GENE THERAPY: LEADING THE CHANGE IN HAEMOPHILIA B

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Currently, patients with Haemophilia B have access to various extended-half life FIX prophylaxis regimens that have helped them achieve a closer to normal lifestyle, offering greater dosing flexibility, higher trough levels and improved clinical outcomes. Despite treatment options though, there are still unmet needs [fluctuating factor levels, (sub)clinical bleeding, inhibitor development], treatment burden (need for regular infusions, difficult venous access, time demand) and psychological burden, negatively impacting patients' quality of life and treatment adherence.

Haemophilia being a monogenic disease, is an ideal gene therapy target and multiple clinical trials assessing gene therapies are underway. Administered as a single dose, recombinant adeno-associated virus (rAAV)-based gene therapy delivers the therapeutic gene (transgene) into the target cell and has been approved for the treatment of certain genetic disorders, including Haemophilia B. The characteristics of the AAV vector have been adapted to make it ideally suited for the transduction of the FIX coding sequence; the discovery of a FIX variant (Padua variant), which leads to an 6-8-fold increase in FIX protein activity compared to wild-type FIX, allows for the use of lower vector doses to achieve adequate FIX activity levels with no signs of increased immunogenicity and liver-specific promoters have been used to ensure that transgene expression of FIX coding sequence occurs only in the host liver cells.

Etranacogene dezaparvovec (rAAV5-Padua hFIX) is a first-in-class approved, one-time gene therapy for Haemophilia B. The phase III trial (HOPE-B) investigates its efficacy and safety in 54 adult patients with severe or moderately severe Haemophilia B (FIX ≤2%), regardless of pre-existing AAV5 neutralizing antibodies (NAbs). After 18 months of treatment, a) the mean annualized bleeding rate (ABR) for all bleeds was reduced by 64% (p=0.0002) during Months 7-18, compared to lead-in FIX prophylaxis period (primary endpoint was met), b) factor expression increased with a mean (SD) FIX activity of 36.9% (21.4) IU/dl at Month 18. Both the reduction in ABR and increases in FIX levels [mean (SD) FIX activity at Month 24: 36.7% (19.0) IU/dl] were sustained at months 7-24. (The 3-year-follow-up data will be presented at the ASH Congress 2023). Of note, there was no clinically meaningful association between baseline AAV5 NAb titer ≤1:678, mean ABR and FIX activity levels through 24 months, and etranacogene dezaparvovec had a favorable safety profile, with no reported treatment-related serious adverse events. Managing haemophilia is complex and, as such ensuring multidisciplinary care with patient-centric collaboration is crucial, especially given the need for ongoing care and monitoring of patients on gene therapy.