

Current Challenges in the Management of Hemophilia

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Abstract

Hemophilia is characterized by genetic mutations resulting in the deficiency of factors critical to the normal process of coagulation, sometimes resulting in spontaneous bleeding into soft tissue, joints, and internal organs. The 2 most common subtypes are hemophilia A, or factor VIII deficiency, and hemophilia B, or factor IX deficiency. Hemophilia affects an estimated 20,000 individuals in the United States. The diagnosis and management of patients with severe hemophilia is complex, and requires preventive treatment (prophylaxis) to avoid bleeding episodes and related complications and the use of replacement therapy with coagulation factors during acute bleeding episodes. To achieve optimal long-term results, the treatment of patients with hemophilia requires a comprehensive approach coordinated by a multidisciplinary team of specialists. Hemophilia imposes a substantial burden from economic, societal, and patient perspectives.

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The body's clotting mechanism is a stepwise process that requires a number of key proteins to ensure the cessation of any type of bleeding, from bleeding due to simple superficial abrasions to deep internal hemorrhages. A group of bleeding disorders referred to as hemophilia is characterized by genetic mutations resulting in the deficiency of factors critical to the normal process of coagulation.¹ Derived from the Greek root "hemo," meaning blood, and "philia," meaning love, these disorders can present with spontaneous bleeding into soft tissue, joints, and internal organs, and were identified in humans as early as the second century.² This article will review the pathophysiology and clinical features of, and management strategies for hemophilia A and B.

Classification

The 2 most common hemophilia subtypes are hemophilia A, or factor VIII deficiency, and hemophilia B, or factor IX deficiency, which are due to inherited mutations in the genes for these coagulation factors. Both genes are located on the X chromosome; therefore, essentially all affected individuals are male, whereas females who inherit the affected X chromosome are carriers.¹ Rarely, females can develop hemophilia A or B if both genes are defective, if there is only 1 X chromosome (eg, Turner's syndrome), or if the normal X chromosome is excessively inactivated (eg, via lyonization).

Hemophilia affects an estimated 20,000 individuals in the United States,³ with hemophilia A accounting for approximately 80% of cases.⁴ Numerous different mutations in the factor VIII gene have been described. Although the majority of patients have a family history of hemophilia, spontaneous mutations account for about one-third of new diagnoses.¹ An inversion mutation of the *F8* gene located on the long arm of the X chromosome⁵ is found in about 40% of patients with severe hemophilia A. A mutation in the *F9* gene in hemophilia B results in a deficiency of the coagulation protein factor IX. Hemophilia B presents phenotypically similarly to hemophilia A.

Both hemophilia A and B show varying clinical symptoms based on the level of factor produced. The classification scheme for these disorders is based on severity and corresponding factor activity levels. The most severe manifestations are associated with factor levels less than 1%, with moderate symptoms associated with factor levels between 1% and 5%, and the mildest cases occurring with factor levels greater than 5%.⁶ Most of the cost in caring for hemophilia is incurred by patients with severe disease, who comprise half of all patients. Forty percent of patients with hemophilia have mild disease, and ten percent have moderate disease.⁷⁻¹⁰

Pathophysiology

In humans, the liver is the predominant source of factor VIII, which is then secreted and circulated in the bloodstream in an inactive form in a complex with von Willebrand factor.¹ Several other tissues produce factor VIII, including the endothelium. Factor IX is produced entirely by the liver.

The coagulation cascade is a multi-step mechanism through which the body stops bleeding. To ensure adequate hemostasis, several key proteins are activated in a sequential fashion to ultimately form a fibrin plug, or clot. The tissue factor: FVIIa complex initiates the coagulation protease cascade, activating both FIX to FIXa and FX to FXa. This results in the formation of small amounts of thrombin, activating the cofactors FV and FVIII. Factor XI undergoes feedback activation by thrombin. The tenase complex (FVIIIa:FIXa) amplifies the clotting cascade by activation of FX to FXa. The prothrombinase complex (FVa:FXa) activates prothrombin to thrombin, the central protease of the clotting cascade. Fibrinogen is cleaved into soluble fibrin monomers by thrombin, which also activates FXIII to FXIIIa, resulting in a fibrin matrix. Thrombin then activates platelets by cleaving protease-activated receptors.¹¹

Clinical Features

Hemophilia A and B are present at birth in affected male infants; however, the disease may not become clinically evident until a few weeks or months into infancy.² Patients with mild hemophilia typically experience excessive bleeding only after serious injury, trauma, or surgery, whereas those with moderate hemophilia bleed excessively after injury but also sometimes spontaneously. Patients with severe hemophilia commonly experience spontaneous bleeding episodes.⁶

The first symptom may be prolonged bleeding after circumcision, which is contraindicated if the diagnosis is suspected. In severe cases, patients experience spontaneous bleeding into joints and soft tissues, which ultimately restricts mobility and promotes inflammation. This can present clinically as impaired movement, posturing, or irritability in the male infant. Other sites of bleeding include mucosal surfaces and the central nervous system, the latter carrying particularly devastating consequences. Without treatment, the disease can be fatal in early infancy.¹

Patients with moderate to mild hemophilia may not present with obvious signs of bleeding as mentioned above, but may experience prolonged bleeding after surgical procedures. This bleeding often prompts laboratory investigation. The clinical course for these patients is favorable, with fewer complications and reduced need for treatment compared with patients with severe hemophilia.¹

Long-Term Complications

Hemarthroses and Hemophilic Arthropathy

Chronic hemarthroses are one of the most common long-term complications of hemophilia.¹² Intra-articular bleeding may resolve on its own or with treatment in an acute case. However, many patients will experience recurrent bleeding and develop single or multiple target joints that are often painful and restrict their daily activity.¹³ Common sites are the knee, elbow, and ankle.¹⁴ Over time, chronic synovitis and chronic hemarthroses can result in degenerative joint disease, osteoarthritis, and osteophyte formation; surgery may be required if other more conservative treatment options are not successful.^{12,14}

Clinical deformity of the joints in chronic hemophilic arthropathy can be difficult to treat. Because of the chronic synovitis and accumulation of fluid in the joint space, the joint can hypertrophy while the attached muscles atrophy. This severely restricts range of motion and may lead to the development of contractures. The large joints are the most commonly affected; arthropathy of the elbow can be especially problematic. Destruction of the elbow joint can result in ulnar nerve compression and neurologic complications. Severe limitations in range of motion, chronic pain, and crippling disability are the ultimate outcomes for many patients who experience chronic hemophilic arthropathy.¹⁵

Hematomas

Hematomas, another complication of hemophilia,

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generally do not arise spontaneously. Nonetheless, they can be problematic because even slight trauma can result in a hematoma, which may potentially impinge on organs, nerves, and vessels. These can form in any location, but are of particular concern when they occur in the muscles of distal limbs, due to the potential risk of compartment syndrome. Depending on the location, hematomas can grow quite large and escape clinical detection until neurologic complications related to nerve compression appear. In some cases, persistent severe anemia is the presenting symptom.¹

Complications of Treatment

The treatment of hemophilia has involved risk for patients in the past. The early therapy for hemophilia involved the transfusion of plasma, which was inefficient because of the large volumes needed to achieve an adequate level of the factor being replaced.¹⁶ Factor therapy in the form of cryoprecipitate and clotting factor concentrates was an improvement over plasma transfusion and improved the quality of life (QOL) for patients with severe hemophilia by allowing home treatment, but the use of this treatment modality was soon hampered by widespread infection by hepatitis viruses and human immunodeficiency virus (HIV) in the early 1980s.^{17,18} Approximately 90% of patients with hemophilia were infected with the hepatitis C virus (HCV), and more than 55% of this cohort was coinfecting with HIV.¹⁹ This problem ultimately led to the development of heat-treated products that reduced the transmission rate of these viruses. With the development of genetically engineered recombinant factor therapy in the 1990s, the risk of acquiring HCV and HIV from factor replacement therapy has been virtually eliminated. Furthermore, improvements in screening of blood donors, plasma purification, and viral inactivation procedures including pasteurization and solvent-detergent treatments have made current plasma-derived factor concentrates extremely safe therapeutic options.²⁰

Development of Inhibitor Antibodies

An inhibitor is an antibody directed against either factor VIII or IX that may be created by the body following treatment to replenish the missing factor. Inhibitor antibodies form in 20% to 33% of patients with hemophilia A and are less likely to be a clinical problem in patients with factor IX deficiency; formation of inhibitors occurs in 1% to 6% of patients with hemophilia B.²¹ Patients with inhibitors experience poorer clinical

outcomes than those who do not develop inhibitors, including more severe bleeding episodes, intracranial hemorrhage, and accelerated disability.²² The highest incidence and greatest severity of joint disease occur in patients with inhibitors.²³

Inhibitors are more likely to develop in patients with severe hemophilia, who are already prone to spontaneous and serious bleeding episodes. The development of an inhibitor is influenced by several factors.²¹ The risk of inhibitors is increased in younger patients receiving the first several doses of factor.²¹ African American and Latino patients are more likely to develop an inhibitor compared with Caucasian patients.²⁴ This variability in inhibitor type, level, and development is likely reflective of the heterogeneity of genetic mutations in hemophilia, particularly in hemophilia A. In addition, genetic differences in an individual's immune system apart from the F8 gene mutation may render certain patients more susceptible than others to inhibitor formation.²¹ It remains controversial whether the type of factor concentrate influences the risk of inhibitor development.²⁵ To address the question of whether recombinant versus plasma-derived factor concentrates influence the risk of inhibitor development, the Survey of Inhibitors in Plasma Product Exposed Toddlers (SIPPET) study has been designed to compare inhibitor incidence in patients exposed to the different concentrates. Results of this ongoing study are awaited.

Comorbid Conditions

With advances in hemophilia care, the increased life expectancy for patients with hemophilia has resulted in older patients experiencing comorbid conditions not previously observed in this population. In a study of patients 40 years or older with hemophilia, the average number of comorbidities was between 3 and 6. The most common comorbidities were identified as chronic HCV, hypertension, HIV, chronic arthropathy, and overweight/obesity.²⁶

Blood-Borne Infection

One of the most serious treatment complications in patients with hemophilia is transfusion-related HCV and HIV infections.²⁷ The high rate of HCV infection in older patients with hemophilia is a contributing factor to the increased prevalence of both renal disease and liver disease.^{28,29} Cirrhosis is a potential outcome for those infected with HCV, and coinfection with HIV has been shown to accelerate the development of liver failure.³⁰

Renal Disease

Compared with the general population, patients with hemophilia are 50 times more likely to die from renal failure.³¹ Renal disease is partly due to the higher incidence of hypertension and HIV coinfection in patients with hemophilia compared with the general population.^{32,33}

Cardiovascular Disease

Patients with hemophilia are also more likely to experience symptomatic cardiovascular disease and intracranial hemorrhage with life-threatening complications.³⁴ The presence of hypertension is likely a contributing factor to the increased risk of cardiovascular disease, with higher rates of hypertension noted in patients with moderate and severe hemophilia compared with those with mild hemophilia.³⁵

Obesity

The proportion of patients with hemophilia who are overweight or obese has been estimated at 50%, which is similar to that of the general population. Overweight/obesity in patients with hemophilia increases the likelihood of hemophilic arthropathy and decreased joint range of motion.³⁶

Quality of Life

Over the years, advances in the treatment of hemophilia have narrowed the life expectancy gap between patients with hemophilia and the general population. Despite this, the need for frequent intravenous infusions of factor therapy, complications of treatment, and comorbidities result in an impaired QOL for patients with hemophilia. This applies particularly to those with severe disease, who require access to medical care and supplies on a regular basis. The requirement that factor therapy be refrigerated further restricts a patient's mobility and lifestyle choices. Traveling to remote areas or regions without medical resources may be challenging. In addition, patients with hemophilia are discouraged from participating in high-risk contact sports or other activities. These restrictions can be difficult to accept for younger, active patients. Family planning concerns may arise in adulthood, and genetic counseling may be needed for the couple wishing to have children if the father has hemophilia or the mother is a known carrier.³⁷ The financial cost associated with a lifetime of therapy and clinic visits can be substantial, and regular doctor and physical therapy appointments take up a substantial amount of both patients' and care-

givers' time. Some patients experience chronic pain that can lead to dependence on opioids or illicit drugs.^{38,39} QOL is significantly improved for patients living in industrialized countries with strong family support compared with those from less developed countries and lower socioeconomic status.⁴⁰

General Challenges With Hemophilia Treatment

The diagnosis and management of patients with severe hemophilia are complex. Preventive treatment (prophylaxis) is required to avoid bleeding episodes and related complications, and use of replacement therapy with coagulation factors is needed during acute bleeding episodes. Optimal care of patients with hemophilia requires a comprehensive approach that is coordinated by a multidisciplinary team of specialists and is provided at a dedicated hemophilia treatment center.⁶ Despite advances in the management of hemophilia, challenges remain, including the shortage of physicians trained in the management of hemostasis and thrombosis and limited access to specialized centers that provide comprehensive care.

Multidisciplinary Approach

The treatment of patients with hemophilia must be comprehensive to achieve optimal long-term results. A multidisciplinary approach is essential, and ideally includes a team of physicians, nurses, psychologists, genetic counselors, pharmacists, case/social workers, and physical therapists. Over the course of their lifetime, patients with hemophilia may need to have access to other specialists, including rheumatologists, pain specialists, infectious disease specialists, hepatologists, surgeons, nutritionists, and dentists.⁴¹

Access to Specialized Centers

Patients with hemophilia require lifelong access to specialized centers and comprehensive care, posing a challenge for many patients and providers. In one study, almost half of survey respondents who treated themselves with factor therapy at home reported concerns with the availability and affordability of their treatment.⁴² Challenges also arise once a young patient enters adolescence and gains a certain degree of autonomy regarding their treatment. Programs designed to target youths with hemophilia during the transition to more autonomous management have been developed and are effective, but require the patients to have Internet access and other support.⁴³ For patients with hemophilia, receiving dental care is also a challenge, and specialized facili-

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ties or hospitalization may be needed for procedures that would otherwise be considered routine.⁴⁴

Shortage of Specialists

To further complicate the management of patients with hemophilia, fewer physicians are adequately trained to treat inherited bleeding disorders because graduates of combined hematology/oncology fellowship programs are more likely to focus on oncologic than on benign hematologic disorders.⁴⁵ Patients with hemophilia require not only experienced hematologic care for their bleeding diathesis, but also care from other specialists such as dental surgeons and orthopedic surgeons who have experience with patients undergoing treatment for hemophilia. Improper or inadequate training in these areas can put the patient at unnecessary risk.

Cost of Therapy

Perhaps one of the most significant challenges facing patients, as well as their physicians, is the cost of therapy. Factor replacement is an expensive and necessary treatment. The use or choice of therapy depends on the severity of disease and presence of inhibitors.²¹ In one study of 1164 patients with hemophilia A or B with and without inhibitors, mean healthcare expenditures were evaluated. Among patients with hemophilia A, the mean healthcare expenditures were nearly 5 times higher in the inhibitor group than in the noninhibitor group.⁴⁶

Prophylaxis

The use of prophylaxis is currently recommended as first-line treatment for children with severe hemophilia, and the use of prophylaxis is increasing for adult patients.⁴⁷ Prophylactic treatment can be primary, secondary, or tertiary. Primary prophylaxis commences before the second joint bleed and before any established joint disease. Secondary prophylaxis occurs after the second joint bleed (at which point a bleeding pattern has likely been established) and ideally before any joint damage. Tertiary prophylaxis takes place when joint disease is already present and established (often in adulthood).⁴¹

Several studies have demonstrated the benefits of early prophylaxis—reducing the risk of spontaneous bleeding and subsequent complications of hemarthrosis.⁴⁸⁻⁵⁰ Other demonstrated benefits of early prophylaxis include prevention of intracranial hemorrhage and other serious bleeds, prevention of pain, improvements in QOL, and reduction in long-term disability.⁴⁹

Despite the clinical advantages of prophylaxis, barriers to implementation exist among physicians and patients. Physicians may be uncertain about the optimal prophylactic regimen,⁴⁹ particularly since the recent FDA approval of several therapies for this indication. For patients, barriers to implementation of prophylaxis include the need for venous access with associated potential for complications (surgical placement of indwelling lines, infections, catheter-related deep vein thrombosis), high cost, and potential need for home nursing or clinic visits to administer infusions until someone at home learns to perform infusions.

A recent survey published in 2012 by Ragni and colleagues regarding current prophylactic practices at 62 US hemophilia treatment centers showed substantial variability regarding the timing of initiating prophylaxis and the specific prophylaxis regimen used. Only 25% of the hemophilia treatment centers surveyed started prophylaxis after the first bleeding episode (of any type), and just 16% began after the second hemorrhage.⁵¹ It is clear that managed care health professionals who treat patients with hemophilia would benefit from education regarding optimal prophylaxis regimens that are based on recent information and research.

The pediatric population receiving prophylactic regimens initially incurs higher costs than the population treated on an on-demand basis. The benefit of prophylaxis, however, may outweigh the cost of complications that reduce QOL later in adulthood. Pediatric patients with severe hemophilia A who receive prophylaxis experience less joint destruction and fewer bleeding episodes than those who receive on-demand therapy.^{52,53} This ability to prevent hemophilic arthropathy, which is one of the most significant factors reducing the QOL in older patients, is one of the greatest advantages to a prophylactic regimen. Benefits can even be seen in adult patients who switch to a secondary prophylactic treatment course after prior on-demand therapy. One year of secondary prophylaxis increases QOL, reduces hemarthroses, and improves musculoskeletal joint assessments.⁵⁴ Although many teenagers and young adults opt to discontinue prophylaxis in favor of less frequent, on-demand therapy, they experience more bleeding episodes and a decreased QOL. In a study of 38 participants comparing those maintained on a prophylactic regimen with 2 groups of patients receiving on-demand therapy, the prophylactic group experienced significantly fewer bleeding episodes and an improved QOL.⁵⁵ Another long-term benefit of primary prophylaxis

■ **Table.** Products for the Treatment of Hemophilia: Brand and Generic Names⁶⁰⁻⁶⁵

Brand name	Generic name
Novoeight ⁶⁰	Turoctocog alfa (recombinant coagulation factor VIII [rFVIII])
KogenateFS ⁶¹	Recombinant antihemophilic factor VIII (formulated with sucrose)
Eloctate ⁶²	Recombinant antihemophilic factor VIII (Fc fusion protein [rFVIII-Fc])
Rixubis ⁶³	Recombinant coagulation factor IX injection
Alprolix ⁶⁴	Recombinant coagulation factor IX (Fc fusion protein)
FEIBA ⁶⁵	Anti-inhibitor coagulant complex

laxis is fewer hospitalizations and surgical procedures on joints, which lowers medical care costs despite the increased expense of factor products.

Current Therapies

Current therapy for hemophilia A and B is replacement of the deficient coagulation factor using either plasma-derived or recombinant factor replacement products. Standard of care is to begin prophylactic therapy in childhood to avoid the long-term complication of joint destruction. However, less than half of adults continue prophylactic therapy with the remainder infusing factor concentrates on demand.⁵⁶ A disadvantage of prophylactic therapy is the frequency of venipuncture required—roughly 2 to 3 times a week and potentially more often if breakthrough bleeding occurs. The relatively short half-lives of the factor replacements—approximately 10 to 14 hours for factor VIII and 15 to 24 hours for factor IX—creates the frequency requirement.⁵⁷ This drawback may be why adult patients opt for less frequent, on-demand treatment regimens. Younger patients also often require means of venous access other than peripheral veins, including central lines and arteriovenous fistulas.⁵⁸

No cases of HIV or hepatitis transmission via first-generation recombinant factor replacement have been reported, but because some of these products contain human plasma proteins, a theoretical risk of infectious disease transmission exists. Second-generation agents eliminate the inclusion of human albumin in the final factor VIII concentrate. These agents utilize sucrose as a stabilizer, an example of which is recombinant antihemophilic factor VIII (formulated with sucrose).⁵⁹

Since October 2013, at least 6 new therapies have received either expanded indications or new approvals by the FDA for the management of hemophilia A or B (Table).⁶⁰⁻⁶⁵

Hemophilia A

Within the past year, several therapies have received FDA approval for treatment and prophylaxis of adults with hemophilia A. In October 2013, the FDA approved turoctocog alfa (recombinant coagulation factor VIII [rFVIII]) for control and prevention of bleeding, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A.⁶⁰ This approval was based on the guardian clinical program, which included more than 210 patients with severe hemophilia A. In these trials, the efficacy of turoctocog alfa in preventing and treating bleeds was demonstrated, and the development of inhibitors was not observed. This additional treatment option is expected to be available in the United States sometime after April 2015.⁶⁰

In May 2014, the FDA expanded the indications for recombinant antihemophilic factor VIII (formulated with sucrose) to include routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A.⁶¹ Antihemophilic factor VIII (recombinant [formulated with sucrose]) previously was approved for the control and prevention of bleeding episodes and perioperative management of adults and children with hemophilia A as well as routine prophylaxis for children.⁶¹ The most recent approval was based on data from the Secondary Prophylaxis in Adults, A Randomized Trial (SPINART) study, which included 84 patients with severe hemophilia (FVIII <1%) aged 15 to 50 years. Patients were randomized to receive either prophylaxis (3 infusions per week) or on-demand therapy as needed to treat bleeding. In this study, patients receiving prophylaxis experienced significantly fewer bleeds than patients treated with on-demand therapy. These results were consistent across baseline subgroups examined, including age, bleeding history, and presence or absence of target joints. Patients in the on-demand group experienced an average of 15.2 times more bleeds than those in

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the prophylaxis group, with mean annualized bleed rates of 37 in the on-demand group versus 2 in the prophylaxis group.⁶¹

In June 2014, the FDA also approved recombinant antihemophilic factor VIII (Fc fusion protein [rFVIII-Fc]) for the control and prevention of bleeding episodes, perioperative management, and routine prophylaxis in adults and children with hemophilia A. rFVIII-Fc was developed to keep circulating levels of infused clotting factor in the body for a longer duration, thereby extending the interval between prophylactic infusions.⁶²

rFVIII-Fc is currently the only treatment for hemophilia A to reduce the frequency of prophylactic infusions to every 3 to 5 days and prevent bleeds. In pivotal clinical trials, rFVIII-Fc was demonstrated to be safe and effective both for routine prophylactic therapy and for treating acute bleeding episodes.⁶² In An Open-Label, Multicenter Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIII-Fc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia A, a trial of 165 male patients 12 years or older with severe hemophilia A, rFVIII-Fc was shown to significantly reduce the number of bleeding episodes when delivered as prophylaxis as well as on-demand therapy. The half-life extension of rFVIII-Fc is modest at 1.5-fold compared with standard recombinant factor VIII.⁶⁶

Concerns about inhibitor formation with these novel agents persist. Studies are ongoing to evaluate the incidence of inhibitor formation with early prophylactic treatment with rFVIII-Fc before the first bleeding episode.⁶⁷

Hemophilia B

In June 2013, the FDA approved recombinant coagulation factor IX injection (rFIX) for treatment in adult and pediatric patients (>16 years of age) with hemophilia B.⁶⁴ As the first new rFIX treatment in 15 years, recombinant coagulation factor IX injection is approved for the control and prevention of bleeding episodes; for routine prophylaxis (twice weekly) to prevent or reduce the frequency of bleeding episodes; and for perioperative management.⁶³ The approval of recombinant coagulation factor IX injection for adult patients was based on a multicenter study of 73 male patients aged 12 to 65 years with severe (<1% FIX) or moderate hemophilia ($\leq 2\%$ FIX). Patients received the drug for routine prophylaxis or as needed (on demand) for symptoms of bleeding for a minimum of 150 exposure days. The 59 patients in the prophylaxis study had a 75% lower annual bleeding rate

compared with the 14 subjects receiving on-demand treatment. During the study, no patients developed antibodies or inhibitors to the drug, and there were no reports of anaphylaxis. Side effects occurred in less than 1% of patients and included distorted taste, pain in an extremity, and atypical blood test results.⁶³

Recently approved novel therapies for hemophilia B have a longer half-life than previous products, resulting in reduced frequency of infusions and better adherence and QOL.⁶⁸⁻⁷³ In March 2014, recombinant coagulation factor IX (Fc fusion protein) received FDA approval for the control and prevention of bleeding episodes, perioperative management, and routine prophylaxis in adults and children with hemophilia B.⁶⁴ Recombinant coagulation factor IX (Fc fusion protein) was approved based on phase 3 results from the B-LONG: An Open-Label, Multicenter Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant, Long-acting Coagulation Factor IX Fc Fusion Protein (rFIX-Fc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia B (B-LONG) clinical study showing a reduction in bleeding episodes in adolescents and adults with hemophilia B receiving weekly prophylactic recombinant coagulation factor IX (Fc fusion protein). In this trial, subjects experienced a prolonged circulation of rFIX in the body, which lengthened the intervals between prophylactic infusions (median overall dosing interval of 12.5 days). In addition, more than 90% of bleeds were controlled by 1 infusion of the rFIX therapy, and none of the study participants developed an inhibitor to the product.⁶⁴ rFIX-Fc has a 3-fold longer half-life than plasma-derived or recombinant factor IX.⁷⁴

Hemophilia A and B With Inhibitors

Inhibitor development is considered one of the most serious complications associated with hemophilia treatment. In fact, up to one-third of previously untreated patients with severe or moderately severe hemophilia A are at risk for developing inhibitors to FVIII. A much lower percentage of patients with hemophilia B develop inhibitors to FIX (1.5% to 3%).⁷⁵⁻⁷⁹ Response to treatment is more difficult to achieve with the development of inhibitors, which also increases the risk of complications.⁶⁵

Patients with inhibitors are identified either through routine screening tests or after failure to respond as expected to treatment after a bleeding episode. Inhibitor levels are quantified by Bethesda assay. It is estimated that 25% to 40% of patients with inhibitors have low titers (<5 Bethesda units [BUs]); in these patients, bleeding may

resolve with increased quantities of replacement factor. At high titers (≥ 5 BUs), which occurs in 60% to 75% of all patients with inhibitors, impaired response to clotting factor concentrates requires a 2-pronged approach of short-term control of acute bleeding episodes with bypassing agents (eg, recombinant factor VIIa, factor VIII inhibitor bypassing activity [FEIBA]) and inhibitor titer reduction over the long term by immune tolerance induction.²⁵

In December 2013, the FDA approved a new indication for anti-inhibitor coagulant complex. This therapy is the first and only treatment for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B who have developed inhibitors.⁶⁵ The approval of this agent was based on data from the phase 3 FEIBA PROOF study, which showed a 72% decrease in median annual bleed rate with anti-inhibitor coagulant complex compared with treatment with an on-demand regimen. Eighteen percent of patients (3 out of 17) in the prophylactic arm reported no bleeding episodes. The most common adverse reactions ($>5\%$ of subjects) were anemia, diarrhea, hemarthrosis, hepatitis B surface antibody positive, nausea, and vomiting.⁶⁵

Anti-inhibitor coagulant complex has been associated with serious adverse drug reactions (stroke, pulmonary embolism, deep vein thrombosis), and the prescribing information includes a boxed warning regarding thromboembolic events; this risk is increased in patients receiving high doses and/or with thrombotic risk factors. The administration of recombinant factor VIIa has also been associated with thrombotic complications and the prescribing information for recombinant factor VIIa includes a boxed warning.

Challenges With the Availability of New Treatments

Despite advances in the treatment of hemophilia A, limitations in management still remain and costs of treatment are high.²⁵ Development of inhibitors, the relatively short half-life of molecules requiring frequent injection to maintain effective concentration, and significant cost of replacement therapy continue to challenge clinicians and third-party payers.

One challenge in the management of severe hemophilia A is the development of inhibitors. According to a study published by Astermark and colleagues, polyclonal antibodies develop in 10% to 20% of patients and may inhibit the function of exogenous factor VIII.²⁵ Once this inhibitor develops, immune modulation and immune tolerance induction are needed for management, which may be complicated and expensive. Treatment guidelines

for inhibitor development are lacking, and there are few data to guide clinical management decisions.²⁵

Other challenges in the management of hemophilia A are individual patient variability in pharmacokinetic response to recombinant factors, and the need for frequent dosing. These make an individual patient's treatment regimen very difficult.³¹ Studies of recombinant factor in patients with hemophilia A demonstrated a substantial level of interpatient variation in pharmacokinetics, factor VIII dosing, and annualized bleed rate, which suggests that individual patient characteristics may contribute to outcome. This finding lends support to the use of pharmacokinetic-guided, individualized treatment in the routine clinical care setting to achieve comparable efficacy with fewer weekly infusions compared with standard prophylaxis.⁸⁰

Although newly approved treatments may have longer duration of action, increased potency, and novel mechanisms of action, several potential challenges accompany their use in the managed care setting, including determination of optimal treatment selection, laboratory monitoring, combination therapy, adverse events, and cost.⁸¹

The process of identifying the optimal treatment regimen for hemophilia patients is likely to grow more complex as managed care organizations determine how to integrate new agents into the current treatment paradigm, posing another challenge to the optimal management of hemophilia.

Also, although laboratory monitoring with conventional factor replacement products is relatively straightforward, this is not necessarily the case with new products and it is not yet clear how FVIII or FIX activity will be measured in patients receiving novel agents. One possibility is that for each product, a specific reference standard will be required. Therefore, laboratories will need to set up standard curves using multiple references, which has a high potential for error.⁸¹

The use of novel long-acting agents in combination with currently available agents presents another challenge. Although products with extended half-lives will improve the QOL for patients, once-weekly products that can maintain adequate trough levels to prevent routine bleeding (prophylaxis) will result in only 1 peak level per week. Therefore, clinicians must consider the importance of peak levels for hemostatic challenges such as surgery or certain types of physical activity. For example, they must determine how to best manage a situation in which serious trauma occurs 1 to 2 days after a long-acting product was given—in this situation, admin-

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istering a dose of the patient's long-acting product could result in a factor level that is too high.⁸¹

Additionally, clinicians must be aware of the possibility of unanticipated adverse events occurring with new therapies, which can have detrimental effects on clinical outcomes and the cost of care.⁸¹

Lastly, novel agents with enhanced properties are generally priced higher than conventional treatments, forcing managed care health professionals to ascertain whether novel and more expensive treatments for hemophilia are worth the greater cost.⁸¹

Future Treatments: Novel Therapies

While the development of recombinant factors has reduced the morbidity and mortality associated with hemophilia, significant concerns with existing therapy remain. Repeated bleeding episodes, which can cause long-term damage in joints and other tissues, still occur in many patients for whom prophylactic therapy is available.³

Gene therapy can potentially eliminate the challenges associated with factor replacement therapy. For example, inserting the gene for FIX into a patient's tissue could permanently restore clotting factor levels in the circulation for the life of the patient. Hemophilia B is an ideal target for gene therapy because it is caused by diminished function of a single protein, which in turn is caused by alteration (mutation or deletion) of a single gene.⁸² Therefore, restoring a functional copy of the affected gene could potentially ameliorate the clinical manifestations of the disease.⁷³ Gene therapy trials that have been performed in subjects with severe hemophilia B are showing promising results.

To address the problem of short recombinant factor half-life, researchers are exploring Fc fusion technology to increase the amount of time that the coagulation factors circulate. Studies have shown that factor VIII and IX developed by this method have a longer half-life and result in fewer overall infusions, particularly in treating hemophilia B.⁸³ Other novel approaches to prolong half-life include pegylated liposomes/pegylation, polysialylation, protein sequence modifications, bioengineered antibodies, RNAi targeting antithrombin, and factor VIII mimetics.^{73,84-89} As advancements in factor-replacement therapy continue to be made with long-acting factor concentrates, these emerging hemophilia strategies may represent treatment options that could possibly supersede traditional factor-replacement therapy in the future.

Conclusion

Hemophilia imposes a substantial burden from both

the societal and patient perspectives. Several key challenges in hemophilia care remain, including the use of early prophylaxis in preventing long-term complications, complexity of management, and adoption of new therapies in existing treatment paradigms.

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