



GENE THERAPY

Comment on Bolous et al, page 1677

Royal gene therapy at a royal cost

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In this issue of *Blood*, Bolous et al¹ analyze the cost-effectiveness of factor IX gene therapy in patients with severe hemophilia B, in a microsimulation Markov model.

Hemophilia is an X-linked disease that affects 400 000 people worldwide, of whom 15% have hemophilia B caused by deficiency of factor IX (FIX), which affected the offspring of Queen Victoria, the most famous carrier. In those with severe deficiency (<1% factor IX activity), the disease is characterized by spontaneous and traumatic bleeding, primarily into joints, which leads to chronic arthropathy, disability, and pain. Current management requires factor infusion several times weekly to prevent bleeding episodes (prophylaxis) and early, intense treatment of acute breakthrough bleeding. Unfortunately, the invasiveness of several times weekly

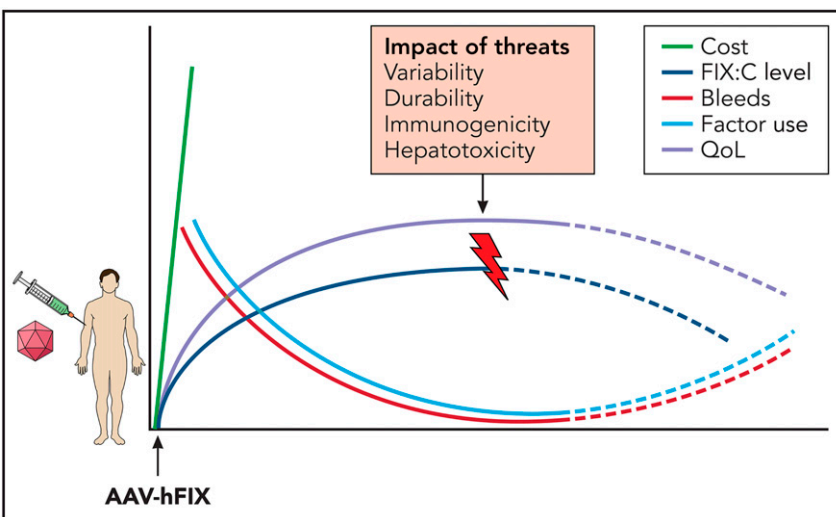
IV therapy deters compliance, and the high cost deprives those in resource-poor settings of life-saving treatment.

Clearly, better therapeutic approaches are needed. The emerging novel agents in development for hemophilia provide great promise. Among these, the “one-and-done” concept of gene therapy is most compelling from a compliance perspective as well as from a global perspective. The goal of gene therapy is to avoid bleeding events in joints and other tissues by long-term factor expression, which generally requires a factor level of 15% or higher. In hemophilia gene therapy,

adeno-associated virus (AAV), which is nonpathogenic in humans, is used to package the gene of interest, in this case human factor IX (hFIX). The AAV-hFIX transgene is intravenously injected, targeting the hepatocyte where FIX is synthesized, and commandeers the hepatocyte nuclear machinery to express and secrete FIX protein into the circulation. (AAV is to be distinguished from adenovirus [Ad] COVID vaccines).

Currently, there are 2 active clinical gene therapy trials for hemophilia B: the Spark/Pfizer bioengineered vector capsid FIX Padua transgene, fidanacogene elaparvovec (PF-06838435; www.clinicaltrials.gov #NCT03861273²), and the UniQure AAV5-FIX Padua construct, etranacogene dezaparvovec (AMT-061; #NCT03569891).³ The FIX-Padua gene, used in each, is a naturally occurring FIX missense mutation associated with eightfold greater specific activity than wild type,⁴ which allows for lower vector dose and potentially fewer adverse effects. To date, these studies demonstrate >90% reduction in bleeding events and factor use, with sustained factor expression for up to 3 years.

In this setting, Bolous and colleagues employed a microsimulation Markov model to compare the cost of single-dose gene therapy vs the cost of lifelong factor prophylaxis and bleeding complications during on-demand, acute bleeding management, orthopedic surgery, and hospitalization in a sample cohort of 500 000 men ≥18 years of age with severe hemophilia B and no past or current inhibitor. The primary end point was annualized bleeding rate, now preferred over factor levels as a direct measure of hemophilia severity. They assessed microsimulation by probabilistic sensitivity analyses, varying multiple parameters across individual-level disease trajectories, and using literature-based, joint-related disutilities. Estimating the cost of gene therapy at \$2 million, the outcome measured in quality-of-life years (QALYs) indicated that hemophilia B gene therapy was more



The cost of gene therapy is balanced against the benefits, including reduced bleeding episodes and factor use and improved quality of life, and the potential threats, including the variability and durability of gene expression, immunogenicity, and hepatotoxicity. Professional illustration by Somersault18:24.

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effective than standard factor-based therapy in >90% of simulations, consistent with findings of cost-effectiveness analyses for hemophilia A gene therapy.⁵ In general, although the price of gene therapy is steep, it is not as costly as factor, orthopedic surgery, bleeding management, and hospitalization over an adult lifetime.

Although these are encouraging findings, much work remains. Novel approaches are needed to adapt current vector-gene technology for those excluded from gene therapy: those with inhibitor alloantibodies, natural AAV antibody,⁶ and active hepatitis B or hepatitis C liver disease.

Approaches to hepatocyte rescue may be needed in individuals who no longer express the transgene because of concomitant drug toxicity, nonalcoholic steatohepatitis, or viral cirrhosis, which is not uncommon in the hemophilia population.⁷ Efforts to develop steroid-sparing immunosuppression or vector decoys to reduce the host anti-AAV capsid T-cell response that limits gene expression⁸ is critical. Finally, careful surveillance is important for determining long-term risks, such as AAV integration and hepatocellular cancer (HCC),⁹ given the continuing risk for HCC in those with hemophilia¹⁰ (see figure).

In summary, it is exciting to consider that after years of complications of hemophilia factor therapy, including inhibitor formation, hepatitis, and HIV, it is now possible to receive a single dose of gene therapy and achieve therapeutic factor levels sufficient to prevent bleeding episodes and avoid factor use and its complications, while providing hope for those globally affected and achieving an improved quality of life.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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HEMATOPOIESIS AND STEM CELLS

Comment on Yu et al, page 1691

Epigenetic plasticity of erythroid progenitors

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In this issue of *Blood*, Yu et al,¹ report unexpected cell fate plasticity in erythroid progenitors (EPs) whereby removal or inhibition of the chromatin modifier LSD1 (also called KDM1a) triggers lineage conversion toward a myeloid fate, both in vitro and in vivo. This finding is important because it shows that progenitors that are typically thought of as being committed to the erythroid lineage have in fact retained the potential to differentiate toward other hematopoietic lineages. Furthermore, these findings provide strong support for the idea that active lineage restriction through epigenetic mechanisms, rather than irreversible loss of cell fate potential, underlies cell differentiation in hematopoiesis.

The search for strategies to reactivate fetal γ -globin genes expression in adult erythroid cells dates back to the discovery that even a small increase in the level of fetal hemoglobin is enough to significantly alleviate symptoms of β -globinopathies, including sickle cell disease and β -thalassemia.² This early finding set the stage for decades-long research that led to the identification of multiple factors that inhibit fetal γ -globin genes expression, including transcriptional repressors (eg, BCL11A³) and chromatin-modifying enzymes. Although recent gene therapy trials targeting BCL11A have shown great promise for patients with sickle cell disease or β -thalassemia,^{4,5} the development of pharmacological agents to reactivate fetal hemoglobin

remains a priority. A promising target for pharmacological induction of fetal hemoglobin is LSD1, an epigenetic enzyme that interacts with BCL11A and represses γ -globin genes transcription through the removal of active histone marks H3K4me1 and H3K4me2.⁶ Although previous studies showed that LSD1 inhibitors increase fetal hemoglobin levels in animal models,⁷ these chemicals also partly block erythroid differentiation, and the effects of prolonged loss of LSD1 activity in erythroid cells remain unknown.

To address this question, Yu et al began by generating a new transgenic mouse model whereby a specific knockout can be induced exclusively in the erythroid lineage starting at the megakaryocyte-EP