Gene transfer in hemophilia B: a big step forward

Giancarlo Castaman

Center for Bleeding Disorders and Coagulation, Department of Oncology, Careggi University Hospital, Florence, Italy

The phase 3 open-label study of gene transfer in hemophilia B using the vector AAV5-etranacogene dezaparvovec (HOPE-B trial) has recently reported the results in 54 men affected by hemophilia B (factor IX activity ≤2 IU/dL).[1] Etranacogene dezaparvovec (previously identified as AMT-061) is derived from a previous AMT-060 vector that consists of an adeno-associated virus 5 vector incorporating a small gene cassette containing codon-optimized wild-type human FIX coding sequence under the control of a liver-specific promoter (LP1).[2] AMT-060 induced sustained FIX levels in the range of 5-10 IU/dL up to 5 years in 9/10 patients with severe or moderately severe hemophilia B.[3] Etranacogene dezaparvopvec has the identical AMT-060 design except for a two- nucleotide substitution in the FIX coding sequence resulting in a single amino acid change (R338L) in the catalytic domain. This change reproduces the highly active FIX-Padua variant, a natural occurring FIX variant associated with very high levels of FIX and inherited thrombophilia.[4] The FIX-Padua protein demonstrates a 6- to 8-fold increase in FIX activity compared to wild type FIX[4] and a preliminary clinical trial showed FIX levels achieved post-gene transfer in the range of mild hemophilia or at near-lower normal level after one year of follow-up.[5]

After a lead-in period (≥6 months) of usual FIX prophylaxis, participants in the HOPE-B study were treated with a single infusion of etranacogene dezaparvovec (2×10^{13} gc/kg) and followed-up for 18 months. In total, 53 participants completed the follow-up period. One participant discontinued treatment after receiving a partial dose of ~10% following an event of hypersensitivity. Etranacogene dezaparvovec significantly increased *FIX* activity, with a mean of 36.2 IU/dL, 38.8 IU/dL and 34.3 IU/dL at 6-, 12- and 18-months post- treatment, respectively.[1] Mean annualized bleeding rate (ABR) decreased from 4.19 (95%CI: 3.22, 5.45) during the lead-in period to 1.51 (95%CI: 0.81, 2.82) during months 7-18 post-treatment. The mean ABR decreased from 1.52 (95%CI: 1.01, 2.30) during the lead-in period to 0.44 (95%CI: 0.17, 1.12) during months 7-18. Overall, 63% of participants had zero bleeding episodes post-treatment, compared with 26% of participants during lead-in. Following treatment with etranacogene dezaparvovec, FIX concentrate prophylaxis was discontinued in 96% (52/54) of participants from day 21 through to month 18.

Notably, transaminitis requiring corticosteroid treatment was observed in about 20% of patients only, a figure by far lower than that observed in a recent gene therapy trial for hemophilia A.[6] Furthermore, successful transgene expression was achieved despite the presence of anti-AAV5 antibodies (up to a titer of 1:700); one participant with a very high AAV5 NAbs titer (1:3212) did not express FIX Padua and remained on FIX prophylaxis.[1]

These results represent an outstanding, big step forward for effective gene transfer in hemophilia B. Early AAV-mediated gene therapy trials focused on hemophilia B in part because the *FIX* cDNA is relatively small (1.5 kb), its expression pathway is significantly less complex than that of FVIII and hepatocytes are the natural site of FIX synthesis. The history of gene therapy for hemophilia began indeed with the first trial published in 2011 in 10 hemophilia B subjects who received a single intravenous infusion of self-complementary AAV2/8-LP1-hFIXco at a dose of 2×10^{11} vg/kg, 6×10^{11} vg/kg, or 2×10^{11} vg/kg.[7] Long-term FIX expression at 1 IU/dL to 8 IU/dL of normal FIX activity was established in all 10 subjects and levels have remained stable over 10 years of follow-up, with a significant reduction in the annual FIX concentrate usage and frequency of spontaneous bleeding.[8]

An important aspect of gene therapy, together with long-term safety, is represented by the durability of transgene expression in individual patients. In clinical trials, no decline of *FIX* expression has been observed in adult patients with hemophilia B up to 8-years post-administration.[8] AMT-060 has demonstrated stability and durability for up to 5-years post-administration and etranaco-

Correspondence: Giancarlo Castaman, Center for Bleeding Disorders and Coagulation, Department of Oncology, Careggi University Hospital, 50134 Florence, Italy.
E-mail: giancarlo.castaman@unifi.it; castaman@aou-careggi.toscana.it

Citation: Castaman G. Gene transfer in hemophilia B: a big step forward. Bleeding, Thrombosis, and Vascular Biology 2023;2:70.

Key words: gene transfer; hemophilia.

Conflict of interest: GC is in the steering Committee of HOPE-B study (CSL Behring).

Funding: GC received speaker fees or for participation into Advisory Boards from Bayer, Biomarin, CSL Behring, Takeda, SOBI, Novo Nordisk, Pfizer, Roche, LFB, Grifols, Kedrion.

Received: 17 March 2023.
Accepted: 21 April 2023.

Bleeding, Thrombosis and Vascular Biology 2023; 2:70
doi:10.4081/btvb.2023.70

gene dezaparvovec has demonstrated stability and durability for up to 3-years post-administration.[9] This pattern contrasts with the decline of FVIII over the first 2-5 years post-administration after gene therapy with valoctocogene roxaparvovec.[10] Whatever the reason for this discrepancy, it should be kept in mind the possibility of a harmful endoplasmic reticulum stress response caused by overexpression of FVIII transgene which, at variance with *FIX*, is not naturally synthesized in hepatocytes, but rather in endothelial cells.[11]

The safety profile of etranacogene dezaparvovec was comparable in patients with and without pre-existing AAV5 Nabs.[1] A serious adverse event of hepatocellular carcinoma (HCC) occurred in a participant in HOPE-B trial with multiple independent risk factors. An independent molecular tumor characterization and vector integration analysis established that the HCC event was unrelated to treatment.[12] Integration analysis measured a low level of integration (0.027%) in both tumor and control liver tissue sample.[12] The data from the original study by Nathwani *et al*. and those from AMT- 060 study however did not report long-term safety issues,[2,7] but clearly accurate long-term follow-up is mandatory to record any safety issue potentially related to gene therapy.

So, what will the role of gene therapy in hemophilia B be with the present therapeutic options? Traditional treatment options for hemophilia B take now huge advantage of the significant prolongation of FIX half-life achieved with extended half-life concentrates which allow for infusion administered every 7-14 days or even 21 days.[13] Thus, the option of gene transfer must be weighted considering the efficacy and safety of the traditional therapy, the fact that gene therapy is available for persons aged ≥18 years only and patient's expectations.

With the recent approval of etranacogene dezaparvovec (Hemgenix®) in US in November 2022 and in EU in February 2023,[14,15] the affordability of AAV gene therapy becomes an urgent issue that should be managed accurately by the regulatory authorities together with the pharmaceutical companies. Payment models for this high-cost one-time therapy should be developed with possible repayment schemes, which should also include the costs of intense follow-up.[16] Hemgenix® has been priced with the highest, unprecedented cost for a *drug* which could result in impeding patient access and strain health care budget. However, successful gene therapy for hemophilia B could offer the potential advantage of continuous endogenous expression of clotting factor, therefore eliminating breakthrough and sub-clinical bleeding, thus reducing the need for frequent medical interventions, improving quality of life and preventing long-term disability. Thus, gene therapy has the potential to yield significant savings for the health care system and society in general but may still prove to be unaffordable for patients living in developing or emerging economies.

Gene therapy is a complex and costly treatment process, and it will likely first be offered at comprehensive care centers with facilities available and significant expertise in the management of patients with hemophilia. A recent joint publication from the European Association for Haemophilia and Allied Disorders and the European Haemophilia Consortium suggested that a modified hub-and- spoke model, incorporating a long-term safety and efficacy surveillance system, should be introduced to ensure appropriate prescription, administration and monitoring of gene therapy results.[17,18]

An active engagement of patients will be very important and can be obtained through an adequate explanation and support given to the patient. Patient association groups can play an important role in this aspect. An adequate laboratory surveillance needs to be available at all stages pre- and post-procedure and a structured follow-up must be provided to all patients, particularly in the first year after gene therapy. All in all, however, gene therapy for hemophilia appears to have taken a path of no return.

References

1. Pipe SW, Leebeek FWG, Recht M, et al. gene therapy with etranacogene dezaparvovec for hemophilia B. N Engl J Med 2023;388:706-18.
2. Miesbach W, Meijer K, Coppens M, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. Blood 2018;131:1022-31.
3. Batty P, Lillicrap D. Hemophilia gene therapy: approaching the first licensed product. Hemasphere 2021;5:e540.
4. Simioni P, Tormene D, Tognin G, et al. X-linked thrombophilia with a mutant factor IX (factor IX Padua). N Engl J Med 2009;361:1671-5.
5. George LA, Sullivan SK, Giermasz A, et al. Hemophilia B gene therapy with a high- specific-activity factor IX variant. N Engl J Med 2017;377:2215-27.
6. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. N Engl J Med 2022; 386:1013-25.
7. Nathwani AC, Tuddenham EG, Rangarajan S et al. Adenovirus-associated virus vector- mediated gene transfer in hemophilia B. N Engl J Med 2011;365:2357-65.
8. Nathwani AC, Reiss U, Tuddenham E, et al. Adeno-associated mediated gene transfer for hemophilia B: 8 year follow up and impact of removing "empty viral particles" on safety and efficacy of gene transfer. Blood 2018;132:491.
9. von Drygalski A, Gomez E, Giermasz A, et al. Stable and durable factor IX levels in hemophilia B patients over 3 years post etranacogene dezaparvovec gene therapy. Blood Adv 2022 [Online ahead of print].
10. Mahlangu J, Kaczmarek R, von Drygalski A et al. Two-year outcomes of valoctocogene roxaparvovec therapy for hemophilia A. N Engl J Med 2023;388:694-705.
11. Fahs SA, Hille MT, Shi Q, et al. A conditional knockout mouse model reveals endothelial cells as the principal and possibly exclusive source of plasma factor VIII. Blood 2014;123:3706-13.
12. Schmidt M, Foster G, Coppens M, et al. Liver safety case report from the phase 3 HOPE- B gene therapy trial in adults with hemophilia B. Res Pract Thromb Haemost 2021;5.
13. Mancuso ME, Lubetsky A, Pan-Petesch B, et al. Long-term safety and efficacy of rIX-FP prophylaxis with extended dosing intervals up to 21 days in adults/adolescents with hemophilia B. J Thromb Haemost 2020;18:1065-74.
14. CSL Behring. Prescribing Information - HEMGENIX 2022. Available from: https://www.fda.gov/media/163467/ download. [Accessed on January 2023].
15. CSL Behring. HEMGENIX - Summary of Product Characteristics 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/hemgenix-epar-product-information_en.pdf [Accessed on March 2023].
16. Vokinger KN, Avorn J, Kesselheim AS. Sources of innovation

in gene therapies- Approaches to achieving affordable prices. N Engl J Med 2023;388:292-5.
17. European Association for Haemophilia and Allied Disorders. EAHAD-EHC joint statement on: promoting hub-and-spoke model for the treatment of haemophilia and rare bleeding disorders using gene therapies. Available online: http://eahad.org/wp-content/uploads/2020/05/Hub-and-Spoke.pdf [Accessed on May 2022].
18. Miesbach W, Chowdary P, Coppens M, et al. Delivery of AAV-based gene therapy through haemophilia centres: a need for re-evaluation of infrastructure and comprehensive care: joint publication of EAHAD and EHC. Haemophilia 2021;27:967-73.