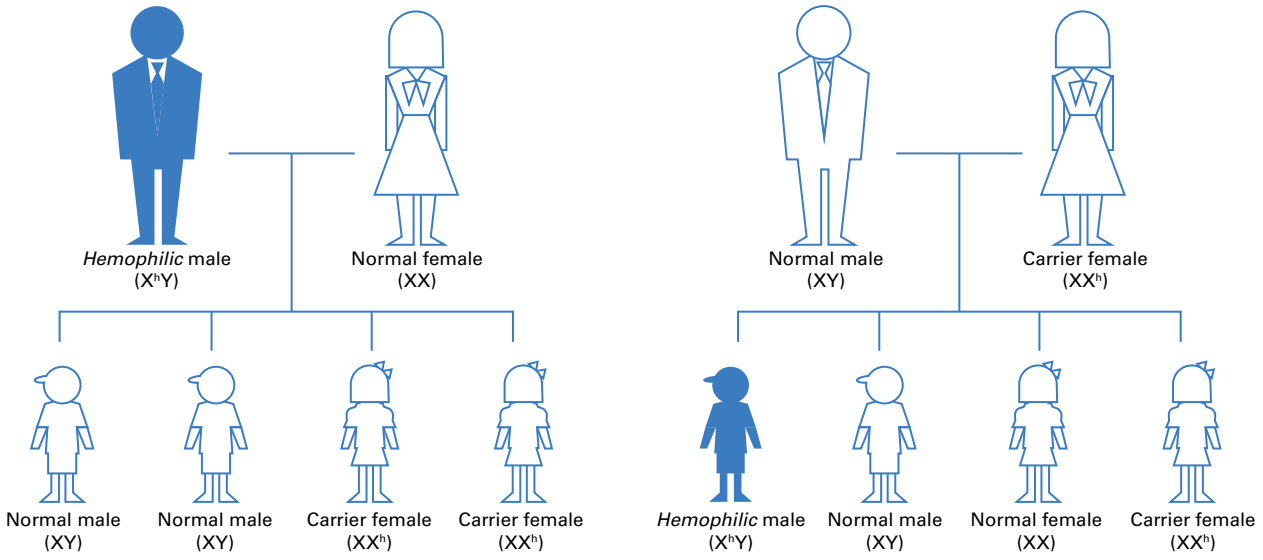
Clinical Manifestations of Hemophilia

Individuals with hemophilia bleed longer because of an impaired ability to form thrombin.[2] The clinical manifestations of hemophilia A and B are indistinguishable, and bleeding and disease severity generally correlate with clotting-factor activity levels.[2,3] Disease severity, which does not change over a patient's lifetime, ranges from mild to severe; it is defined by the amount of clotting-protein activity in the body, and is expressed as a percentage.[1,3,4] The level of clotting-factor activity in mild disease ranges from 6% to less than 40% (0.06-0.40 IU/mL). Moderate disease is defined as 1% to 5% of factor activity (0.01-0.05 IU/mL), and severe is less than 1% of factor activity (<0.01 IU/mL).[3,4]

Severe hemophilia presents with bleeding early in life, often in the first year, either following circumcision in the newborn period or as recurrent palpable hematomas.[2] Patients with severe hemophilia may experience frequent spontaneous bleeding into joints or muscles, usually without any identifiable hemostatic challenge. Moderate hemophilia may present with bleeding after minor trauma, injury, surgery, or dental work.[4,5] Patients with mild hemophilia may never have a bleeding problem and rarely experience spontaneous bleeding; they may only experience it after major trauma or surgery.[3-5]

For author information and disclosures, see end of text.

Figure 1. Inheritance Pattern of Hemophilia[1,2]



When the father has hemophilia (and the mother is not a carrier), no sons will be affected, but all daughters will become obligate carriers of the hemophilia gene. When the mother is a carrier, sons will inherit the hemophilia gene and suffer symptoms with a probability of 50%; for daughters, the risk of receiving the gene and becoming a carrier will also be 50% (100% if the father has hemophilia).[2,3]

The hallmark of hemophilic bleeding is joint (hemarthrosis) and muscle bleeding; in patients with severe hemophilia, the bleeding begins after a child becomes mobile. Other common manifestations include palpable bruising, which can be spontaneous or occur after minor trauma. Hemarthrosis manifests as swelling and pain in the joints, along with decreased range of motion, most commonly affecting the knees, ankles, and elbows.[1,2]

In patients without a family history of hemophilia who have bleeding manifestations such as palpable hematomas and joint and muscle bleeds early in life, a diagnostic workup can lead to a diagnosis of severe hemophilia. In patients with a positive family history, diagnosis can be confirmed in the newborn period through cord-blood testing soon after delivery. In patients with mild hemophilia, the diagnosis may not be made until prolonged bleeding is noted after a trauma-related bleed or procedure in adulthood.[4]

Hemarthroses, recurrent hemorrhages into joints, can result in serious musculoskeletal sequelae, such as joint arthropathy, affecting the patient's bone health and resulting in chronic pain and diminished quality of life.[6] Furthermore, life-threatening bleeds can occur in the central nervous system, retroperitoneal cavity, or gastrointestinal tract. Even a minor head injury can lead to a life-threatening intracranial hemorrhage in those with severe hemophilia.[2]

Clinical Burden of Hemophilia

Hemophilia is present in an estimated 1 in every 5000 males born, with approximately 400 babies born with the condition each year in the United States. The estimated prevalence in the United States is approximately 20,000 (1 in 13,600). Approximately one-third of these affected individuals do not have a family history of the condition.[7] In the 1980s, clotting factor manufactured from human blood had inadequate viral inactivation, leading to patient infection with human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV). This resulted in substantial mortality in patients with hemophilia from blood-borne infection.[8,9] As a result, the modern hemophilia population is skewed toward youth, with 1 in 7 patients with hemophilia being 45 years or older.[9]

The Hemophilia Experiences, Results and Opportunities (HERO) initiative assessed psychosocial issues experienced by young adults, between 18 and 30 years, with moderate to severe hemophilia.[10] The analysis found that adherence to treatment regimen was low (<50%), and access to treatment was an issue for 26% of respondents. Common comorbidities included bony arthritis, chronic pain, and viral infections. Almost 50% reported anxiety and/or depression, and most respondents acknowledged that pain interfered with their daily activities in the previous 4 weeks. Finally,

although 78% of young adults were employed at least part time, the majority reported that hemophilia had a negative impact on their employment.

These young adults face unique challenges in their transition into adulthood, ranging from changes in their hematology care—from pediatric to adult centers—to taking control of their own care.[11] Other concerns include psychosocial issues related to maturity, increased independence, and the need to accept responsibility for the management of their disease and insuring their own medical coverage. Additionally, they begin a chapter of their lives in which they are building personal relationships with the understanding of the inherited nature of their disorder. These young adults are fortunate that treatment options for hemophilia now undergo extensive purification and viral inactivation, bringing the life expectancy of a patient with hemophilia closer to that of a healthy, normal adult.[9] Along with the extensive use of preventive treatment with clotting-factor concentrates (prophylaxis), these safety measures have resulted in fewer joint-related problems and lower rates of HIV and HCV infections.[11] However, although mortality has declined, disability risks from hemophilia remain high because of the risk of bleeding into muscles and joints.[9] Understanding the challenges that individuals with hemophilia face, particularly young adults, is critical for the development of strategies that will effectively address their needs.

Treatment of Hemophilia

The treatment of hemophilia has made great progress in the past 3 decades. Hemophilia has transitioned from a neglected and often fatal disease to a group of disorders with a defined molecular basis for which safe and effective treatments are available. Although hemophilia is a lifelong bleeding disorder, ongoing clinical trials in gene therapy are making strides toward a future cure. Currently, comprehensive care of hemophilia includes treatment of bleeding episodes, prophylaxis with the use of preventive factor-replacement therapy, genetic counseling for patients and carriers to make appropriate choices for procreation, and physical and psychosocial health measures that help improve quality of life.[3]

An acute bleed should be treated immediately. In patients who recognize early symptoms of bleeding, replacement therapy should be initiated before strategies are used to identify the cause of the bleed.[3] Bleeding is treated by administering FVIII or FIX concentrate intravenously (IV), usually self-administered by the adult patient or by the parent if the patient is a child. Although these coagulation-factor concentrates were initially used for on-demand or episodic treatment once bleeding started, they are increasingly being used prophylactically.[12]

Prophylactic Treatment

For patients with hemophilia, prophylaxis is the administration of replacement clotting-factor concentrates in anticipation of bleeding or to prevent it.[3,12] Safe prophylaxis was made possible in 1992 with the approval of the first recombinant factor for replacement therapy, as well as with the improved safety of plasma-derived products. The concept of prophylaxis was based on the observation that patients with moderate or mild hemophilia rarely have spontaneous bleeding, very seldom develop chronic joint arthropathy, and have much better-preserved joint function than those with more severe hemophilia.[3,13] In essence, prophylaxis aims to convert severe hemophilia to moderate/mild hemophilia by the infusion of clotting factor on a regular basis (often 2 to 3 times per week), even in the absence of a bleed. Newer extended half-life agents may help reduce the frequency of prophylaxis administration. The World Federation of Hemophilia (WFH) and the Medical and Scientific Advisory Commission of the National Hemophilia Foundation recommend the use of prophylaxis to prevent bleeding and joint destruction and preserve musculoskeletal function.[3,14,15]

The concept of prophylaxis, which was published in 1992 by Inga Marie Nilsson, MD, was initiated in Sweden in the 1960s. It was based on the difference in bleeding patterns of patients with mild, moderate, or severe hemophilia.[16,17] Sixty patients with severe hemophilia treated prophylactically with factor concentrates were protected from the development of hemophilic joint arthropathy, regardless of age at initiation or intensity of treatment. Furthermore, early initiation and intensive treatment were associated with improved joint outcomes. Since then, clinical trials have ensued to determine optimal strategies based on long-term outcomes. However, optimal strategies to conduct prophylaxis in an economically prudent manner have not yet been well-defined.

In a randomized US multicenter trial of young boys (30 months or younger) with severe hemophilia A, prophylaxis with regular infusions of recombinant FVIII was compared with enhanced on-demand infusion at the time of a joint hemorrhage. At 6 years of age, 93% of boys in the prophylaxis group had normal index-joint (elbows, knees, and ankles) structure on magnetic resonance imaging (MRI) compared with only 55% of those in the on-demand therapy group (P = .006). On-demand

therapy had a relative risk of 6.1 (95% CI, 1.5-24.4) of MRI-detected joint damage compared with prophylaxis. Overall, better orthopedic outcome—prevention of damage in index joints and lower frequency of joint and other hemorrhages—was associated with prophylaxis with recombinant FVIII than on-demand treatment in young boys with severe hemophilia A.[14]

The ESPRIT study from Italy was a longer trial designed to understand the impact of prophylaxis on joint arthropathy when prophylaxis was not initiated in the first few years of life. The randomized 10-year trial of children 1 to 7 years of age with severe hemophilia A compared the efficacy of prophylaxis with recombinant FVIII (25 IU/kg 3 times/week) to on-demand therapy (≥25 IU/kg every 12-24 hours until clinical resolution of bleeding) in preventing hemarthrosis and image-proven joint damage. The patients had no clinical or radiologic signs of joint disease at baseline but did have at least 1 bleed within the 6 months before trial initiation. The results demonstrated that children receiving prophylaxis had fewer hemarthroses than those with on-demand therapy (0.20 vs 0.52 events per patient per month; P <.02). Signs of joint arthropathy were detected by plain film radiology in 6 patients (29%) on prophylaxis compared with 14 (74%) who had on-demand treatment (P <.05). Prophylaxis was found to be more effective when started early, confirming the effectiveness in preventing bleeds and joint arthropathy.[18]

In addition to reducing the number of bleeds per year in patients with hemophilia, prophylaxis has been demonstrated to reduce the risk of life-threatening hemorrhages, including intracranial hemorrhage, compared with patients receiving only on-demand treatment.[17] It should be noted that although prophylaxis may decrease the frequency of bleeding episodes and decrease the progression of disease, it does not reverse established joint disease.[3]

It is recommended that prophylaxis be initiated early and factor levels maintained at more than 1% of normal at all times. Although prophylactic replacement of clotting factor has been shown to be useful even when factor levels are not maintained above 1 IU/dl at all times, levels greater than 1% have been shown to ensure avoidance of breakthrough bleeds.[3,17] Studies have shown that the earlier prophylaxis is initiated, the greater the likelihood of preventing joint damage.[17] However, there is ongoing debate regarding the timing, dosing, and duration of prophylaxis.

Continuous Versus Intermittent Prophylaxis

Prophylaxis can be conducted as a continuous or an intermittent regimen.[1] Continuous prophylaxis is defined as treatment that is initiated with the intent of treating for 52 weeks of the year and is accomplished for at least 45 weeks of that year. Prophylactic treatment that is administered to prevent bleeding but does not exceed more than 45 weeks in a year is considered intermittent, or periodic, prophylaxis.[3]

Based on when the treatment was initiated, continuous prophylaxis can be defined as primary, secondary, or tertiary.[1] Primary prophylaxis is the regular, continuous use of treatment that is started before the second clinically evident large joint bleed (bleeds in ankles, knees, hips, elbows, or shoulders). It is initiated before 3 years of age in children without documented osteochondral joint disease, as determined either by a physical examination and/or imaging studies. Secondary prophylaxis is a treatment regimen initiated after 2 or more bleeds into large joints but before the onset of joint disease documented by physical examination and imaging studies. Finally, tertiary prophylaxis is the continuous treatment started after the onset of joint disease, as documented by physical examination and plain radiographs of the affected joints.[12]

Studies in adolescents and adults with hemophilia have shown significant benefits of secondary prophylaxis. In an open-label study of 20 adults (aged 30 to 45 years) with severe hemophilia A who were already using on-demand therapy, patients were given 6 months of on-demand therapy followed by 7 months of secondary prophylaxis using FVIII concentrate (20-40 IU/kg, 3 times/week). The median number of joint bleeds decreased significantly with prophylaxis (0 [0-3]) compared with on-demand therapy (15 [11-26], P <.001), with similar significant decreases in the number of all bleeds.[19]

In another long-term open-label study (Prophylaxis vs On-demand Therapy Through Economic Report [POTTER] study), long-term late secondary prophylaxis with recombinant FVIII-FS (formulary sucrose) (20-30 IU/kg 3 times/week) demonstrated reduced bleeding frequency, improved joint status, and improved health-related quality of life (HRQoL) compared with on-demand treatment in patients aged 12 to 55 years with severe hemophilia A. This prospective, controlled trial included 58 patients evaluated over more than a 5-year period during 2004 to 2010. Annualized joint bleeding rates in the prophylaxis group were 1.97 in younger patients and 2.46 in older patients compared with 16.80 and 16.71, respectively, in patients using on-demand treatment (P = .0043). Prophylaxis was also associated with significantly fewer target joints (P <.001) and better HRQoL.[20]

Table 1. Pipeline of EHL Agents[22]

EHL Agent Name	Indication	Mechanism of Action	Status
Nonacog beta pegol (N9-GP)	Hemophilia B	GlycoPEGylated rFIX	Phase III
BAY 94-9027 (EHL rFVIII)	Hemophilia A	PEGylated rFVIII	Phase III
NN-7088-3776, N8-GP	Hemophilia A	GlycoPEGylated rFVIII	Phase III
rIX-FP	Hemophilia B	rFIX fusion protein (albumin)	Phase I
PSA FVIII	Hemophilia A	PSA added to rFVIII	Preclinical
SC long-acting FVIII	Hemophilia A	PEGylation to allow SC administration	Preclinical

EHL indicates extended half-life; PEG, polyethylene glycol; PSA, polysialic acid; rFIX, recombinant factor IX; rFVIII, recombinant factor VIII; SC, subcutaneous.
Adapted from Carr ME, Tortella BJ. Emerging and future therapies for hemophilia. *J Blood Med.* 2015;6:245-255. doi: 10.2147/JBM.S42669.

Long-term prophylaxis is now common and widely used in patients diagnosed with moderate to severe hemophilia and is generally initiated in patients after 2 years of age or after the first joint bleed.[17,21] Clinical trials have shown the efficacy and value of prophylaxis in childhood, and although the evidence is less strong for adults, data demonstrate the effectiveness of prophylaxis in these patients, as well.[12,14,18-20]

When access to treatment is an issue or continuous prophylaxis is not preferred, the WFH recommends intermittent prophylaxis for 4 to 8 weeks, in addition to intensive physiotherapy or synoviorthesis, in patients with repeated bleeding, especially into target joints (a joint in which 3 or more spontaneous bleeds have occurred within a consecutive 6-month period).[3]

Prophylaxis Protocols

The protocol used for prophylaxis is recommended to be individualized, taking into account the patient's age, venous access, bleeding phenotype, susceptibility to joint arthropathy, and availability of clotting factors.[3,17] Two commonly used protocols that are supported by clinical data include[1,3]:

- The Bonn-Malmö Protocol: 25-40 IU/kg per dose
  - 3 times a week for hemophilia A
  - 2 times a week for hemophilia B
- The Utrecht Protocol: 15-30 IU/kg per dose
  - 3 times a week for hemophilia A
  - 2 times a week for hemophilia B

As researchers seek out the most optimal strategies, clotting-factor concentrates and replacement strategies are continuously evolving. Optimal dosing schedules, dose, and dosing intervals have yet to be defined and vary from center to center.[3,17] However, most experts agree that prophylaxis started early in the life of a child with hemophilia and continued until 18 years of age may prevent the development of hemophilic joint arthropathy and its consequences.[6]

New and Emerging Prophylaxis

The treatment landscape for hemophilia is continually evolving, and several recent developments surrounding emerging longer-acting factor concentrates have demonstrated the potential for improved management strategies and compliance for improved outcomes.

Extended Half-life Recombinant Agents

Extended half-life clotting factors, also known as enhanced half-life (EHL) clotting factors, help reduce the frequency of infusions to better support prophylaxis. Common strategies for enhancing the half-life of a molecule include[22]:

- Linkage to the fragment crystallizable (Fc) region of the antibody
- Linkage to polyethylene glycol (PEG) in a process called PEGylation
- Linkage to recombinant albumin

Table 1 highlights EHL clotting factors currently in clinical trials.[22]

Antihemophilic Fc Fusion Proteins

Based on safety and efficacy data from an 18-month clinical trial of 123 patients with severe hemophilia B, recombinant FIX Fc fusion protein (rFIXFc) was the first of these products to be approved by the FDA in March 2014. It is approved for use as an on-demand treatment, as prophylaxis, and to manage bleeding during surgical procedures in children and adults with hemophilia B.[22,23] This drug, consisting of the FIX molecule linked to the Fc protein fragment found in antibodies, is the first treatment for hemophilia B designed to last longer in circulation, thereby requiring less frequent injections when used as prophylaxis. In the open-label, multicenter trial of 123 previously treated individuals with severe hemophilia B comparing rFIX to rFIXFc as prophylaxis and on-demand treatment, rFIXFc demonstrated a longer terminal half-life (82.1 hours) and lower annualized bleeding rate (ABR) compared with rFIX (P <.001 for both).[24] Over

the 1.5-year follow-up period, no inhibitors were detected in any clinical trial participants receiving rFIXFc, and most adverse events were consistent with those expected in the general population of patients with hemophilia.

Next was the approval in June 2014 of recombinant FVIII Fc fusion protein (rFVIIIFc) for use as on-demand therapy and prophylaxis in children and adults with hemophilia A and managing bleeding during surgical procedures in these patients. In a study of 117 patients, the efficacy of rFVIIIFc as routine prophylaxis (individualized and weekly) was evaluated against on-demand treatment. Patients within the individualized protocol group demonstrated a statistically significant reduction in ABR of 92% (P <.001), and those in the weekly prophylaxis arm, 76% (P <.001), compared with on-demand treatment.[25] As with rFIXFc, rFVIIIFc is the first treatment for hemophilia A designed to require less frequent injections when used as prophylaxis.

PEGylated FVIII and FIX

PEGylated rFVIII (rFVIII-PEG), formerly known as BAX 855, was approved in November 2015 for use in patients 12 years and older with hemophilia A, based on phase III trial data demonstrating that rFVIII-PEG effectively controlled and prevented bleeding episodes when used as a twice-weekly prophylaxis in previously treated patients 12 years and older. Compared with on-demand treatment (n = 17), rFVIII-PEG as prophylaxis (n = 120) resulted in a 95% reduction in median ABR for patients (41.5 and 1.9, respectively).[26]

GlycoPEGylated rFIX (rFIX:PEG), nonacog beta pegol, employs targeted PEGylation to preserve the protein's catalytic activity while maintaining prolonged duration of action.[22] Currently in clinical trials, rFIX:PEG has demonstrated dose-dependent increase in mean half-life (85 hours with a single 10IU/kg dose and 111 hours with a single 40 kg/IU dose) and mean 7-day rFIX trough levels after IV injection (8.5 IU/dL and 27.3 IU/dL, respectively). In phase III trials, both doses had lower ABRs than on-demand treatment.[22]

Data from phase III studies assessing the efficacy and long-term safety of an investigational long-acting fusion protein linking recombinant coagulation FIX with recombinant albumin (rFIX-FP) support prolonged dosing intervals up to 14 days for routine prophylaxis in patients with hemophilia B. In addition, the majority of adult and pediatric patients using rFIX-FP for routine prophylaxis in clinical trials had an annualized spontaneous bleeding rate of 0. These results suggested an improved pharmacokinetic treatment profile for patients with hemophilia with active lifestyles who require prophylaxis and who could benefit from less frequent dosing. rFIX-FP was recently approved (March 2016) for use in children and adults with hemophilia B.[27]

In a trial of 186 patients, N8-GP, NN-7088-3776, a PEGylated FVIII concentrate, demonstrated a median ABR of 1.3 on prophylaxis, compared with 30.9 in the on-demand treatment group (n = 11). The prophylaxis group included 175 patients treated with a prophylactic regimen of 50 IU/kg every fourth day.[28]

Single-Chain Agents

CSL627 is a single-chain rFVIII with a mean half-life of 13 hours, as demonstrated in phase I studies. The single-chain agent is designed to enhance the stability of FVIII by preventing the heavy and light chains from dissociating during production and potentially in vivo. Phase I clinical data are promising, and phase III trials are currently under way.[28]

BAY 81-8973, a full-length human rFVIII, has demonstrated superiority when used as prophylaxis compared with on-demand therapy in patients with severe hemophilia A. In this study of 80 patients (LEOPOLD II), twice- or thrice-weekly prophylaxis with BAY 81-8973 reduced the median ABR by 97% compared with on-demand therapy.[29]

Gene Therapy

Characterization of FIX and FVIII have made hemophilia A and B targets for gene therapy. After more than 30 years of preclinical studies and hope of clinical success, scientists are beginning to see signs of an individual with hemophilia adequately synthesizing the endogenous clotting factor needed to avoid lifelong clotting-factor infusions.[22,30] Although options for FVIII gene therapy are still in the discovery or preclinical stages, those for FIX have moved into the phase I and II stages (**Table 2**[22,30-32]).[22]

Multiple vectors, the vehicles for gene therapy, have been investigated for hemophilia gene transfer, including viral and nonviral vectors, with the goal of delivering cDNA (a DNA copy synthesized from mRNA) to targeted cells via transduction. Successful transfer is defined by the stability of transgene expression—levels of factor activity sufficient to reduce spontaneous bleeding. The main differences among current open trials include type of vector (single-stranded vs self-complementary vector), type of capsid, ratio of empty to full vector capsids, and variations in cDNA sequence and resulting translated protein.[22,30]

Progress in the use of gene therapy for hemophilia A is hampered by the ability of the vector to accommodate the large size of the gene. In hemophilia B, results have been more promising. Activity levels for FIX sufficient enough

Table 2. Gene Therapy Programs for Hemophilia B[22,30-32]

Vector Name	Transgene	Vector	Dose	Results	Status
scAAV2/8-LPI-hFIXco	hFIX	scAAV2/8	2E11-2E12 vg/kg	Sustained FIX with some reduction in expression with prednisone; no significant safety concerns	Phase II
Modified AAV8 (AAV8-hFIX 19)	hFIX	ssAAV8	Dose-escalating study	Pending	Phase I/II
BAX335 (Ask-Bio009)	hFIX-R338L (FIX Padua)	scAAV8	2E11-2E12 vg/kg; dose-escalating study	Efficacy data pending; no significant safety concerns	Phase I/II
SPK-9001	hFIX-R338L (FIX Padua)	ssAAVSpark100	Not available	Pending	Phase I/II
AMT-060 (AAV5-hFIX)	hFIX	AAV5	5E12-2E13 vg/kg	Pending	Phase I/II

AAV indicates adeno-associated virus; FIX, factor IX; hFIX, human factor IX; scAAV, self-complementary adeno-associated virus; ssAAV, single-stranded adeno-associated virus; vg, vector genomes.

to substantially reduce spontaneous bleeding have been maintained for a period of 3.2 years in 10 patients with severe disease.[22] A single IV infusion of vector (AAV8) demonstrated dose-dependent increases in circulating FIX to a mean level of 5.1% of normal in the high-dose group. The result was a 90% reduction in bleeding episodes and elimination or reduction of the use of prophylaxis.[33]

Gene therapy holds the hope of a paradigm shift in the treatment of hemophilia to the point where recombinant clotting-factor administration is relegated to the role of supportive therapy rather than standard of care.

Barriers to Optimal Prophylaxis Use

Despite great strides in the development of safe and effective on-demand and prophylactic treatments for hemophilia, barriers to long-term prophylaxis limit their use and overall real-world success. The development of inhibitory antibodies is the most significant limitation to optimal prophylaxis. Physiologic and pharmacokinetic barriers are also implicated in potential treatment failure. These include baseline joint status and unfavorable pharmacokinetic variation in patients and products (ie, too-rapid elimination of coagulation factors, variation of half-life based on age). Patient barriers include compliance in adults, feasibility of compliance in children because of cumbersome venous access, dosing regimens, impact on patient and family quality of life, education regarding disease symptomatology and therapeutic strategies, and affordability and access to treatment. Overcoming these barriers is key to preventing treatment failure.

Development of Antibodies

The development of recombinant products devoid of animal and human proteins, as well as improvements in the plasma-derived products, have contributed greatly to addressing safety concerns when treating hemophilia. However, the increased use of these products has come at the expense of an increased risk of antibody development (inhibitors) against the administered clotting factor. It has been estimated that 25% to 30% of patients with severe hemophilia A and 1% to 5% of those with severe hemophilia B develop inhibitors.[34] A recent randomized study of 251 children younger than 6 years with severe hemophilia A showed that the combined risk of developing a high- or low-titer inhibitor within the first 50 exposure days of using recombinant factors was 1.87-fold higher than when using plasma-derived factor concentrates.[35]

Although treatments do exist for patients with inhibitors (high-dose clotting-factor concentrates, bypassing agents, immune-tolerance induction therapy, immunosuppressive therapy), the economic burden associated with the care can be staggering. Patients with hemophilia who develop inhibitors are twice as likely to be hospitalized for a bleeding complication, and the treatment cost associated with inhibitors is significant.[36-38] Currently, the only prophylaxis approved for use in inhibitor patients is factor VIII inhibitor bypass activity (FEIBA), a bypassing agent that is an activated prothrombin complex concentrate. Recombinant coagulation factor VIIa (activated) is the alternative bypassing agent used to treat bleeding. Development of less immunogenic and more cost-effective treatments to eradicate antibodies is needed.

Physiological and Pharmacokinetic Barriers

Individualizing prophylaxis is one solution to overcoming the physiologic and pharmacokinetic barriers associated with suboptimal treatment. Individualizing treatment based on an individual's age, physical activity level, bleed-

ing pattern, condition of musculoskeletal health, and trough levels of coagulation factor may help obtain the best possible outcome within the available resources.[39]

Up to 15% of patients with hemophilia A exhibit a mitigated disease phenotype determined by underlying mutations and associated with a reduced frequency of spontaneous bleeding and lower need for factor concentrates to stop the bleed.[39] Recognizing this change in bleeding pattern may mean that the patient needs a less intensive regimen, thus reducing costs and emphasizing the need to identify this subset in order to tailor prophylaxis.

Data in patients with hemophilia A have shown that increasing time with an FVIII activity level less than 1 IU/dL is associated with increased total bleeds and hemarthroses. However, along with trough FVIII activity on prophylaxis, the rate of bleeding can also be influenced by FVIII half-life and clearance.[40] Half-life and dose frequency may also have an impact on the effectiveness of prophylaxis, and the combination of these factors results in substantial interpatient variability in the amount of FVIII concentrate required to sustain a desired trough factor activity level. These pharmacokinetic parameters may, in turn, be influenced by the patient's age.[41] Knowledge of a product's half-life and alteration of frequency of infusions, along with the patient's individual pharmacokinetic profile, may allow more clinically efficacious and cost-effective administration of prophylactic antihemophilic factor.[39,41]

Patient Barriers

Compliance is critical to treatment success. Proper patient and parent education can help whether the objection is lack of time, inconvenience, or cumbersome venous access. Education is the most easily remedied barrier to treatment. Helping patients and parents understand the importance of treatment in the short and long term is the key to increasing compliance. A survey conducted by the HERO initiative found that although 59% of parents treated their son's hemophilia exactly as they were instructed, 39% (n = 209) did not.[42] A lack of awareness of the early signs of bleeding, the importance of early treatment of bleeds, and familiarity with the long-term sequelae that results from untreated bleeds are common educational barriers among patients with hemophilia and their parents/caregivers. Increasing patient awareness through educational initiatives, such as instructional aids and programs aimed at children through summer camps, peer and mentor counseling services, or interactive video games and programs, may help solve the lack of awareness.[43] Additionally, providing tools to help patients and parents stay organized may help them schedule treatment into their busy lives and ensure that they are prepared to treat spontaneous bleeds, however infrequently they may occur.

Economic Barrier: Cost

Finally, the high costs associated with prophylaxis can complicate the use of and recommendations for universal prophylaxis.[6] Although the combination of primary and secondary prophylaxis is increasingly viewed as the gold standard for the treatment of severe hemophilia in childhood and adolescence, a dilemma surrounds determination of the most cost-effective utilization of prophylaxis. Clinical trial data on prophylaxis is needed to develop uniformity in protocols for dosing, frequency, and length of treatment. Once those parameters are established, cost-utility studies from the long-term use of prophylaxis can help determine the savings in direct costs, such as hospital use, and indirect costs, including lost productivity.

Conclusions

Preventing painful, disabling, and costly joint arthropathy is a major goal of hemophilia management. Prophylactic treatment with clotting-factor concentrates is the standard of care for hemophilia A and B. Data have demonstrated the clinical efficacy and overall benefits of prophylaxis in young children, adolescents, and adults. Early initiation of primary prophylaxis is ideal, but secondary prophylaxis in adolescents and adults has also demonstrated significant success. With data showing that prophylaxis with rFVIII can prevent joint damage in patients with hemophilia, prophylaxis is now more common and needs to be addressed in all clinical settings, including managed care.

Long-term prophylaxis is now widely used in severe hemophilia, even as clotting factors and replacement strategies continue to evolve. However, further research is needed to help clinicians develop individualized protocols and understand the impact of long-term use into adulthood. WFH guidelines do not have definitive recommendations on continuing prophylaxis into adulthood. The optimal regimen for initiating primary prophylaxis, the duration of treatment, and different dosing regimens continue to be studied.

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