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REVIEW ARTICLE

Hemophilia gene therapy: first, do no harm

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Abstract

The introduction of adeno-associated virus–mediated, liver-directed gene therapy into the hemophilia treatment landscape brings not only great promise but also considerable uncertainty to a community that has a history punctuated by the devastating effects of HIV and hepatitis C virus. These infections were introduced into people with hemophilia through the innovation of factor concentrates in the 1970s and 1980s. Concentrates, heralded as a major advance in treatment at the time, brought devastation and death to the community already challenged by the complications of bleeding into joints, vital organs, and the brain. Over the past 5 decades, considerable advances in hemophilia treatment have improved the survival, quality of life, and participation of people with hemophilia, although challenges remain and health equity with their unaffected peers has not yet been achieved. The decision to take a gene therapy product is one in which an informed, holistic, and shared decision-making approach must be employed. Bias on the part of health care professionals and people with hemophilia must be addressed and minimized. Here, we review data leading to the regulatory authorization of valoctocogene roxaparvovec, an adeno-associated virus 5 gene therapy, in Europe to treat hemophilia A and etranacogene dezaparvovec-drlb in the United States and Europe to treat hemophilia B. We also provide an overview of the decision-making process and recommend steps that should be taken by the hemophilia community to ensure the safety of and optimal outcomes for people with hemophilia who choose to receive a gene therapy product.

KEYWORDS
efficacy, gene therapy, harm, hemophilia, safety

1 | INTRODUCTION

Hemophilia is a lifelong inheritable bleeding disorder due to the deficiency of the activity of coagulation factor VIII (FVIII) (hemophilia A) or factor IX (FIX) (hemophilia B) [1]. Living with hemophilia has a significant impact on health-related quality of life due to the impact of frequent bleeding events, economic burdens associated with health care resource utilization, and mental health burden [2,3]. Without

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treatment, people with hemophilia (PwH) can bleed internally because of trauma, but sometimes spontaneously, from everyday activities with no apparent cause. This bleeding can lead to severe joint damage and permanent disability or can even lead to death if a bleed involves major organs and/or the brain [1]. Prevention of bleeding with medications derived from human blood plasma or created by recombinant DNA technology is highly effective but extremely burdensome and expensive [4–12]. Newer advances in recombinant DNA technology have reduced but have not eliminated therapy burden [13,14].

The care, treatment, and support provided for PwH over the past 5 decades have steadily advanced, resulting in improved health outcomes in countries with the economic capacity to afford them [15]. This is largely due to widespread availability of integrated, comprehensive, and multidisciplinary care [16] and access to innovative products used to prevent bleeding [17]. For PwH who have had consistent and fully optimized access to these treatment advances, life expectancy [18–20] and quality of life have improved and, in some countries, are approaching those of their unaffected peers [21,22], but in countries unable to provide diagnosis and afford treatment, morbidity and mortality remain high and participation in activities of daily life continues to be impacted by the disease and its treatment [23–29]. None the less, even in high income countries, generational differences exist as access to comprehensive care and preventative treatments have differed and were only first implemented in the 1970s [30–35] but were not widespread until decades later. The burden of joint disease due to repeated bleeding and chronic infection due to treatment products contaminated with viral pathogens also have added to the morbidity and mortality of PwH. Today, access to care and treatment is not universally available to all PwH as those with nonsevere disease and girls and women [36] still experience challenges with access to care. These challenges are magnified in low and low-middle income countries, where most PwH have not been diagnosed [29]. However, even then, there are lifestyle choices and education, career, and work decisions that PwH must make that require consideration of their underlying hemophilia. Moreover, these outcomes come with the burden of treatment, requiring regular intravenous injections of clotting factor concentrates or subcutaneous administration of a bispecific monoclonal antibody, which functions as a FVIII mimetic [11,12,37]. Ongoing access to treatment products and adherence to the treatment plan are requisites to ensure optimal outcomes [38,39].

In the early 1990s, hemophilia was identified as an ideal test case for gene therapy as it is a monogenic disorder with a clearly defined phenotype and a wide therapeutic window. Moreover, preclinical transgenic mouse models could be created and dog models existed [40]. The hemophilia community has long awaited the availability of a "cure" that would provide optimal outcomes while alleviating the burden of treatment with a safe, 1-time administration achieving predictable and durable levels of FVIII or FIX to prevent bleeding and the need for chronic treatments [41–44].

In 2022, the European Medicines Agency granted conditional marketing authorization to valoctocogene roxaparvovec (AAV5-hFVIII-SQ), an adeno-associated virus (AAV) 5 gene therapy to treat hemophilia A [45], and the US Food and Drug Administration (FDA) granted approval to etranacogene dezaparvovec-drlb (AAV5-FIX Padua) to treat hemophilia B [46]. This was also granted conditional marketing authorization by the European Medicines Agency in early 2023. An excellent review of ongoing hemophilia A and B AAV gene therapy trials can be found in the publication of Samelson-Jones and George [47].

2 | HEMOPHILIA A. SUMMARY OF CLINICAL TRIAL DATA FOR VALOCTOCOGENE ROXAPARVOVEC

A phase 1/2 dose-escalation study of valoctocogene roxaparvovec enrolled 13 participants, 7 of whom received 6e13 vector genomes per kilogram (vg/kg) body weight and 6 of whom received 4e13 vg/kg in a single dose of an AAV-5 vector expressing the B-domain–deleted form of FVIII. Treatment-related adverse events in year 1 were reported by 86% of participants who received 6e13 vg/kg and by 100% of those who received 4e13 vg/kg, but only 1 in this latter group was classified as a treatment-related serious adverse event. Elevation of the alanine aminotransferase (ALT) liver enzyme was common and occurred in approximately 85% of participants in year 1 in both dosing cohorts. Infusion-related reactions occurred in 43% and 67% of recipients, respectively. The gene transfer resulted in an elevation in the plasma FVIII level in most participants. For the 7 participants who received 6e13 vg/kg, the mean (SD) and median FVIII activity after 5 years of observation were 11.6 (12.2) and 8.2%, respectively, as measured by chromogenic substrate assay (CSA) and 18.7 (17.5) and 15.7% IU/dL, respectively, as measured by 1-stage assay. For the 6 participants who received 4e13 vg/kg body weight, after 4 years of observation, the FVIII activity was 5.6 (5.6) and 4.8%, respectively, as measured by the CSA and 9.5 (7.0) and 7.5%, respectively, according to a 1-stage assay [48–50].

The phase 3 trial of valoctocogene roxaparvovec enrolled 134 men with severe hemophilia A, including 132 who were HIV negative. Participants received a single dose of 6e13 vg/kg AAV5-hFVIII-SQ. All participants experienced at least 1 adverse event, and 16% reported a serious adverse event. Similar to the phase 1/2 trial, elevations of ALT were a common occurrence in 86% of participants (79.1% of participants received steroids for a median treatment duration of 230 days), and all were treated with immune suppression. After a median follow-up of 110.9 weeks (range, 6.1-197.4), data were available for 132 participants. In the postprophylaxis period, the mean annualized treated bleeding rates were 1.2, 0.5, and 0.6 bleeding events per year at years 1, 2, and 3, respectively. At these same time points, the median values were all zero. The median FVIII activity by CSA was 11.2, 6.4, and 4.6 IU/dL at years 1, 2, and 3, respectively. Remarkedly, 31 of the original 134 participants enrolled who remained in the study at 2 years had a median FVIII activity of <5% as measured with a CSA [51,52].

3 | HEMOPHILIA B. SUMMARY OF CLINICAL TRIAL DATA FOR ETRANACOGENE DEZAPARVOVEC-DRLB

The precursor of etranacogene dezaparvovec-drlb, AMT-060, was studied in a phase 1 to 2 trial that enrolled 10 participants in 2 cohorts, with participants receiving 5e12 or 2e13 vg/kg body weight. AMT-060 consists of an AAV-5 capsid and a liver-specific promoter driving expression of a codon-optimized wild-type human FIX gene [53]. The product was deemed safe, but FIX expression levels achieved were 5.2% and 7.4% for 5e12 and 2e13, respectively, and thus were considered to be below the desired therapeutic range [54]. Therefore, it was decided to change the transgene to the high specific activity FIX Padua (R338L) variant (AMT-061) for continued development.

Etranacogene dezaparvovec (AMT-061) is identical to AMT-060 aside from the 2 nucleotide substitutions in the FIX coding sequence to reflect the R338L conversion to the Padua variant. A small phase 2b trial was performed with AMT-061, in which 3 participants received 2e13 vg/kg. No safety signals were reported, and FIX plasma levels were 33, 51, and 57 IU/dL at 26 weeks using a 1-stage activated partial thromboplastin time assay [55].

The open-label, phase 3 study included 54 participants with an FIX activity of <2% of the normal value. No treatment-related serious adverse events were reported. There was an increase in ALT level, which was considered treatment-related in contrast to valoctocogene roxaparvovec 17% of the participants received tapering courses of glucocorticoids for transient ALT elevations. One case of hepatocellular carcinoma (HCC) that occurred 12 months after treatment was reported in a participant who had multiple independent risk factors. The etiology of the HCC was "undetermined" and considered to be unrelated to the vector [56]. The annualized bleeding rate (ABR) decreased from 4.19 during the lead-in period prior to administration of the gene therapy to 1.51 during months 7 through 18 after treatment. The usage of FIX concentrates decreased by a mean of 248 825 IU per year per participant [57].

4 | EFFORTS TO PROTECT PATIENTS FROM HARM

In 2022, the National Hemophilia Foundation submitted a citizen petition (docket number FDA-2022-P-1444-0001) to the FDA requesting that a risk evaluation and mitigation strategy (REMS) be required as a condition of approval for both valoctocogene roxaparvovec and etranacogene dezaparvovec. Other organizations including the World Federation of Hemophilia, Hemophilia Federation of America, and the European Haemophilia Consortium joined this effort submitting separate but supportive statements to the FDA. However, the FDA reasoned that the requirements for the REMS for etranacogene dezaparvovec were not met, and it has received marketing authorization from the FDA without the requirement for the REMS. While this may be the case for people living with hemophilia B, for whom the benefit to risk equation for gene therapy is generally favorable [58], it may not be the same for people with hemophilia A when considering gene therapy. Standard and extended half-life products for the prevention of bleeding for people living with either hemophilia A and B may provide very good outcomes but at a substantial burden of treatment and also fail to prevent all bleeding. The introduction of the monoclonal antibody emicizumab for prevention of bleeding in people with hemophilia A has markedly reduced the treatment burden as this product is administered by subcutaneous injection and on a less frequent basis while also improving bleed control. A similar option for people with hemophilia B is not yet available. In addition, the short- and long-term unknowns of hemophilia A gene therapy combined with its uncertainties of safety and durability argue for a more cautious approach [59]. Valoctocogene roxaparvovec remains under evaluation with a Prescription Drug User Fee Act date of June 30, 2023.

A postmarketing study to assess the association between the serious risk of bleeding related to the failure of expected pharmacological action of HEMGENIX and preexisting anti-AAV5 NAb to the capsid of HEMGENIX with a validated assay (required in postmarketing requirement 1). The study will evaluate at least 35 patients with hemophilia B treated with HEMGENIX to include at least 10 patients with high (1:1400 or higher) pretreatment anti-AAV5 NAb titers. The assessment will compare pretreatment and posttreatment ABRs, with a lead-in period, to establish the patients' baseline ABR on routine treatment and that at the 18-month follow-up after HEMGENIX administration (Hemgenix Biologics License Application Approval Letter BL 125772/0 November 22, 2022).

5 | THE REMS PROGRAM

The FDA is responsible for the review, approval, and postmarket monitoring of drug products in the United States. The usual case for most drugs is that the prescriber information contained in the FDA-approved label is sufficient to give health care providers (HCPs) the necessary information regarding the safety and effective use of the drug to ensure that the benefits of the drug outweigh its risks. In some cases, especially when there are unknowns, additional risk mitigation measures beyond prescriber information may be necessary to protect patients from potential harm. These products may still be approved with the addition of a REMS [60,61].

Another approach is a restrictive introduction, such as a conditional marketing authorization in which a medicine fulfills an unmet medical need but there is still a need for comprehensive safety, efficacy, and quality data generation after approval [62]. Such approvals are granted for 1 year but can be renewed annually. Compliance with specific obligations with defined timelines is a necessary prerequisite for continued authorization [63]. This mechanism was utilized in the case of onasemnogene abeparvovec, an AAV9 gene therapy for spinal muscular atrophy [64].

The essential elements of a REMS program would help to ensure the safety and optimal outcomes for PwH who choose to receive a gene therapy product. The current standard of care for PwH living in the United States results in an excellent quality of life because of

access to comprehensive, integrated care and the most technologically advanced treatments for hemophilia. Gene therapy is a complex biological "drug" for which, despite 30 years of development, there are many unresolved questions, and the unknowns remain top of mind for clinicians and PwH alike [59]. Evaluation of the risks and benefits of any new therapy requires careful consideration of all the available information, and a shared decision-making approach should be employed [65–67]. This is particularly important in the consideration of gene therapy, given the fact that AAV-mediated gene therapy is a 1-time irreversible therapy. A fully informed decision must be ensured and a robust shared decision-making approach is mandatory for these therapies. Both known and unknown adverse events occur after administration of gene therapy products for hemophilia. Steroid use and the associated complications should be carefully monitored and reported given the reported use of glucocorticoids in the 2-year data analysis of valoctocogene roxaparvovec (79.1% of participants received steroids for a median treatment duration of 230 days), and the high proportion of related adverse events that were reported. Additionally, recent events with hemophilia AAV gene therapy, including thrombosis, requirement for acute and prophylactic anticoagulant treatment, as well as at least 3 additional reports of cancer following the original HCC event (all deemed unrelated to the vector) [56,68,69], highlight the many considerations for PwH. Long-term data assessing safety and efficacy from all PwH who receive a gene therapy should be collected using a standard set of outcome measures and instruments such as the coreHEM core outcome set [2] that represents the most important outcomes to PwH [3,70,71]. These outcomes should be collated into national registries and aggregated into the global gene therapy registry initiated by the World Federation of Hemophilia to facilitate early signal detection [2,3,72,73]. Special attention should be focused in the areas of short-term adverse events (liver toxicity, short-term immune response to FVIII/FIX, immune response to gene therapy, and thrombosis), long-term adverse events (development of other disorders, vector integration into host genome, and duration of vector-neutralizing response) and mortality [2].

The expected benefit of gene therapy to a PwH is that this 1-time therapy relieves patients from the treatment burdens of ongoing prophylaxis and the significant risk of bleeding and the associated comorbidities and impact on health-related quality of life when their circulating FVIII/IX activity level drops below a therapeutic level [74–76]. However, gene therapy requires rigorous adherence to a demanding follow-up regimen by the patient, which includes significant lifestyle modifications, including abstinence from alcohol ingestion and use of barrier contraception for a minimum defined period of time. Similarly, the health care ecosystem within which the gene therapy is delivered must be prepared [77–79]. Currently, the efficacy data for both valoctocogene roxaparvovec and etranacogene dezaparvovec-drlb demonstrate similar impacts on bleeding rates compared with factor replacement therapy in adherent PwH. Given this, the risks of the therapy must be clearly understood, and Panglossian thinking regarding gene therapy must be eliminated by clinicians and PwH [80].

If the goal is a lifelong effect following gene therapy, the durability of the effect on factor activity levels and/or ABRs is important in the decision making of the PwH [81]. For example, in hemophilia A those who received valoctocogene roxaparvovec, the year-over-year decline in FVIII activity was evident [48,51]. Using values from a chromogenic substrate FVIII assay, 23.5% of participants who had at least 104 weeks of follow-up had a median FVIII activity of <5 IU/dL, and 13.6% of participants had a median FVIII activity of <3 IU/dL at year 2 following administration of valoctocogene roxaparvovec [51]. Among these, 6 participants resumed regular prophylaxis after gene therapy. Mahlangu et al. [51] d the "half-life" of the gene therapy to be 2.5 years using FVIII activity values collected from week 76 to 104 and entered into a pharmacokinetic model, which was then used to extrapolate individual FVIII activities for years 3, 4, and 5. Median FVIII activity was 11.2, 6.4, and 4.6 IU/dL at years 1, 2, and 3, respectively. Similar year-to-year downward trends in FVIII activity were also shown in a recent review [47] that included other FVIII gene therapies, including SB-525 and SPK-8011 [82].

What we do know is that in approximately one-quarter of PwH who receive valoctocogene roxaparvovec the FVIII level falls to <5% after 2 years (31 of 134). Because of the immune response to the vector capsid, induction of very high levels of long-lasting neutralizing antibodies against the capsid, and cross-reactivity with other AAV serotypes, redosing with any other currently identified AAV vector is not possible, therefore limiting the administration to a 1-time opportunity. At present, no solution exists to overcome this problem, meaning that if patients get suboptimal responses or lose activity over a comparatively short period, they have lost their opportunity for subsequent AAV gene therapy. Immunologic and nonimmunologic processes that may limit durability are actively being explored, and strategies to intervene will need to be tested [83]. Until a solution is identified, the duration of the effects of the treatment is lifelong.

The outlook for those with hemophilia B following FIX gene therapy may be different. Data collected after administration of a novel self-complementary AAV8 vector have demonstrated stable FIX activity for 7 years after dosing [84], and an AAV5-expressing wild-type FIX has similarly shown stable levels over time [53]. After administration of a single dose of etranacogene dezaparvovec-drlb, participants were observed to have stable FIX levels for 3 years after dosing [85]. Statistical modeling was used to estimate long-term durability of FIX activity levels after a single dose of etranacogene dezaparvovec-drlb, which showed a durable effect for 25.5 years [86].

Health equity is a goal for the hemophilia community in the United States and internationally [87]. Adequate treatment, which is not available for 80% of the world's 400 000 PwH [88,89], makes the development of a cure compelling. Clinical trials have imposed exclusionary criteria—age of <18 years, women with hemophilia, people with mild forms of hemophilia, people with preexisting immunity to AAV5, history of an inhibitor, and/or significant liver disease, along with other exclusion criteria—that reduce the eligible population. The lack of heterogeneity in clinical trials is increasingly being recognized as an important omission in clinical trial design. Clinical trials have not historically been balanced to reflect race and ethnicity thus lacking representativeness in trial data for segments of the target population for the therapy. Expansion of the opportunities

to receive gene therapy to these populations must be a priority for the community and a mandate to be followed by the drug developers. Achieving equity in the development of and access to gene-targeted therapies will not only require innovations in research, clinical, regulatory, and reimbursement frameworks but also necessitate increased attention to the ethical, legal, and social implications when establishing research paradigms and translating research results into novel interventions for rare genetic diseases [90].

In the end, many PwH will choose not to receive gene therapy at this time for a variety of reasons, including the complexity and uncertainty of the gene therapy product and the required follow-up. It is also likely that many will consider these current gene therapy treatments to be "inadequate" and not living up to the expectations of the community for a cure [91] given the declining FVIII levels following valoctocogene roxaparvovec administration. The unknown effects of gene therapy in both the short- and long-term are also likely to impact decision making. The psychosocial impacts of gene therapy must also be considered as the loss of identity and the "burden of normalcy" as the PwH transitions to a symptom-free life may weigh heavily on some PwH [91–93].

6 | RECOMMENDATIONS

Here, we recommend that the following steps be taken by the hemophilia community to ensure the safety and optimal outcomes for PwH who choose to receive a gene therapy product:

1. Training and education must be provided for physicians and HCPs on gene therapy and the management of PwH who receive a gene therapy product [77,78].
2. Training and education on shared decision making must be provided for physicians and HCPs who will evaluate, administer, and follow PwH who are candidates to receive a gene therapy product [67,94–96].
3. Facilities administering valoctocogene roxaparvovec and etranacogene dezaparvovec must receive adequate training and instruction on all aspects of gene therapy [78,97].
4. Valoctocogene roxaparvovec and etranacogene dezaparvovec must only be administered at or in conjunction with a hemophilia treatment center with knowledge and expertise in evaluating, administering, and managing PwH who have received investigational gene therapy products [77,79].
5. Individuals receiving valoctocogene roxaparvovec and etranacogene dezaparvovec must be enrolled in the global gene therapy registry initiated by the World Federation of Hemophilia in order to collect robust data, including adverse events of special interest [3,72].
6. Educational support should be developed in a transparent and unbiased way to facilitate learning by PwH so that they may participate in shared decision making [66,98,99], understand their key role as a stakeholder, and share in the pharmacovigilance responsibilities [100].
7. Formal collaboration between the relevant national hemophilia patient organizations and the centers administering gene therapy on the provision of education and information should be ensured so that the PwH is ready to fully participate in a shared and informed decision-making process.
8. Work to ensure that postmarket studies, registries, and future registrational studies take into consideration principles of health equity in their design.

AUTHOR CONTRIBUTIONS

L.A.V. conceptualized the design of the manuscript and wrote the first draft of the manuscript. Each author has reviewed subsequent drafts and contributed to the refinement and development of the concepts and contents presented in the manuscript. Each author reviewed and approved of the final version of the manuscript.

DECLARATION OF COMPETING INTERESTS

R.K. received research funding from Bayer. G.F.P. is a consultant for ASC Therapeutics, BioMarin, Frontera, Metagenomi, Pfizer, Regeneron, and Spark Therapeutics. M.W.S.'s institution has received research funding from BioMarin, Freeline, Spark Therapeutics, and uniQure. The other authors have no competing interests to disclose.

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