GeNeXpreSS

Promising New Therapies for Genetic Disorders: Hope for a Brighter Future

Neelam Saini, Prajnya Ranganath

Department of Medical Genetics, Nizam's Institute of Medical Sciences, Hyderabad, India

Correspondence to: Dr Prajnya Ranganath *Email:* prajnyaranganath@gmail.com

Hunting down huntingtin to cure Huntington Disease (Tabrizi et al., 2019)

Huntingtin (HTT)-lowering approaches with various genetic engineering techniques like genome editing, transcript targeting and protein targeting are current areas of research providing hope for a cure for Huntington disease (HD). A phase III clinical drug trial by Tabrizi et al. based on an allele-unspecific second-generation, chemically modified synthetic oligomer complementary to a 20-nucleotide portion of HTT mRNA (IONIS-HTTRx/RG6042) has shown very promising results. In the nucleus, hybridization of RG6042 with HTT pre-mRNA and mRNA leads to endogenous RNase H1-mediated degradation, which prevents further translation to HTT protein. The study showed that with four intrathecal injections of 120 mg HTTRx via lumbar puncture every 4 weeks, a significant reduction of mutant HTT protein in the cerebrospinal (CSF) fluid of about 40% at the two highest doses of 90 mg ($p < 0.01$) and 120 mg ($p < 0.01$) could be achieved. This effect was persistent during the subsequent 2-month follow-up period. Apart from headache due to lumbar puncture, no serious adverse events were reported.

Anti-sickling therapy for sickle cell disease (Vichinsky et al., 2019)

Deoxygenated HbS polymerization and subsequent dehydration causing sickling is the main molecular pathology behind sickle cell disease (SCD). Voxelotor (GBT-440) is a HbS polymerization inhibitor that stabilises the oxygenated Hb state by reversible covalent binding to Hb. In a phase III clinical trial (HOPE) by Vichinsky et al., voxelotor significantly increased haemoglobin levels and reduced markers of hemolysis. In this multicentric study, 274 adolescent and adult SCD patients (most of them with the HbSS or HbS-β0thalassemia genotype), were randomly assigned in an equal ratio, to receive a once-daily oral dose of 1500 mg of voxelotor, 900 mg of voxelotor, or placebo. A significantly higher percentage of participants had a haemoglobin response in the 1500 mg voxelotor group than in the placebo group ($P<0.001$) regardless of concurrent hydroxyurea use or severity of anemia at the baseline. The absolute mean Hb change from baseline to 24 weeks was 1.1g/dl, 0.6g/dl and 0.1g/dl in the groups receiving 1500 mg voxelotor, 900 mg voxelotor and placebo, respectively. At week 24, the 1500mg voxelotor group had significantly greater reductions from baseline in the indirect bilirubin level and percentage of reticulocytes than the placebo group. The incidence of vaso-occlusive crisis was same in all the three groups. Thus, voxelotor was shown to provide significant and sustained increase in the haemoglobin level in persons with sickle cell disease and was granted accelerated approval by the United States Food and Drug Administration (U.S. FDA) for children (aged ≥12 years) and adults with SCD in November 2019.

Triple combination CFTR modulator therapy for cystic fibrosis-two heads are better than one, but three are better than two (Heijerman et al., 2019)

Heijerman et al. conducted a phase III clinical trial to determine whether addition of a third next generation CFTR corrector, oral elexacaftor (VX-445) to the previously used dual combination of tezafactor plus ivacaftor in patients with

the homozygous *F508del* mutation significantly improved the outcome as compared to dual combination. In this multicentric trial in patients with cystic fibrosis homozygous for the *F508del* mutation, in which all participants had a 4-week pre-treatment period with tezacaftor plus ivacaftor, treatment with the triple combination regimen of elexacaftor plus tezacaftor plus ivacaftor resulted in substantial improvements in lung function, sweat chloride concentration, respiratory-related quality of life, and nutritional parameters compared with tezacaftor plus ivacaftor alone. The triple combination therapy was well tolerated, with a safety profile comparable to that in the group receiving tezacaftor plus ivacaftor alone.

Iron chelation therapy for PKAN – curing the eye of the tiger

(Klopstock et al., 2019)

Pantothenate kinase-associated neurodegeneration (PKAN), is an NBIA (neurodegeneration with brain iron accumulation) disorder, which is characterized by progressive generalised dystonia and brain iron accumulation. Klopstock et al. conducted a randomized controlled trial (RCT) on the use of membrane-permeable iron chelator oral deferiprone (30 mg/kg/day) in 88 patients with PKAN. The study has shown that there is excellent safety and tolerability of deferiprone in PKAN over 36 months, and there is strong evidence that deferiprone leads to a marked reduction in brain iron. Disease progression seemed to slow down in patients who switched from placebo to deferiprone in the extension trial. Importantly, the reduction in brain iron load induced by deferiprone was not accompanied by systemic iron depletion. The only significant hematological adverse effect seen was anemia, which was easily manageable with iron supplements. Although the clinical endpoints were not met for the intention-to-treat population in this RCT, this trial provides the first indication of a decrease in disease progression in patients with NBIA especially PKAN.

References

1. Heijerman HGM, et al. Efficacy and safety of the Elexacaftor plus Tezacaftor plus Ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: A double-blind, randomised, phase 3 trial. Lancet 2019; 394:1940–1948.
2. Klopstock T, et al. Safety and efficacy of deferiprone for pantothenate kinase-associated neurodegeneration: a randomised, double-blind, controlled trial and an open-label extension study. Lancet Neurol 2019;18: 631–642.
3. Tabrizi SJ, et al. Targeting Huntingtin Expression in Patients with Huntington's Disease. N Engl J Med 2019; 380: 2307–2316.
4. Vichinsky E, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med 2019; 381: 509–519.