Expanding the Treatment Landscape for Patients With Hemophilia A

Source: Advances in Hemophilia A: Expert Guidance and Practical Case Discussions

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Historically, treatment of hemophilia A has revolved around replacing the missing factor VIII (FVIII) protein with a functional FVIII. This started in the 1800s with blood transfusions, progressed to plasma-derived concentrates, and finally led to the development of recombinant factors. Recombinant FVIII concentrates have been the mainstay of hemophilia A treatment for almost 20 years, and they have drastically reduced the risk of patients with hemophilia becoming inadvertently infected with blood-borne pathogens, such as HIV and hepatitis. However, replacement therapy can be burdensome for patients.

As we will discuss in an upcoming symposium in Orlando (link removed), emerging therapies have made strides to reduce the treatment burden for patients with hemophilia A, but there is still room for improvement.

Limitations of FVIII Replacement Therapies
The main limitations of FVIII replacement therapies are their frequent dosing - as often as every other day - their IV administration, and their inconsistent FVIII levels.

Extended half-life FVIII therapies require fewer doses and can be given every 3-5 days depending on the product. This decrease from 185 to just 90 infusions per year has substantially reduced the treatment burden. Nevertheless, extended half-life FVIII therapies still require IV administration, and there are adherence difficulties associated with IV infusions that increase the risk of bleeding and bleeding symptoms in patients.

Even patients who do adhere to their prophylactic treatment schedule have peaks and troughs of FVIII in the blood from infusion to infusion: The FVIII level in the blood steadily decreases between each dose, so there is never a consistent level. This creates difficulties for patients because it requires them to plan certain activities around their infusions, when they know their FVIII levels will be the highest.

Improving Therapies
Moving forward, there are multiple ways in which replacement therapy can be improved. First, a simpler and easier route of administration would greatly reduce the burden. Second, less frequent administrations would further improve the patient experience. Finally, treatments that maintain a consistent drug level between infusions rather than decreasing from infusion to infusion would also improve patient quality of life.

New nonfactor therapies improve upon some of these limitations. Emicizumab is currently the only approved nonfactor therapy and is licensed for the treatment of patients with hemophilia A with and without inhibitors. Emicizumab is a humanized bispecific monoclonal antibody that bridges activated factor IX and factor X, mimicking the function of the missing FVIII. Because it has no structural homology to FVIII, it is not expected to induce or be affected by inhibitors. Other benefits include subcutaneous administration with maintenance administration every 1-4 weeks and the ability to maintain a steady level in the blood.

Other novel treatments are entering phase III trials. These include therapies that rebalance the coagulation pathway, such as fitusiran, the siRNA that targets antithrombin, and concizumab, an antibody that targets tissue factor pathway inhibitor. These essentially "remove the brakes" at various points of the coagulation pathway by decreasing coagulation inhibitors. Like emicizumab, they can be administered subcutaneously, mitigating the negative effects of IV infusions.

Gene Therapy

The ultimate goal of new therapies would be a single-dose treatment that would functionally cure hemophilia by normalizing functional FVIII levels for the life of the patient. Gene therapy treatments that introduce a functional FVIII gene through viral vector delivery to the liver are attempting to accomplish this. Although there are still questions regarding durability, and it is unclear if gene therapy will normalize FVIII levels for one's entire life, even 5-10 years would greatly reduce the treatment burden compared with current treatments. Several of these therapies are in phase II or III clinical trials, so we continue to await results on safety, efficacy, and durability.

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