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Intravenous Enzyme Replacement Therapy for Metachromatic Leukodystrophy (MLD)

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Thirteen children (5M/8F) with late infantile MLD (median age 34 months; range 24-59) were enrolled in a Phase I/II open-label, dose-escalation enzyme replacement trial. Recombinant human arylsulfatase A (rhASA) was administered by intravenous infusion every other week for 52 weeks. Four children received low-dose (0.625 mg/kg), five mid-dose (1.25 mg/kg) and four high-dose (2.50 mg/kg) infusions; there was no placebo-control group. Nine of the 13 children enrolled in the study had advanced disease at baseline. Eleven children completed the trial; two withdrew due to disease progression and inability to travel at Weeks 18 and 30, respectively. Enzyme infusions were well tolerated in general and continued without interruption over the course of the trial. Seven children developed infusion-related reactions that were mild to moderate in intensity and transient in nature. The reactions were characterized by low grade fever, nausea and vomiting, pallor, malaise and urticaria, singly or in combination. Symptoms were managed with medication or pre-medication as needed. A screening assay revealed antibodies to rhASA in these 7 children. Analysis of potential biomarkers in cerebrospinal fluid (CSF) revealed a reduction in galactocerebroside-3-sulfate (sulfatide) levels in the high-dose group that emerged at Week 10 and reached a trough value at Week 26 that was durably maintained at Week 52 ($p<0.10$ compared with baseline). No readily discernible effects of enzyme replacement on motor or cognitive function became apparent during the trial. A concurrent, placebo-control group would be needed to detect beneficial effects of enzyme replacement on clinical progression rate in the setting of advanced disease. We conclude that rhASA can be safely infused intravenously in children with late infantile MLD for periods up to 52 weeks. A pharmacologic response consisting of a reduction in CSF sulfatide levels occurred at a rhASA dose of 2.50 mg/kg every other week. To demonstrate clinical benefits, a future clinical trial, currently in the planning stages, will possibly explore weekly intravenous doses of enzyme, and higher levels of exposure in patients with early stage disease; a concurrent placebo-control will likely be required.