CLIPPINGS

OnasemnogeneAbeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of *SMN2* (STR1VE) (Lancet Neurol. 2021;20:284-93)

Spinal muscular atrophy (SMA) is caused due to biallelic variations in SMN1 gene. The results of an open-labelled single-arm multicentric phase 3 trial (STR1VE) to evaluate the safety and efficacy of OnasemnogeneAbeparvovec (marketed as Zolgensma), for treatment of infantile SMA, were published recently. This drug was approved by the Food and Drug Administration (FDA) in 2019. Twenty-two patients fulfilled the inclusion criteria for the study. All of them were younger than 6 months and had biallelic variants in SMN1 and one or two copies of SMN2. All of them received a single dose of OnasemnogeneAbeparvovec ($1{\cdot}1\times10^{14}$ vector genomes per kg) as intravenous infusion. The patients were monitored regularly till 18 months of age. The ability to sit independently for 30 seconds and survival at 14 months of age were the outcomes assessed. The results were compared with a natural cohort of untreated children with SMA from Pediatric Neuro-muscular Clinical Research (PNCR) dataset. Thirteen out of twenty-two patients showed a statistically significant improve-ment in sitting independently for 30 seconds or more when compared to the untreated group. In the treatment group, survival at 14 months without ventilation was significant when compared to the untreated group. Respiratory infection, elevated hepatic aminotransferases and hydrocephalus were the serious adverse events that were noted. The study concluded that gene therapy for SMA showed a clinically significant response and the safety profile supported the clinical use of gene therapy for treatment of SMA.

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia (N Engl J Med. 2021;384:252-60)

Beta thalassemia and sickle cell anemia are common Mendelian disorders caused by biallelic variants in HBB gene. The available treatment options for these disorders include regular blood transfusion, hematopoietic stem cell transplantation, hydroxyurea and other supportive measures. BCL11A, encoded by BCL11A gene, is a transcription factor that represses the production of gamma globin chains, which constitutes the fetal hemoglobin. Some single nucleotide variations in BCL11A gene are known to cause down regulation of BCL11A and thus an increase in gamma chain and fetal hemoglobin level. The clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 nuclease system helps in creating specific alterations in specific sites in DNA. In this study, patient 1 was a 19-year old female with transfusion dependent beta thalassemia. Patient 2 was a 33 year old female with sickle cell disease. Both these patients underwent autologous hematopoetic stem cell transplantation with CRISPR-Cas9- edited CD34+ hematopeotic stem cells. These cells were edited by using a single guide RNA which directed the CRISPR-cas9 to silence the enhancer region of BCL11A and thus cause an increase in gamma chain production and fetal hemoglobin. The fetal hemoglobin levels showed an early and sustained increase in both the patients during a 12-month follow up period. The authors concluded that CRISPR-cas9-edited hematopeotic stem cells underwent good engrafment and resulted in a phenotype mimicking heriditary persistent fetal hemoglobin.

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