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In utero enzyme replacement therapy for lysosomal storage disorders

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Objective

To describe considerations, challenges, and available data after treating the first three fetuses in a first-in-human phase 1 clinical trial of in-utero enzyme replacement therapy (IUERT) in fetuses with lysosomal storage diseases (LSDs) aimed to prevent ongoing organ damage and induce tolerance to the recombinant enzyme.

Methods

After publishing preclinical data showing safety and efficacy in MPS VII mice, we obtained an IND to perform IUERT in fetuses with one of eight LSDs with FDA-approved postnatal disease-specific ERTs. IUERT is given between 18-35 weeks' gestation (WG) via umbilical vein injection q2-4 weeks until delivery, followed by standard postnatal ERT. An Enrollment Advisory Board evaluates genotype/phenotype correlations; early onset -severe phenotypes are enrolled. Enzyme trough levels (ETLs) are checked to examine fetal-specific pharmacokinetics. Maternal and fetal anti- drug antibodies (ADAs) are monitored to avoid allergic reactions.

Results

A CRIM-negative infantile-onset Pompe Disease (IOPD) fetus received six doses of IUERT in Canada using the UCSF protocol (due to COVID restrictions). IUERT prevented the development of a heart failure and resulted in normal cardiac function and normal developmental milestones in a family where two siblings died of the disease. We treated two additional patients with MPS I and MPS I at UCSF. All were diagnosed prenatally due to known positive family history. The average time of inclusion was 25^{+2} WG. A fetus with MPS II received five IUERT doses, a fetus with MPS I received three IUERT doses, and both were delivered at term. Infusions were given safely despite the technical challenges of posterior placentas. All patients had low ETLs throughout gestation, indicating the phenotypic severity of these genotypes and the appropriate dosing interval. Maternal and fetal ADAs were not detected in the MPS patients. The efficacy of the in-utero ERT was confirmed by the measurement of biomarkers (heparan- and dermatan sulfate), which decreased appropriately during treatment. Similarly, MPSI and II markers in the dried fetal blood spots decreased to normal levels. Placenta electron microscopy showed no lysosomal storage compared to historic untreated controls.

Conclusion

Multiple doses of IUERT were well tolerated with evidence of efficacy in decreasing disease-associated biomarkers in injected fetuses and it did not result in preterm labor or allergic reactions. A 5-year follow-up will evaluate long-term efficacy in specific organs, including the brain. Carrier screening and expanded prenatal testing should be considered to optimize patient education and rapid initiation of ERT.