ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Beyond Factor Replacement Therapy: New and Experimental Agents for Hemophilia

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H&O What are the limitations of factor VIII administration to prevent and treat bleeding in hemophilia?

AV Factor VIII administration entails frequent intravenous infusions, which require travel to a health care facility unless the infusions are given at home. Some patients need to have a port implanted, which is an additional burden. Even with frequent infusions of factor VIII products, breakthrough bleeds still occur. Patients are vulnerable to spontaneous bleeds when factor VIII levels reach the trough level, which occurs regardless of whether the product has a conventional half-life or an extended half-life.

Another problem with the current clotting factor preparations is that they can lead to the development of inhibitors, which is most likely to occur in patients with hemophilia A. Patients in whom inhibitors develop generally require immune tolerance induction with daily infusions of high-dose factor VIII. If this approach is successful in eradicating the inhibitors, as it is in 70% to 80% of patients, standard bleeding prophylaxis with factor VIII can resume. In the remaining 20% to 30% of patients, factor VIIa-based bypassing agents are required to treat bleeds: either recombinant factor VIIa or factor VIII inhibitor bypassing activity, a plasma-derived product. This approach not only has a suboptimal effect but also leaves patients vulnerable to complications such as rapid joint deterioration and possibly even intracranial bleeding.

H&O What new agents are being used to achieve a normal hemostatic balance in patients with hemophilia?

AV The newest agents are non–factor-based agents. So far, the US Food and Drug Administration (FDA) has approved just one of them: the factor VIII mimetic emicizumab (Hemlibra, Genentech). This agent has been approved for several years now for the prevention of episodes of bleeding in adults and children who have hemophilia A with or without factor VIII inhibitors. Emicizumab is a bispecific antibody that links factors IXa and X, mimicking factor VIII cofactor function. The idea is to rebalance hemostasis rather than just replace a clotting factor product.

Emicizumab was first approved in 2017 for patients who have hemophilia A with factor VIII inhibitors on the basis of results of the phase 3 HAVEN 1 and HAVEN 2 trials. In HAVEN 1, which enrolled 102 adults and adolescents with hemophilia A who had inhibitors, emicizumab prophylaxis reduced the annualized rate of treated bleeding events from 23.3 to 2.9, an 88% reduction. In HAVEN 2, which enrolled 85 children with hemophilia A who had inhibitors, the annualized rate of treated bleeding events with emicizumab prophylaxis ranged from 0.2 to 2.2, depending on the dose.

In the phase 3 HAVEN 3 study, 152 people aged 12 years or older with hemophilia A who did not have factor

VIII inhibitors, a 96% to 97% reduction in treated bleeds occurred with emicizumab vs no prophylaxis. The phase 3 HAVEN 4 study also supported the use of emicizumab in adults and adolescents with or without inhibitors, with an annualized bleeding event rate of 0.6 for treated spontaneous bleeds**.** The most common treatment-related adverse event was injection site reaction, which occurred in 9 of 41 patients (22%).

Emicizumab is given subcutaneously rather than intravenously. The treatment interval can be once a week, once every 2 weeks, or once every 4 weeks depending on the dose given—less frequent administration requires larger doses. We have several years of experience with this drug in the clinic and know that it is relatively safe.

> Although fitusiran is an RNA interference therapy and concizumab is a monoclonal antibody, they have the same purpose—to enhance hemostasis.

One caution regarding emicizumab is that we need to be careful not to overestimate the balancing effect. We have very few data regarding which blood levels of emicizumab offer complete protection against breakthrough bleeding. The company uses factor VIII equivalency levels, but one cannot measure clotting factor activity or any drug activity. A mouse study by Ferrière and colleagues, published in *Blood* in 2020, suggested that emicizumab at 1.5 mg/kg (the usual weekly dose for patients with hemophilia) resulted in factor VIII–like activity of 9% in plasma. However, these equivalency levels are difficult to interpret in a clinical context, especially when breakthrough bleeding occurs.

H&O What experimental agents are being used to rebalance hemostasis?

AV The 2 agents that are farthest along in development are fitusiran and concizumab, both of which are being investigated in late-stage clinical trials. One of the advantages of these agents is that they are showing an effect in both patients with hemophilia A and those with hemophilia B, and in those with and without inhibitors. Like emicizumab, they are administered subcutaneously.

Fitusiran works by antagonizing antithrombin III (AT3), which is a natural anticoagulant that inhibits thrombin. When AT3 is reduced, thrombin formation is enhanced, resulting in more-balanced clot formation and stabilization. Concizumab works by binding to the Kunitz 2 domain of tissue factor pathway inhibitor (TFPI), which is another natural anticoagulant. This binding prevents TFPI from binding to factor Xa, so that the factor VIIa-tissue factor complex can produce enough factor Xa to achieve hemostasis. Although fitusiran is an RNA interference therapy and concizumab is a monoclonal antibody, they have the same purpose—to enhance hemostasis.

H&O What ongoing studies are looking at the use of fitusiran and concizumab?

AV The ATLAS clinical trial series is looking at fitusiran, and the Explorer clinical trial series is looking at concizumab. In results from the phase 3 ATLAS-INH trial, which Dr Guy Young presented at the 2021 American Society of Hematology (ASH) annual meeting, 57 patients with hemophilia A or B who had inhibitors were randomly assigned in a 2:1 ratio to prophylactic fitusiran or on-demand bypassing agents. The median annualized bleeding rate was 0.0 for fitusiran vs 16.8 for on-demand bypassing agents. In a related phase 3 trial of 120 patients with hemophilia A or B who did not have inhibitors, called ATLAS-A/B, prophylactic fitusiran reduced the annualized bleeding rate by 89.9% in comparison with on-demand factor concentrates. These results were presented by Pipe at the International Society on Thrombosis and Haemostasis (ISTH) 2022 congress.

In results from the phase 3 Explorer 7 trial, presented by Jiménez-Yuste at the ISTH 2022 congress, the median annualized bleeding rate in people with hemophilia A or B who did not have inhibitors was 0.0 with concizumab vs 9.8 for no prophylaxis. A companion study, Explorer 8, is looking at concizumab in people with hemophilia A or B who have inhibitors (NCT04082429).

H&O What are the drawbacks of fitusiran and concizumab?

AV Fitusiran confers a risk for thromboembolic complications, especially in conjunction with bleeds that require factor VIII rescue. In addition, liver enzyme elevations develop in approximately 20% of patients. With concizumab, approximately one-fourth of patients experience nasal pharyngitis. It is difficult to say what these side effects mean; we need to wait for the final clinical trial results to have clarity. We know that approximately 10%

to 20% of patients who receive fitusiran or concizumab experience injection site reactions, such as bruising and pain, but they are mild.

H&O What are some of the other strategies that are being investigated for the management of hemophilia?

AV One strategy is a factor VIII half-life extension therapy from Sanofi called efanesoctocog alfa, which received breakthrough therapy designation in June for use in hemophilia A. This novel fusion protein, which represents a new class of factor VIII replacement agents, is designed to provide high, sustained levels of factor VIII activity. In results from the phase 3 XTEND-1 trial that I presented at the most recent ISTH congress, patients had nearly normal factor VIII levels for the first 4 days after infusion and activity levels of approximately 10% to 20% at the end of the week before the next infusion. These are revolutionary results for patients who are comfortable using factor VIII products and wish to continue with the approach of replacing the clotting factor that is missing in the body rather than using rebalancing agents.

In addition, 2 gene therapies are close to being evaluated by the FDA. The first one, which is a factor VIII gene therapy from BioMarin, is valoctocogene roxaparvovec. This therapy received conditional marketing authorization in Europe, where it is known as Roctavian, for the treatment of severe hemophilia A in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5). BioMarin submitted a biologics license application for valoctocogene roxaparvovec to the FDA in September 2022.

The second gene therapy that is close to FDA evaluation is etranacogene dezaparvovec, which is an AAV5-based gene therapy for patients who have hemophilia B with a severe bleeding phenotype. The treatment was initially developed by uniQure and has since been acquired by CSL Behring. Etranacogene dezaparvovec uses the Padua variant of factor IX, so that its specific activity of factor IX is 5-fold higher than that of the regular factor IX. It is currently undergoing accelerated assessment by the European Medicines Agency. I expect both these products to be available in the United States soon. Overall, I see more promise with factor IX gene therapy than with factor VIII gene therapy because patients lose factor VIII expression over several years, and 70% to 80% of them require prolonged immune suppression with corticosteroids. In the meantime, we still have several exciting possibilities for treatment based on balancing of hemostasis, as well as a next-generation FVIII extended half-life product (efanesoctocog alfa) that should be available soon.

Disclosure

Dr Von Drygalski has received fees from ASC Therapeutics, BioMarin Pharmaceutical, Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Takeda, Regeneron, and uniQure for participation in industry-sponsored education events and advisory boards. She has received research funding from Bioverativ/Sanofi and Pfizer and is a co-founder and member of the board of directors of Hematherix.

Suggested Readings

Ferrière S, Peyron I, Christophe OD, Kawecki C, Casari C, Muczynski V, Nathwani A, Kauskot A, Lenting PJ, Denis CV. A hemophilia A mouse model for the in vivo assessment of emicizumab function. *Blood*. 2020;136(6):740-748.

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Young G, Srivastava A, Kavakli K, et al. Efficacy and safety of fitusiran prophylaxis, an siRNA therapeutic, in a multicenter phase 3 study (ATLAS-INH) in people with hemophilia A or B, with inhibitors (pwH) [ASH abstract 4]. *Blood*. 2021;138(suppl 1).