Clinical Advances and Challenges in Gene Therapy for Hemophilia

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The goal of hemophilia treatment is to normalize hemostasis and optimize health and well-being. The aspirational promise of gene therapy is to provide safe, durable factor expression at a level sufficient to prevent bleeding in all recipients. Adeno associated viral (AAV) vectors for both hemophilia A and hemophilia B have recently received regulatory approval in several countries. These approvals were based on pivotal phase 3 studies in both hemophilia A and hemophilia B that demonstrated multiyear clinical efficacy with decreased annualized bleeding rates without major safety concerns. Most treatment related adverse events involved infusion reactions and elevations of liver enzymes without evidence of liver injury. Elevations in liver enzymes in some recipients were associated with decreased transgene-factor levels, which responded to corticosteroids for many but not all recipients. Gene therapy for hemophilia B benefits from the widespread use of the hyperactive factor IX variant Padua (R338L). However, several challenges still remain for AAV-based approaches for gene therapy, including 1) variability of transgene-factor level between recipients, 2) multiyear decreases in factor VIII level, and 3) exclusion of children, females, and people with high-titer pre-existing anti-AAV antibodies or inhibitors. The current high costs of approved products also limits worldwide availability. Though accruing results support the long-term durability for hemophilia B AAV gene therapy products, long-term efficacy and safety remains unknown.

To address these limitations of current gene therapy for hemophilia A and B, new approaches are being investigated. Next-generation AAV strategies for hemophilia A using gain-of-function factor VIII variants—analogous to the used of factor IX Padua for hemophilia B—have entered clinical trials, though several safety concerns including immunogenicity remain. Gene editing targeting safe harbors using dual AAV and lipid nanoparticle delivery of Cas9 are being investigated for both hemophilia A and hemophilia B. Ex vivo hematopoietic stem cell approaches have recently reported encouraging early phase proof-of-concept clinical trial results for hemophilia A and an ex vivo B cell approach for hemophilia B has recently entered clinical trials.

People with hemophilia and their medical teams are confronted with an expanding array of therapeutic options. This range of treatment choices allows people with hemophilia to prioritize and balance aspects of the drugs most important to them, such as hemostatic efficacy, safety considerations, and convenience of administration. Though gene therapy for hemophilia continues to advance, it has yet to redeem its promises; however, the continued development of the field warrants cautious optimism.