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Gene therapy: An Addition to the Novel Therapies for Hemophilia

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Valoctocogene roxaparvovec gene therapy for hemophilia A (Ozelo et al., 2022)

Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is an adeno-associated virus (AAV5) vector-based gene-therapy that expresses a B-domain–deleted human factor VIII coding sequence from a hepatocyte-selective promoter. After 5 years follow up showing effectiveness in phase 1 and 2 studies, it was evaluated in an open-label, single-group, phase 3 study. The efficacy and safety of valoctocogene roxaparvovec was evaluated in 134 adults with hemophilia A and results compared at 52-weeks and 2-years from a subgroup of participants. Absence of pre-existing anti-AAV5 antibodies or a history of development of factor VIII inhibitors was a prerequisite for enrolment in the study. No participants were receiving emicizumab. Among the 132 human immunodeficiency virus–negative participants, the mean factor VIII activity level at weeks 49 through 52 had increased by 41.9 IU per decilitre. Among the 112 participants enrolled from a prospective noninterventional study, the mean annualized rates of factor VIII concentrate use and bleeding episodes after week 4 had decreased after infusion by 98.6% and 83.8%, respectively. All the participants had at least one adverse event; 22 of 134 (16.4%) reported serious adverse events. Elevations in alanine aminotransferase levels occurred in 115 of 134 participants (85.8%) and were managed with immunosuppressants. No development of factor VIII inhibitors or thrombosis occurred in any of the participants.

Gene therapy for hemophilia A: how long will it last? (Schutgens, 2022)

The first successful adeno-associated vector (AAV)-based gene therapy trial in hemophilia B was published ten years back and for hemophilia A five years back. This article summarizes longer follow-up in hemophilia A. Trials compared were - Pfizer/Sangamo (Giroctocogene, fitelparvovec, Visweshwar et al., 2021), BioMarin (Valoctocogene roxaparvovec, Ozelo etal., 2022), and Spark (Spk200 (AAV3 based)-hFVIII-SQ, George et al., 2021). AAV-based gene therapy for hemophilia A is successful with patients demonstrating ongoing FVIII expression in majority of cases, which is associated with a dramatic positive effect on bleeding rates. Optimal dosing has not yet been achieved. One study was put on hold due to factor levels of more than 150% in some patients. Other concerns included transaminitis and loss of expression with time. Loss of response has been reported to vary from 7.5% to 44% per year.

In vivo delivery of CRISPR–Cas9 using lipid nanoparticles enables antithrombin gene editing for sustainable hemophilia A and B therapy (Han et al., 2022)

Adeno-associated virus (AAV) gene therapy demonstrated efficacy in restoring deficient clotting factors, but it is not suitable for patients with inhibitors for factor VIII or factor IX. Non-viral approach is not hampered by the size of the payload, pre-existing immunity, or long-term Cas9 expression–associated immunogenicity, which are some of the main limitations encountered when using the viral delivery systems. In this study they developed and optimized lipid nanoparticles (LNPs) to deliver Cas9 mRNA along with single guide RNA that targeted antithrombin (AT) in the mouse liver. They assessed whether genome editing of SERPINC1 encoding AT can be used as a potential advanced therapeutic option for treating patients with hemophilia. The LNP-mediated CRISPR-Cas9 delivery resulted in the inhibition of AT that led to improvement in thrombin generation in both hemophilia A and B mice. No active off-targets, liver-induced toxicity, and substantial anti-Cas9 immune responses were detected, indicating that the LNP-mediated CRISPR-Cas9 delivery was a safe and efficient approach for hemophilia therapy.

The hemophilia gene therapy patient journey: questions and answers for shared decision-making (Wang et al., 2022)

Patient centricity is defined as engaging with patients to achieve the best experience and outcomes for the individual and their family. The introduction of a new option, such as gene therapy, provides opportunities for shared decision-making to ensure patients understand their best, individualized option. Availability of emicizumab has markedly changed the lives of patients with hemophilia. At the same time,the long-awaited gene therapy has arrived. To make informed decisions about the choice of therapy needs patient education about the risks and benefits associated with each treatment option. The Council of Hemophilia Community (CHC) has developed a question-answer based educational resource material to empower them with the knowledge about various treatments. It was developed with the aim of helping health care professionals in discussions with the hemophilia patients who were consulted while making the document. Easy-to-read material will definitely be useful in dissipating correct and complete information to patients and will avoid the bias and lacunae in health workers' knowledge.

Gene therapy of hemophilia – hub centres should be haemophilia centres: a joint publication of EAHAD and EHC (Miesbachet al., 2022)

With the availability of gene therapy, there is excitement among patients and treating physicians. Hemophilia care centres and patient support groups for hemophilia are well established worldwide. This joint European Association for Haemophilia and Allied Disorders (EAHAD) and European Haemophilia Consortium (EHC) publication describes criteria for centres participating in gene therapy care and how they can be equipped to take up the responsibility of gene therapy. With available investigational, evaluational and supportive care facilities at existing hemophilia centres, they can provide better follow-up for safety and efficacy of gene therapy.

References

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