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Gene Therapies for Genetic disorders

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Gene therapy for RPE65–associated Leber's congenital amaurosis (RPE65–LCA) (Wang et al.,2020)

RPE65-associated LCA is an inherited retinal degeneration. In 2017, the US Food and Drug Administration (FDA) approved the first directly administered gene therapy that targets *RPE65*, voretigeneneparvovec-rzyl (Luxturna). Voretigeneneparvovec-rzyl uses the adeno-associated virus (AAV) vector and is delivered as a single subretinal injection. After this the retinal cells start producing the protein. However, cautious optimism is necessary, as the drug is not expected to restore normal vision, and only about half of treated patients had minimally meaningful improvement in short-term studies. Wang et al. reviewed six studies with 82 patients, of which only one was a randomised control trial. They found that gene therapy was effective up to 2 years post treatment in terms of improvement of best-corrected visual acuity and full-field light sensitivity threshold to blue flashes.

Personalized oligonucleotide therapy for CLN7 neuronal ceroid lipofuscinosis (Kim et al., 2019)

Neuronal ceroid lipofuscinoses (NCL or CLN) are a heterogeneous group of neurodegenerative disorders. CLN7 is caused by homozygous or compound heterozygous variants in the *MFSD8* gene. Kim et al. reported a 6 years old girl with CLN7, who was found to have two pathogenic variants in the *MFSD8* gene, one being a known pathogenic missense variant and the other a novel insertion of a retrotransposon which causes mis-splicing of the MFSD8 mRNA. Antisense oligonucleotide therapy (termed as milasen) consisting of 22 nucleotides was designed to target the i6.SA cryptic splice-acceptor site and nearby splicing enhancers. Repeated injections through the intrathecal route resulted in an increase in the ratio of normal to mutant mRNA. Over the course of 300 days the frequency of seizures decreased. No adverse reactions were noted. This 'personalized drug' was developed within one year of the diagnosis.

AAV5–hFVIII–SQ gene therapy for Hemophilia A (Pasi et al., 2020)

Pasi et al. have studied the 2-year and 3-year safety and efficacy data after administration of single infusion of adeno-associated virus (AAV)–mediated gene therapy in 15 adults with severe hemophillia A. They had received a single infusion of AAV5-hFVIII-SQ at various dose levels. There was a substantial reduction in annualized rates of bleeding events and complete cessation of prophylactic factor VIII use in all participants who had received an adequate amount of the gene therapy. No adverse event was noted. The gene therapy appears to be effective.

European Medicines Agency approval of Zynteglo for beta thalassemia and sickle cell disease (Schuessler-Lenz et al., 2020)

Recently the European Commission approved the gene therapy Zynteglo for transfusion-dependent beta thalassemia. In their trial, they included

32 patients of ages 12 years and above. This therapy is an ex vivo gene therapy, consisting of an autologous $CD34^+$ cell-enriched population that contains hematopoietic stem cells transduced with a lentiviral vector encoding the beta globin gene. After myeloablative preconditioning with busulfan, these transduced cells are given in a single injection. They get engrafted in the bone marrow and differentiated into red blood cells that produce therapeutic hemoglobin called HbA^{T87Q}. Till now, two trials were completed and 11 out of 14 patients reached the primary endpoint of transfusion independence. In the two trials that are ongoing, 4 out of 5 patients no longer need blood transfusion. Five out of eight patients with the severest form treated with this therapy have not benefitted and returned to blood transfusion. Therefore, this therapy is not approved for the most severe type of beta thalassemia. The reason for no benefit is that a higher percentage of blood cells carrying the transgene sequences was required for the most severe type. Zynteglo is also being used in trials for sickle cell disease and the early results are promising. This therapy aims to dilute the levels of the defective protein that distorts the red blood cells into a sickled shape. In the twelve months follow up of four patients, $\beta^{A\text{-}T87Q}$-derived hemoglobin production increased to ≥50% of total hemoglobin, and symptoms such as acute chest syndrome and serious vaso-occlusive crisis were eliminated.

Gene therapy for X–linked chronic granulomatous disease (Kohn et al., 2020)

In the first study in humans, nine patients with X- linked chronic granulomatous disease (CGD) received ex vivo autologous $CD34^+$ hematopoietic stem and progenitor cell-based lentiviral gene therapy. Pre-treatment myeloablative conditioning was given. Two enrolled patients died within 3 months of treatment from pre-existing co-morbidities. At 12 months, six of the seven surviving patients demonstrated stable vector copy numbers (0.4-1.8 copies per neutrophil). No new CDG-related infections occurred in the surviving patients suggesting that the lentivirus-based gene therapy holds promise for CGD.

RNAi therapeutic Givosiran for acute intermittent porphyria (Balwani et al., 2020)

Up-regulation of hepatic delta-aminolevulinic acid synthase 1 (ALAS1), with resultant accumulation of delta-aminolevulinic acid (ALA) and porphobilinogen, is central to the pathogenesis of acute attacks and chronic symptoms in acute porphyria. This study on 94 symptomatic patients (48 in the givosiran group and 46 in the placebo group) with acute hepatic porphyria and 89 patients of acute intermittent porphyria (AIP) showed efficacy of givosiran, an RNA interference therapy which inhibits ALAS1 expression. After receiving subcutaneous or placebo monthly for 6 months, among the 89 patients with acute intermittent porphyria, the mean annualized attack rate was 3.2 in the givosiran group and 12.5 in the placebo group, representing a 74% lower rate in the givosiran group ($P<0.001$). The results were similar among the 94 patients with acute hepatic porphyria. There was lowering of levels of urinary ALA and porphobilinogen in patients with AIP.

References

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