Impact of intracerebroventricular enzyme replacement therapy in patients with neuronopathic mucopolysaccharidosis type II

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Introduction

Mucopolysaccharidosis II (MPS II) is a lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (IDS). Lack of IDS lead to progressive lysosomal accumulation of glycosaminoglycans (GAGs), resulting in a wide spectrum of symptoms, including mental retardation, hepatosplenomegaly, joint contracture, and cardiac dysfunction. In patients with MPS II with central nervous system (CNS) involvement, severe and progressive cognitive impairment is observed. Enzyme replacement therapy (ERT) has been available for the treatment of MPS II. However, because intravenously administered enzyme cannot penetrate the blood-brain barrier, it cannot reach the cerebral parenchyma. To improve the CNS symptoms, enzyme preparations that can reach the cerebral parenchyma have been sought. This article presents the 100-week results of a multicenter, open-label, non-controlled, phase 1/2 clinical study to evaluate the efficacy and safety of intracerebroventricularly (i.c.v.) ETR in patients with MPS II.

Methods

The study was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Guideline for Good Clinical Practice. The protocol and patient informed consent form were approved by the Institutional Review Board. All legally acceptable representatives of patients provided signed informed consent. Six male patients with severe MPS II were enrolled, with a mean age (range) at screening of 42.2 (23–66) months. A CSF reservoir was implanted under the patient’s scalp for i.c.v. administration. Idursulfase beta i.c.v. injection (15 mg/mL) was used. Intravenous ERT was continued. In order to evaluate the efficacy and safety, Heparan sulfate concentration, urinary uronic acid, immunogenicity tests (IDS antibody, anti-IDS antibody), Adverse events (AEs), the Kyoto Scale of Psychological Development 2001 (KSPD). The primary endpoint was the HS concentration in the CSF. The secondary endpoint was developmental age (DA) determined by the KSPD.

Results

HS concentrations in CSF (primary endpoint) decreased in all patients. A rapid decrease was observed in the first 20 weeks, and concentrations were maintained throughout 100 weeks of treatment. The mean HS concentration was 7.75 μg/mL at baseline, 2.90 μg/mL at week 52, and 2.23 μg/mL at week 100. The mean reduction in the HS concentration relative to baseline was 62.6% at week 52 and 71.2% at week 100. The HS concentration in CSF at week 100 was lower than at baseline in all patients. Five patients had a ≥50% decrease from baseline at weeks 52 and 100.

The mean overall DA, determined by the KSPD, increased from the screening period (23.2 months) up to week 76 (28.8 months), then decreased slightly (27.3 months) at week 100. The differences in overall DA from the screening period to week 100 in the six patients were +16.0, +14.0, +4.0, −1.0, +5.0, and −13.0 months. The mean difference in the change in DA from the screening period to week 100 between the six patients and the historical control group was 5.1 months. In the comparison with the historical control group, the developmental improvement was confirmed in five of six patients in the study group. AEs suspected as being related to the study drug were observed in all six patients (vomiting [100%], pyrexia [50.0%), procedural nausea [33.3%], and blood bilirubin increase and urticaria [16.7%]). No deaths or discontinuations owing to AEs occurred during the study. All patients were negative for anti-IDS antibodies in serum at week 100. Anti-IDS antibodies in CSF were not detected in all patients during this study.

Conclusion

Monthly i.c.v. administration of idursulfase beta using the implantable CSF reservoir for 100 weeks in Japanese pediatric patients with severe MPS II reduced CSF HS concentrations, maintained DA, and appeared to be well tolerated. These results suggest that i.c.v. idursulfase beta penetrates the brain and improves CNS manifestations.