BLOOD ADVANCES TALK

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Gene therapy for hemophilia: anticipating the unexpected

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Abstract

The treatment of hemophilia, which has undergone many transformative changes over the past 60 years, is poised for yet another disruptive change: the use of gene therapy to produce functional cures in some persons with hemophilia A or B. The path toward achieving subnormal to normal levels of factor VIII and factor IX activity has not been straightforward and is littered with failures over these past 25 years. Through setbacks and iteration, adeno-associated virus (AAV) proved to be a useful vector to carry the factor VIII and IX transgenes; once cassettes were optimized and dose escalation proceeded, therapeutic levels of clotting factors were achieved by several groups. Because these transgenes produce fully active proteins, breakthrough bleeding and the use of exogenous clotting factors have nearly been eliminated for most clinical trial participants when they express a sufficient amount of protein. These first-generation gene therapies, which have initiated regulatory review, will decrease or eliminate the burden of hemophilia for many of the patients who are eligible to receive them. However, many are ineligible, including those who are seropositive or cross-reactive to multiple AAV serotypes, children, those with comorbid conditions, and those who live in countries where even the most basic plasma-derived clotting factors are not reliably available. Thus, although the first-generation gene therapies will have an important impact on the burden of hemophilia, many questions remain to be answered regarding safety, durability, and reliability as this technology advance progresses toward individuals worldwide with hemophilia.

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The complete text of this *Blood Advances* Talk is available as a data supplement.

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