ABSTRACT FORM ECAT SYMPOSIUM 15 – 16 SEPTEMBER 2022

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Title:

Hemophilia and Gene therapy

Abstract:

Since the first successful study of intravenously administered AAV-based liver-directed gene therapy in patients with severe hemophilia B in 2011, marked progress has been made in the development of gene therapy for hemophilia A and B in the last decade. Several gene therapy studies, using AAV vectors with various gene constructs, showed FVIII and FIX expression, thereby significantly reducing the number of bleeds and the need for prophylaxis. This resulted in great clinical benefit for nearly all patients, less joint bleeding and improvement in Health-related Quality of Life. In the first hemophilia A AAV-directed gene therapy study FVIII levels of 100 U/dL were obtained 26 weeks after gene therapy, however the level of expression decreased over time.(Pasi KJ, Haemophilia 2021) Over a period of five years hemostatic efficacy was maintained in all individuals, however only 50% of patients had levels >5 IU/dL. In a more recent phase 3 study in 134 patients the mean FVIIII activity increased by 41.9 IU/dL 1 year after gene therapy. (Ozelo MC, NEJM 2022) Most patients developed liver function abnormalities that required corticosteroid use. Several phase 1-2 gene therapy studies in hemophilia B patients, showed expression levels between 20-50 IU/dL using the FIX Padua variant (R338L-FIX) . Levels of FIX after gene therapy were stable over time, even 5 years after gene therapy with wild-type FIX and at least 2 years with the FIX Padua variant, with persisting hemostatic efficacy. (van Drygalski, Blood Advances 2019) Currently several gene therapies are reviewed by the FDA and EMA for approval, and market authorization is expected in 2022. The nice results on efficacy of gene therapy have to be balanced to the reported side effects and drawbacks associated with gene therapy. Therefore the limitations of gene therapy will also be discussed during the presentation. Several issues have to be resolved before gene therapy will become available for hemophilia patients. (Leebeek , Blood 2021). One of the remaining questions is which assay to use to measure FVIII or FIX after gene therapy: a one stage assay or a chromogenic assay. This is of major importance to assess the efficacy of gene therapy. Chromogenic assay measure FVIII and FIX levels that are around 1.6 fold lower than factor activities measured with one-stage assays. It is therefore of utmost importance to assess factor levels after gene therapy with similar standardized tests, for which chromogenic assays are now preferred.
During the lecture the most recent findings of reported and ongoing gene therapy trials and updates on market authorization of gene therapy products will be discussed.