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Lysosomal Storage Disorders: New Therapies in the Horizon

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Chemically modified recombinant human sulfamidase (SOBI003) in MPS IIIA patients (Harmatz et al., 2022)

This phase 1/2 clinical trial studied the effects of a chemically modified (glycan modification) variant of recombinant human sulfamidase (SOBI003), which was previously shown to cross the blood-brain barrier (BBB) and achieve good CSF levels in mice. The study evaluated the safety, efficacy, pharmacodynamics, and pharmacokinetics of this drug in six patients with MPS IIIA when used upto 104 weeks. Six children with developmental age more than or equal to 12 months were given 3 mg/kg or 10 mg/kg weekly intravenous injections. Serum and CSF concentrations of the drug increased with the dose, and 79% reduction in levels of heparan sulphate (HS) in the CSF was noted. Stabilisation of cognition was observed, and the drug was well tolerated; however,there was no significant benefit noted in the quality of life and sleep pattern.

Intravenous 2– hydroxypropyl–beta–cyclodextrin demonstrates biological activity and impacts cholesterol metabolism in the central nervous system and peripheral tissues in adult subjects with Niemann–Pick disease type C1 (Hastings et al., 2022)

This phase 1 trial involving intravenous 2-hydroxypropyl-beta-cyclodextrin (HPßCD; Trappsol® Cyclo™) was conducted following positive results in preclinical studies. Patients above 18 years with Niemann-Pick disease type C, with systemic manifestations including hepatosplenomegaly and central nervous system (CNS) involvement/ neurodegeneration, were included in the study. Thirteen patients were enrolled, of whom ten patients completed the study; six patients received 1500 mg/kg and four received 2500 mg/kg intravenous dose every 2 weeks for 14 weeks. The drug HPßCD was found to clear cholesterol from the liver and to improve peripheral markers of cholesterol homeostasis. A reduction of between 19-42% was noted in the CSF total Tau levels. HPßCD was detected in the CSF suggesting that it crosses the blood-brain barrier even with intravenous administration.

Venglustat, an orally administered glucosylceramide synthase inhibitor: Assessment over 3 years in adult males with classic Fabry disease in an open label phase 2 study and its extension study (Deegan et al., 2022)

Venglustat inhibits the conversion of ceramide to glucosylceramide and acts as a substrate-reducing agent for synthesis of complex glycosphingolipids. This study was a multicentric, open-label, single arm, phase 2a uncontrolled 3-year study to assess the safety, efficacy, pharmacodynamics, and pharmacokinetics of venglustat given once orally (15 mg dose) in treatment-naive adult male patients with classic Fabry disease. Nine of the 11 enrolled patients completed the 26-week initial clinical study followed by a 130-week extension study. Reduction in lysosomal GL-3 in skin biopsy by light microscopy was noted only at the end of 156 weeks, but plasma GL-1 and GL-3 levels decreased rapidly and significantly. Overall, the data from the study is promising.

References

1. Deegan PB, et al. Venglustat, an orally administered glucosylceramide synthase inhibitor: Assessment over 3 years in adult males with classic Fabry disease in an open-label phase 2 study and its extension study. Mol Genet Metab. 2022;https://doi.org/10.1016/j.ymgme.2022.11.002
2. Harmatz P, et al. Chemically modified recombinant human sulfamidase (SOBI003) in mucopolysaccharidosis IIIA patients: Results from an open, non-controlled, multicenter study. Mol Genet Metab. 2022;136:249-259.
3. Hastings C, et al. Intravenous 2-hydroxypropyl-β-cyclodextrin (Trappsol® Cyclo™) demonstrates biological activity and impacts cholesterol metabolism in the central nervous system and peripheral tissues in adult subjects with Niemann-Pick Disease Type C1: Results of a phase 1 trial. Mol Genet Metab. 2022;137:309-319.