

The Benefits of Sustaining High Factor VIII Levels in People With Hemophilia A

HIGHLIGHTS

- › Clinical and Economic Impact of Hemophilia A
- › Approved Hemophilia A Therapies and FVIII Levels
- › Managed Care Considerations

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OVERVIEW

This supplement to *The American Journal of Managed Care*® explores hemophilia A, including its clinical and economic impact, treatment goals, and the role of managed care in optimizing outcomes for people with hemophilia A.

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The Benefits of Sustaining High Factor VIII Levels in People With Hemophilia A

Russell Gollard, MD

Introduction

Hemophilia A is a bleeding disorder inherited in an X-linked recessive pattern and caused by a deficiency in clotting factor VIII (FVIII).¹ Because bleeding associated with hemophilia can result in musculoskeletal damage and other complications, the World Federation of Hemophilia (WFH) has established a clinical goal of zero bleeds for people with hemophilia A (PwHA) and advises prophylactic rather than episodic (“on demand”) therapy for all patients.² Intravenous prophylaxis using plasma-derived or recombinant clotting factor concentrates (CFCs) serves as the standard replacement therapy for PwHA.^{2,3} However, prophylaxis does not entirely prevent joint damage, and it cannot reverse it.⁴ Prophylaxis also does not appear to change the rate of chronic pain reported by PwHA.^{5,6}

Maintaining high FVIII levels has demonstrated considerable clinical benefit.² Such maintenance requires provider knowledge of best practices, understanding of the treatment landscape, and careful navigation of current challenges within managed care. This supplement reviews the clinical and economic impact of hemophilia A, and goals for attaining and sustaining FVIII levels. It also considers the ability of FDA-approved therapies to help patients to achieve these goals and highlights managed care considerations in the management of this rare blood disorder.

Clinical Impact

According to WFH guidelines, patients with mild hemophilia A (FVIII levels, 5-40 IU/dL [5%-40% of normal]) are vulnerable to traumatic, joint, and surgical bleeds.² In a retrospective study that included 63 patients with severe hemophilia A, approximately half (49.2%; 95% CI, 37.3%-61.2%) of all patients with FVIII levels of 5 IU/dL were predicted to experience any bleed—spontaneous or traumatic, at any anatomical site—over a 1-year period.⁷ These bleeds are associated with substantial clinical impact.⁸

People with hemophilia have reduced thrombin generation when compared with the general population.² They often experience recurring joint bleeds that occur most often in the knees, ankles, and elbows; these can cause hemophilic arthropathy, joint impairment, pain, and diminished quality of life (QOL)

ABSTRACT

Hemophilia A is a bleeding disorder caused by a deficiency in clotting factor VIII (FVIII), leading to recurrent joint bleeds, musculoskeletal damage, and chronic pain. The World Federation of Hemophilia (WFH) recommends prophylactic FVIII replacement therapy to reduce bleeding risk, yet joint deterioration and pain persist. Maintaining high FVIII levels provides clinical benefits but requires awareness of best practices and managed care considerations. This publication examines the clinical and economic impact of hemophilia A, treatment goals, FDA-approved therapies, and managed care factors. People with hemophilia experience lower bone mineral density, increased osteoporosis risk, and significant effects on mental health, mobility, and quality of life. Treatment options—including standard and extended half-life FVIII therapies, non-factor therapies, and gene therapy—vary in sustaining FVIII levels and preventing bleeds. The high cost of care burdens patients and health systems, though prophylaxis reduces emergency visits and hospitalizations. Adherence challenges arise as patients transition to self-infusion, and insurance restrictions often limit access to comprehensive care. The WFH supports individualized, patient-centered management with pharmacokinetic-guided dosing, multidisciplinary care, and shared decision-making. Maximizing FVIII levels, rather than maintaining minimal thresholds, may improve long-term health. A holistic approach—combining early intervention, personalized prophylaxis, and strategies to address treatment barriers—is essential to better outcomes and achieving the WFH goal of zero bleeds.

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For author information and disclosures, see end of text.

(Figure A).^{2,8} The repeated bleeds allow for an accumulation of iron from erythrocyte lysis, which can provoke inflammation, hyperplasia, and angiogenesis.⁸ Even one bleed can cause vascular changes that facilitate further bleeding, chronic inflammation, and permanent damage to cartilage and bone.⁸ Early prophylaxis is associated with a lower rate of joint bleeding and higher rates of preserved joint function (Figure B).^{9,10} However, prophylaxis does not completely halt, and cannot repair, joint damage.⁴ In a study of 65 boys with severe hemophilia A, 12 of 14 participants (85.7%) randomly assigned to receive prophylaxis prior to 2.5 years of age had osteochondral damage at a mean (SD) age of 17.5 (1.7) years.¹¹ Similarly, as noted by O'Hara and others in a survey of individuals aged 18 to 35 years with hemophilia A, recurrent bleeding into target joints can develop even as patients receive recommended prophylaxis. Among 166 patients given prophylaxis with standard half-life (SHL) clotting factor therapy since the time of diagnosis, 65 (39%) presented with recurrent bleeding in at least 1 joint at a median age of 24 years (IQR, 21-26 years).⁶ Asymptomatic bleeds also may increase joint deterioration.¹² Ultrasonography and MRI of clinically asymptomatic joints in 20 adults with severe hemophilia A have revealed prevalent joint effusion, synovial hypertrophy, and cartilage erosion, which constitute signs of early arthropathy.¹³

Joint bleeds and hemophilic arthropathy are associated with pain, which is a primary concern for people with hemophilia.^{8,14} Results of a meta-analysis of 11 studies revealed that 47% (95% CI, 34%-59%) of people with hemophilia experience chronic pain.⁵ Prophylaxis does not appear to change this rate; in the aforementioned study by O'Hara et al, 46% of the 166 men receiving primary prophylaxis reported ongoing pain.⁶

Joint impairment and pain negatively impact the daily lives of people with hemophilia. Hemophilic arthropathy and joint impairment lead to a decreased range of motion, limited mobility, and lower QOL.^{2,8} In a study of 381 men with hemophilia, work and activities in a 4-week period had been limited by functional impairment for 65% of participants and by pain for 75%.¹⁵

Hemophilia-related depression and anxiety have been positively correlated and have been shown to have a negative impact on treatment adherence.¹⁶ For up to one-third of young adults with hemophilia, the disease negatively impacts their ability to develop close relationships.¹⁷ Standard-of-care prophylaxis does not appear to mitigate disease-related mental health for patients with hemophilia, as young adults receiving primary prophylaxis report anxiety and depression at rates similar to those of patients receiving on-demand treatment.⁶

People with hemophilia tend to have reduced bone mineral density (BMD) and an increased risk of osteoporosis, osteopenia, and bone fractures compared to the general population; this may be attributed to joint bleeds and a lack of physical activity.¹⁸ Patients receiving prophylaxis have a higher BMD than do those receiving

on-demand therapy; moreover, patients with severe hemophilia who receive prophylaxis have a comparable BMD to individuals of the same age with mild hemophilia who are not receiving prophylaxis.¹⁹ The exact pathophysiology of reduced BMD in individuals with hemophilia is not completely understood, yet evidence indicates that FVIII may play a role in bone remodeling.¹⁸

During the AIDS epidemic, treatment for hemophilia A was associated with high rates of HIV infection and mortality.²⁰ Subsequent safety measures including pathogen elimination techniques and the introduction of recombinant CFCs and concentrates devoid of human proteins eliminated the risk of infection from HIV and other serious blood-borne viruses.^{20,21} Similarly, the addition of anticoagulants to prothrombin complex concentrates (PCCs) and a decreased prevalence of PCC use have reduced the risk of treatment-associated thrombosis for PwHA, particularly during breakthrough bleeds and in the perioperative setting.²

Despite these and other advances that have significantly improved patient outcomes, individuals with hemophilia still face joint and functional impairments, acute and chronic pain, and poor mental health, all of which negatively affect their QOL.^{6,11}

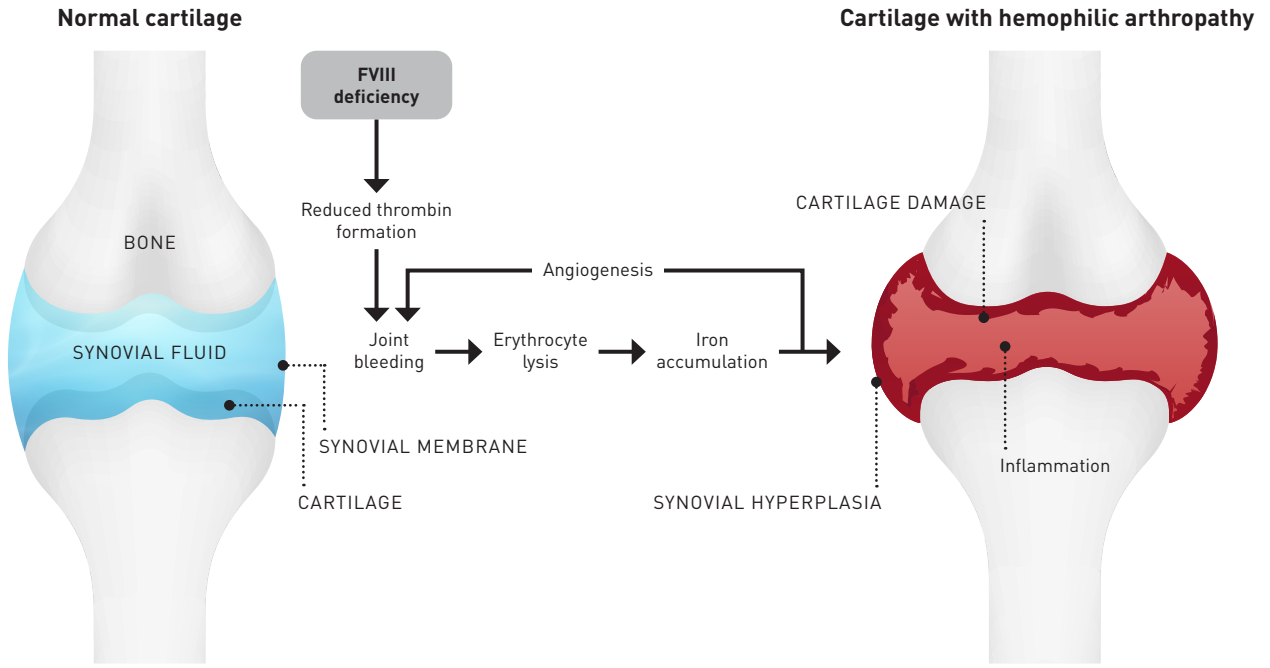
Economic Impact

The expenses involved in managing hemophilia A in the United States can lead to financial strain for patients, their families, and health care systems.²² A meta-analysis of 40 studies on health care resource use and economic costs for managing hemophilia A that were published from 2010 to 2022 found that annual health care costs per patient ranged from \$213,874 to \$869,940 (2021 US\$); therapeutic costs made up the largest portion of these expenses. Differences in drug-specific costs, patient age, and prophylaxis intensity contributed to the wide variation in treatment expenses. Additionally, annual costs for all factor products appeared to have risen over the study period.²³

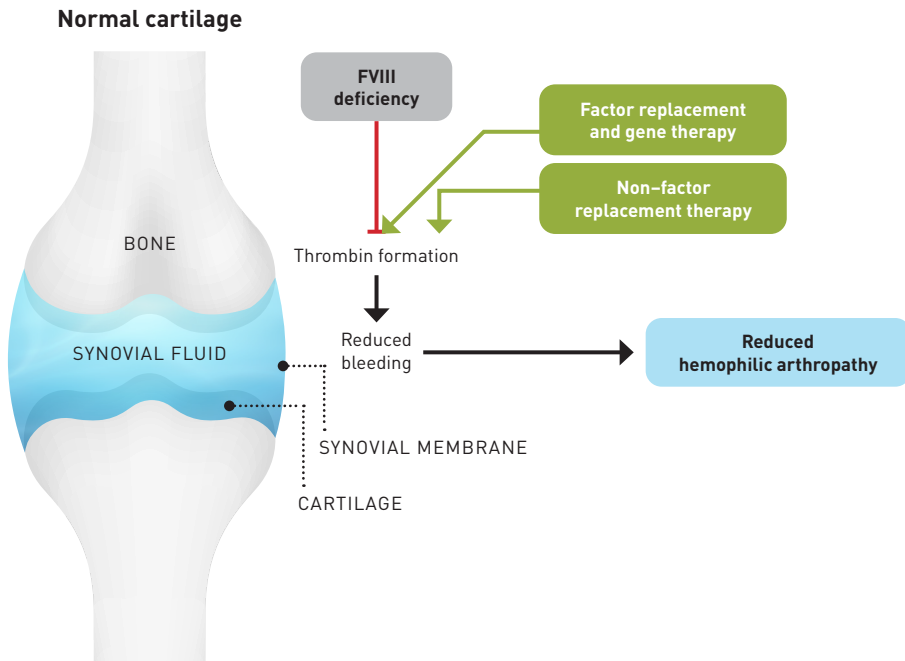
Despite high therapeutic costs, prophylaxis is associated with reduced use of health care resources in PwHA compared with on-demand treatment following a bleed. In a study involving patient survey, medical chart, and drug dispensation data for 222 PwHA recruited from 2005 to 2007, 34.2% of participants had at least 1 emergency department (ED) visit, and 19.4% had at least 1 hospitalization during a mean follow-up of 12 months. However, compared with 51 patients treated episodically, 86 patients given prophylaxis had a lower mean (SD) number of ED visits (1.0 [1.8] vs 0.4 [0.9]; $P = .0127$), a lower rate of hospitalization (23.5% vs 16.3%), and a numerically lower mean length of hospital stay (7.8 vs 3.9 days; $P = .0895$) during this time. Moreover, ED visits, hospitalization, and other medical costs not associated with therapy were substantial; the average (SD) cost (2011 US\$) was \$6857 (\$22,451) among all study participants. Average (SD) costs rose to \$14,481 (\$41,881) among the patients with severe hemophilia A who were treated episodically.²⁴

FIGURE. Joint Health in Hemophilia A^{2,8-10}

A. Pathogenesis of Hemophilic Arthropathy in Hemophilia A^{2,8}



B. Therapeutic Strategies to Reduce Bleeding and Preserve Joint Health in Hemophilia A^{9,10}



StudioGraphic / vik_y - stock.adobe.com (Modified by Julianne Costello)

Treatment Goals

The WFH sets a zero-bleed goal to allow patients with hemophilia to lead healthy, social, and physically active lives that are comparable to those led by people with no hemophilia. WFH guideline authors acknowledge that although a primary goal of prophylaxis has historically been to maintain factor levels above 1 IU/dL (1%), the results of studies like those cited above demonstrate that factor trough levels of 1 to 3 IU/dL (1%-3%) are insufficient to prevent disease progression in all people with hemophilia.² WFH guideline authors now advocate for maximizing FVIII trough levels, noting, "In general, the higher the factor levels at all times, the less the bleeding."² A study of expert opinions recommended minimum FVIII activity levels of 4% for low-risk activities and 38% for high-risk activities in individuals without joint morbidity and of 7% and 47%, respectively, for those with known joint disease.²⁵

Regular prophylaxis and recombinant FVIII (rFVIII) replacement have allowed people with hemophilia to attain a life expectancy similar to that of the general population.^{2,26} Treatment goals are shifting from what is minimally feasible (eg, preventing early death, reducing spontaneous bleeds and related complications) to focusing on achieving optimal health equity.^{27,28} This may require a reevaluation of the FVIII break points traditionally used to distinguish severity.²⁸ A 7-step treatment model proposed by Skinner et al provides a progressive definition of cure for people with hemophilia that culminates in normal hemostasis. Such functional cure would enable health equity, allowing individuals to live without fear of bleeding episodes.^{27,29} In addition to striving for the zero-bleed goal set by the WFH, providers may seek to reduce treatment burden and improve treatment adherence by reducing injection frequency of FVIII replacement therapies.² Moreover, the capacity to endure minor trauma without bleeding could support a more unrestricted lifestyle, while the ability to undergo surgery or experience major trauma without extra intervention would enable access to elective or emergency care.²⁷ Reaching these treatment goals would relieve PwHA from the ongoing psychological burden of constantly focusing on their condition.²⁹

Higher FVIII levels are associated with a lower risk of bleeding during activities, and they may enable patients to lead more active lifestyles.^{2,25,30} Sustaining higher FVIII levels may provide greater protection from bleeds,³¹ help preserve joint health,¹⁰ and reduce pain³²; the level of bleed protection depends upon FVIII levels.⁷ In this, area under the curve (AUC), which is FVIII concentration multiplied by time, should be considered alongside peak FVIII levels and time spent above target FVIII levels. For instance, results from a post hoc analysis of data from a pharmacokinetic-guided prophylaxis trial (NCT00243386) revealed that among 34 males with moderately severe to severe hemophilia A, a median weekly AUC of 1363 IU × h/dL⁻¹ (range, 130-4265 IU × h/dL⁻¹) was observed. Based on a multivariate regression model, a higher AUC was associated with lower annualized bleed rate (ABR) ($P < .05$).³¹

Enhancing bleed protection could enable PwHA to engage in activities that are closer to what is considered *normal*. FVIII activity levels above 50% of normal may enable individuals to participate in high-impact activities including sports without disease-related pain.^{2,25,30} FVIII levels of 5% to 40% of normal constitute mild hemophilia and have minimal impact on physical activity, and rigorous athletic activity may be possible for PwHA whose FVIII levels are 15% to 30%. Nevertheless, levels of physical activity should be assessed individually for each person with mild hemophilia A. For patients with moderate hemophilia (FVIII levels, 1%-5%), factor levels of 3% to 5% are needed to engage in mild physical activity.^{27,30} Patients with severe hemophilia (FVIII level, < 1%) have a high risk of spontaneous bleeds and pain even while minimally active. PwHA are less likely to experience bleeds as FVIII levels approach normal.²

Although certain PwHA appear to be *naturally coagulated*, many are still at risk for atherosclerosis and cardiovascular disease. In PwHA who require antithrombotic therapy, but have baseline FVIII levels above 20%, targeting higher levels may not be appropriate.³³

Approved Hemophilia A Therapies and FVIII Levels

For the treatment of hemophilia A, the FDA has approved 2 non-factor replacement therapies, a gene therapy, standard and extended half-life FVIII replacement therapies, and a high-sustained FVIII replacement therapy (Table).³⁴⁻⁵⁰ These therapies differ in their ability to sustain elevated FVIII trough levels.

Non-Factor Replacement Therapies

Emicizumab-kxwh (Hemlibra) is the first FDA-approved non-factor replacement therapy for hemophilia A.^{34,38} It is approved for routine prophylaxis to prevent or decrease the frequency of bleeding episodes in both adult and pediatric patients with hemophilia A regardless of the presence of inhibitors. The bispecific antibody binds to both activated factor IX and factor X, compensating for the missing activated FVIII needed to achieve hemostasis. It is administered subcutaneously (SC); following an initial 4-week loading period, it can be dosed weekly, every 2 weeks, or every 4 weeks.³⁴

Data from the HAVEN studies (NCT02622321, NCT02795767, NCT02847637, and NCT03020160) show that prophylaxis with emicizumab results in low bleed rates, reduces bleeds in target joints, and enhances QOL as compared to previous treatments.^{34,51,52} However, for emicizumab, determining FVIII equivalence in humans has not been possible, and the FVIII equivalence may not be enough to prevent breakthrough bleeds or enable participation in high-risk physical activities such as contact sports.⁵³

Marstacimab-hncq (Hympavzi), another non-factor replacement therapy, is the only FDA-approved tissue factor pathway inhibitor (TFPI) antagonist for the treatment of hemophilia A.⁵⁴ It was approved in October 2024 for routine prophylaxis to prevent

or reduce the frequency of bleeding episodes in patients aged at least 12 years with hemophilia A or hemophilia B and without factor inhibitors.^{36,54} This human monoclonal immunoglobulin G1 antibody neutralizes TFPI (the primary inhibitor of the extrinsic coagulation cascade) and thereby enhances coagulation. Marstacimab-hncq is administered SC at a recommended dosage of 150 mg once weekly after administration of a 300-mg loading dose.³⁶

Approval was based upon results of an open-label, multicenter, phase 3 trial demonstrating that 150 mg of marstacimab-hncq given once-weekly for 12 months to males aged 12 to 75 years with severe hemophilia A (and severe or moderate to severe hemophilia B) was superior to on-demand and routine prophylaxis with factor replacement therapy.^{54,55} Long-term safety, tolerability, and efficacy of marstacimab-hncq treatment have not been established; these are being evaluated in an open-label extension.⁵⁶

Gene Therapy

Valoctocogene roxaparvovec-rvox (Roctavian) is the only FDA-approved gene therapy for hemophilia A.^{35,38} Its use is approved for adults with severe hemophilia A without preexisting antibodies to adeno-associated virus serotype 5. In the liver, the agent introduces a functional copy of a transgene encoding a deleted form of FVIII, thereby expressing the deleted form and replacing the missing FVIII. Valoctocogene roxaparvovec is administered intravenously 1 time only.³⁵

Results of an open-label, multicenter, phase 3 trial demonstrated that men with severe hemophilia A treated with valoctocogene roxaparvovec showed an increase in FVIII activity and a reduction in bleeding sustained over 2 years.⁵⁷ However, FVIII expression is expected to decrease over time, and variability in FVIII activity levels both within and between patients has been observed by year

TABLE. Approved Therapies for Hemophilia A^{34-50,a,b}

Therapy type	Agent	Mechanism of action	Frequency of administration
Non-factor replacement therapy	Hemlibra (emicizumab-kxwh)	Bispecific monoclonal antibody that binds to both FIXa and FX and allows the coagulation cascade to continue despite deficient FVIII	Weekly to every 4 weeks
Non-factor replacement therapy (TFPI antagonist)	Hypnavzi (marstacimab-hncq)	Monoclonal antibody that targets TFPI, the primary inhibitor of the extrinsic coagulation cascade, and thereby enhances coagulation	Weekly
Gene therapy	Roctavian (valoctocogene roxaparvovec-rvox)	Introduces a transgene that encodes FVIII, which is transcribed by the liver. The resulting product replaces the missing factor VIII.	One-time dose
SHL recombinant FVIII replacement therapies	Advate (FVIII [recombinant]) Afstyla (FVIII [recombinant], single chain) Kovaltry (FVIII [recombinant]) Novoeight (FVIII [recombinant]) Nuwiq (FVIII [recombinant]) Recombinate (FVIII [recombinant]) Xyntha (FVIII [recombinant])	Exogenous FVIII that temporarily replaces missing endogenous FVIII	Every other day to 2 times per week
EHL recombinant FVIII replacement therapies	Adynovate (FVIII [recombinant], PEGylated) Eloctate (FVIII [recombinant], Fc fusion protein) Esperoct (FVIII [recombinant], glycopegylated-exei) Jivi (FVIII [recombinant], PEGylated-aucl)	Exogenous FVIII that temporarily replaces missing endogenous FVIII	Two times per week to every 4 days
High-sustained recombinant FVIII replacement therapies	Altuviiiio (FVIII [recombinant], Fc-VWF-XTEN fusion protein-ehtl)	Exogenous FVIII that temporarily replaces missing endogenous FVIII	Weekly

EHL, extended half-life; SHL, standard half-life; TFPI, tissue factor pathway inhibitor.

^aHuman plasma-derived concentrates have been FDA approved and may still be available.³⁸

^bClassification of FDA-approved recombinant FVIII replacement therapies is based on: Ay C, Napolitano M, Hassoun A, et al. Classification of recombinant factor VIII products and implications for clinical practice: a systematic literature review. *Haemophilia*. 2024;30(3):577-588. doi:10.1111/hae.15001.³⁷

2 following gene therapy. The causes of this variability are not well understood; they may involve molecular factors related to gene transfer and expression.^{57,58}

Standard and Extended Half-Life Recombinant FVIII Replacement Therapies

Individuals on regular prophylaxis with SHL FVIII replacement generally require infusions 3 to 4 times a week. Extended half-life (EHL) FVIII replacement therapies can be administered less frequently or, if given at the same frequency, can offer greater bleed protection.² Results of a meta-analysis of 11 clinical crossover, head-to-head studies of FVIII replacement therapies indicate that EHL products are associated with a different AUC when compared to one another, and with a greater AUC when compared with SHL products.⁵⁹

Data from the PROPEL study (NCT02585960) indicate that targeting higher trough levels with an EHL more effectively reduced bleed rates than did targeting lower trough levels. However, 72% of trial participants targeting the higher trough levels (~10%) required dosing at least every other day.⁶⁰ Such frequent dosing may necessitate central venous access devices in young children and could decrease adherence in adults and older children.^{2,61} Additionally, while increasing the frequency of FVIII replacement dosing has been shown to enhance quality of life in patients with severe chronic pain, it does not have the same effect in patients with mild or moderate pain.⁶²

High-Sustained FVIII Replacement Therapy

Efanesoctocog alfa (Altuviiio) is a first-in-class FVIII replacement therapy that was approved by the FDA in 2023 for routine prophylaxis of, treatment of bleeding episodes in, and perioperative management of adults and children with hemophilia A.^{50,63} The rFVIII analogue fusion protein is independent of the endogenous von Willebrand factor that imposes a half-life ceiling on other SHL and EHL agents; its use has been associated with a 3- to 4-fold prolonged half-life relative to those agents.⁵⁰

In the XTEND-1 study (NCT04161495), use of once-weekly efanesoctocog alfa offered superior bleed protection compared to previous standard-of-care FVIII prophylaxis; the mean ABR decreased by 77% (2.96 [95% CI, 2.00-4.37] to 0.69 [95% CI, 0.43-1.11] [$P < .0001$]). In the overall study population, efanesoctocog alfa demonstrated an acceptable safety profile, and no cases of inhibitor development to FVIII were observed. The independence of efanesoctocog alfa from von Willebrand factor may reduce interpatient pharmacokinetic variability compared to other rFVIII products, enhancing the predictability of FVIII activity levels over time.⁶³

Managed Care Considerations

The WFH guidelines for hemophilia A prophylaxis recommend that PwHA receive care from a comprehensive, multidisciplinary team of health care professionals specialized in hemophilia. This care

should be provided at a designated hemophilia treatment center or comprehensive care center, and the patient's relationship with the center should be maintained throughout their lifetime.²

Prioritizing Comprehensive Care and Individualized Treatment

The WFH advocates for a patient-centered approach to treatment and decision-making, where PwHA are seen as integral members of the comprehensive care team and as experts in managing their own hemophilia care.² Treatment adherence is a concern in hemophilia management, especially when PwHA transition to self-infusion during adolescence and assume full responsibility for their treatment in early adulthood.² Lower adherence is linked to decreased treatment effectiveness—it can result in bleeding and its complications.² Taking patient preferences, experiences, and values into account and having them agree to the treatment plan are essential for medication adherence and effective management.²

Dosage and frequency should be personalized, continuously monitored over time, and adjusted based upon bleeding patterns, body weight, and other factors.^{2,3} Monitoring tools consist of self-reporting, pharmacy reports, and the use of VERITAS-Pro, a validated questionnaire designed for patients or caregivers to evaluate adherence to FVIII prophylaxis.^{3,64} For FVIII prophylaxis, dosing can be tailored according to the patient's pharmacokinetic profile.³ This approach can enhance efficacy and minimize excess dosing; it also may lower the risk of inhibitor development, treatment nonadherence, and morbidity and overall treatment costs.^{2,65}

A meta-analysis of 73 studies showed that the primary barrier to adherence in patients with hemophilia was the perceived high burden of treatment, as it often involved frequent, time-consuming, and seemingly complex administration.^{2,66} Another barrier was the lack of perceived benefit from treatment. Because prophylaxis prevents bleeding and long-term complications, PwHA receiving prophylaxis may experience little to no burden from bleeding and may doubt the necessity of continuing treatment.^{2,66} This viewpoint, along with resulting complacency, may be most evident in children and adolescents with hemophilia A who have received excellent care and have not experienced significant bleeding or related complications.²

Along with regular checkups and treatment, care team members can provide personalized support and continuous education to patients and their families about the importance of a prophylaxis treatment plan, self-management skills, maintenance of a dosing and bleeding diary, and administration of home therapy.² Working with a specialty pharmacy and applying efficient utilization management strategies can improve outcomes and help manage costs.^{67,68}

Factors Hindering Access

Limited access to a comprehensive hemophilia care center and restrictions on medical insurance can serve as barriers to treatment

and adversely affect patient outcomes.² An analysis of data from August 2019 that were sourced from the Tufts Medical Center Specialty Drug Evidence and Coverage Database and health plan websites showed that coverage policies for hemophilia A differed across 17 commercial health plans. In all, 57% of 296 commercial coverage policies for 26 hemophilia A treatments covered a more limited patient population than specified by the FDA labeling.⁶⁹ Strict coverage requirements were primarily based on bleeding frequency and included restrictions such as requiring patients with mild or moderate disease to have experienced 2 or more spontaneous joint bleeds before approving reimbursement for FVIII therapy. Among the policies with additional coverage requirements, 30% included step-therapy mandates that required patients to fail other treatments before reimbursement for specific FVIII products would be given.⁶⁹

Conclusions

Despite the WFH target of zero bleeds for PwHA, standard-of-care prophylaxis does not prevent or reverse joint damage or change the rate of chronic pain reported by PwHA.^{2,4-6} Acknowledging this, WFH guideline authors advocate for maximizing FXIII trough levels.² Nevertheless, FDA-approved treatments for hemophilia A vary in their ability to sustain high FXIII levels.⁵⁷⁻⁵⁹ Replacement therapy with high-sustained FVIII activity offers an alternative mechanism of action that circumvents the half-life ceiling of other SHL and EHL agents.⁵⁰ Comprehensive care, individualized treatment, and overcoming barriers to treatment access constitute fundamental goals in the managed care of patients with this rare disease. ■

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