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Outcome of a Phase I/II Trial of Intravenous Enzyme Replacement with Recombinant Human Arylsulfatase A (rhASA) in Children with Metachromatic Leukodystrophy (MLD)

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Abstract

Objective: To evaluate the effects of intravenous enzyme replacement with rhASA in children with late infantile MLD.

Background: Several lysosomal storage diseases are successfully treated with intravenous enzyme replacement therapy.

Design: Thirteen children (5M/8F; median age 34 months) were enrolled in a Phase I/II dose-escalation enzyme replacement trial; enzyme was administered intravenously biweekly in three dose cohorts. Endpoints included assessments of motor and cognitive function, MRI score, demyelinated white matter volume, brain metabolites by MR spectroscopy, CSF sulfatide levels, neurophysiological tests, and sural nerve morphology and (lyso)sulfatide levels. Evaluations occurred at baseline, 26 and 52 weeks.

Results: Eleven children completed the trial; 2 withdrew due to disease progression at Weeks 18 and 30, respectively. Enzyme infusions were well tolerated in general. Motor and cognitive function progressively deteriorated in all children during the trial without any apparent enzyme dose effects. Likewise, no dose dependent responses were observed for sural nerve morphology, neuroradiological and neurophysiological assessments. Although a durable reduction in CSF sulfatide levels was observed at Weeks 26 and 52 in the high dose cohort, this effect was associated with substantial blood brain barrier leak in 3 patients with advanced disease. Sural nerve sulfatide and lysosulfatide levels remained unchanged at Week 26 in all dose groups; these latter data document absence of clearance of storage material from a relevant target tissue.

Conclusion: Intravenous delivery of rhASA to nervous system was insufficient to clear stored sulfatide, prevent further demyelination and stabilize motor function. Direct delivery of enzyme to CNS may be beneficial.