Practical Hematologist

Emerging Gene Therapies and Targeted Agents for Patients with Hemophilia

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What are the current challenges associated with managing hemophilia?

People with hemophilia A or B are missing a single clotting factor protein, either factor VIII (FVIII) or factor IX (FIX), respectively. This predisposes them to spontaneous and traumatic bleeding events. In their severest forms, repeated bleeding (which occurs primarily into joints) leads to progressive osteochondral damage and potentially crippling arthropathy. Thus, the foundation of care for hemophilia has been to provide therapeutics that can not only effectively treat bleeding when it occurs, but also prevent bleeding and avoid the complications of bleeding in order to preserve healthy joints and, ultimately, to allow persons with hemophilia to achieve good quality of life (QOL).

For several decades, we've been seeking to accomplish this prophylactically with clotting factor replacement therapy. However, this has left us with several unmet needs. Despite the effectiveness of prophylaxis, breakthrough bleeds still occur, and joint disease has not been completely abrogated in all patients. In addition, the treatment burden of prophylaxis is quite challenging as it requires regular, frequent, intravenous (IV) access to facilitate the infusions. Finally, up to a third of the patients with hemophilia A develop an immune response to the infused FVIII, necessitating the use of alternative, less-effective bypassing agents to treat those bleeds. As a result of these unmet needs, the overall health-related QOL of those with hemophilia is generally lower compared with unaffected peers.

What is gene therapy and how is this treatment approach being utilized in hemophilia?

The principle of gene therapy is to provide a new functional copy of the defective gene that can then code for the missing clotting factor protein. We know from existing therapeutic approaches that factor replacement therapy via IV infusion gives us repeated peaks and troughs with risk for bleeding increasing as the plasma factor level drops down to critically low levels. Novel gene therapy approaches represent a shift in the treatment paradigm because they provide a steady-state hemostatic effect that appears to be a key contributor to the enhanced efficacy of these therapies as compared to traditional factor replacement. Furthermore, with gene therapy, this effect may be achieved following a single treatment intervention, allowing for a drastically different picture in terms of treatment burden.

What is the data supporting gene therapy for hemophilia?

In severe hemophilia A, there is long-term follow-up data from the phase 3 GENEr8-1 trial for valoctocogene roxaparvovec, an investigational gene therapy.[1] The original study showed that this treatment reduced the mean annualized FVIII use and mean treated bleeding rate by 99% and 84%, respectively (both $P<0.001$).[2] One-year follow-up data from the study showed that patients receiving valoctocogene roxaparvovec experienced substantially reduced annualized bleeding rates (ABR), reduced FVIII utilization, and increased FVIII activity than they did in the year prior to study enrollment.[1] For hemophilia B, final analysis of the HOPE-B study of etranacogene dezaparvovec gene therapy showed that this therapy reduced the adjusted ABR by 64% ($P=0.0002$) and all FIX-treated bleeds by 77% ($P<0.0001$) over months 7-18, and eliminated the need for prophylaxis in 98% of subjects.[3]

What has been encouraging about these studies is the overwhelming impact of factor expression on bleed protection. After the single treatment event, the majority of patients have been able to discontinue prophylaxis without any significant bleeding. This really allows these patients to live their life unhindered; they are experiencing not only measurable improvements in some joint characteristics, but also improvements in overall health-related QOL. However, as we look forward to the approval of these gene therapies, we also have to establish methods of incorporating gene therapy into clinical practice, and potentially expanding the types of health professionals that are involved in therapy, particularly with regard to observed liver toxicity and the need for liver analysis.

Which patients are likely to qualify for gene therapy, if and when it is approved?

Patient selection will be key. Those who are going to be eligible for gene therapy are almost certainly going to match the characteristics of the patients that have been included in the clinical trial: adult men with no concurrent FVIII inhibitor and no history of inhibitor development. In addition, they will likely need evidence of good liver health, with assurance that any hepatitis C virus has been eradicated with antiviral therapies and that human immunodeficiency virus (HIV) is under good control. The presence of fatty liver disease may also be problematic, and we are likely going to develop cutoff criteria for what constitutes good liver health, particularly related to evidence of liver fibrosis. Finally, patients will need to be able to comply with the protocol, which requires intensive follow-up and ongoing assessment of liver enzymes and factor level.

What are anti-tissue factor pathway inhibitors (TFPIs) and how are they being developed for hemophilia?

Hemophilia occurs as a result of an imbalance between the procoagulants and the anticoagulants that leads to impaired thrombin generation. Current conventional treatment approaches (eg, factor replacement therapy or FVIII-mimetics) are designed to restore hemostasis by acting on the procoagulant side of the balance. However, alternative approaches

are also being investigated. Anti-TFPIs act on these anticoagulant pathways, and also restore sufficient thrombin generation and rebalance hemostasis. Because anti-TFPIs act on the anticoagulant pathway, they are effective for both hemophilia A or B, regardless of the presence or absence of inhibitors directed against FVIII or FIX. In this way, these agents are considered to be cross-platform therapies that may expand access to hemophilia treatment for a broad set of patients.

There are several anti-TFPIs in the hemophilia pipeline. Long-term results of concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors were recently presented as an extension of phase 2 trials. The estimated ABRs were 4.8-6.4, and the treatment was well-tolerated for a period of at least 76 weeks.[4] Similarly, the anti-TFPIs marstacimab was evaluated in patients with severe hemophilia A and B, with or without inhibitors, in a phase 2 study. Long-term treatment (up to 365 days) was shown to be well-tolerated and efficacious, with this treatment reducing mean ABR by 92.6% and 84.5% in the 300-mg QW cohort and 150-mg QW cohort, respectively.[5]

There are numerous challenges still associated with these agents that will need to be addressed if they are to be utilized effectively. The anti-TFPIs drugs exhibit what are called "target-mediated drug disposition." Once the drug and target elimination pathway become saturated, the clearance decreases and the half-life is prolonged substantially, meaning that the pharmacokinetics become non-linear. Another challenge with anti-TFPIs is that the target size is determined by the pool of endothelium TFPI, which can vary considerably between subjects. What that means is that after initiation of an anti-TFPIs, there is likely going to be a need for some sort of bioassay to determine the optimized dosing for patients to keep them in the target plasma level range.

What other innovations are likely to change the future of hemophilia treatment?

Certainly, bioengineering of FVIII and FIX has already led to improved pharmacokinetic profiles that extend their half-life in plasma, which reduces treatment burden while also maintaining higher trough levels. However, despite vast improvements in pharmacokinetics of FIX, these early bioengineering innovations really only had a modest impact on prolonging the half-life of FVIII. This is due to the affinity of FVIII for von Willebrand factor (VWF) in plasma, a primary stabilizer of FVIII, which has effectively placed a ceiling on the half-life for FVIII because it is linked to the clearance of VWF.

There is now a bioengineered molecule called BIVV001, or efanesoctocog alfa, which is able to stabilize FVIII independent from VWF in the plasma. This molecule is demonstrating an approximate five-fold prolongation of FVIII half-life, allowing for once-weekly dosing in order to achieve effective prophylaxis.[6] This agent currently has a Breakthrough Status from the FDA, and we are eagerly waiting to see how this agent will be received by regulators.

There is also a growing field of gene editing for hemophilia. Gene editing involves either insertion of a gene directly into the chromosomes of a patient or altering existing mutations to achieve normal expression of FVIII or FIX. The effects of gene editing strategies could be maintained, even in patients with growing livers (ie, infants and children), as opposed to current gene replacement strategies, which are designed to be applied to livers that have reached maturity. Considering the potential benefits of gene editing for a pediatric patient in attaining definitive bleed control early in life and avoiding all of the ensuing complications of bleeding and joint disease, this approach could have a significant impact on outcomes for this patient population.

In conclusion, I believe that the future of treatment for hemophilia is hopeful, and that patients with this disease are likely to experience dramatic gains in outcomes and QOL as these approaches are developed and perfected.

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