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Safety of laronidase delivered into the spinal canal for treatment of cervical stenosis in mucopolysaccharidosis I

Patricia I. Dickson [a,*], Ilkka Kaitila [b], Paul Harmatz [c], Anton Mlikotic [d], Agnes H. Chen [a,e], Alla Victoroff [a], Merry B. Passage [a], Jacqueline Madden [c], Steven Q. Le [a], David E. Naylor [e], for the Mucopolysaccharidosis I Intrathecal Research Collaborative

[a] Department of Pediatrics, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, United States
[b] Medical Genetics, University of Helsinki, Helsinki University Hospital, Helsinki, Finland
[c] UCSF Benioff Children's Hospital Oakland, Oakland, CA, United States
[d] Department of Radiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, United States
[e] Department of Neurology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, United States

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ABSTRACT

Enzyme replacement therapy with laronidase (recombinant human alpha-L-iduronidase) is successfully used to treat patients with mucopolysaccharidosis type I (MPS I). However, the intravenously-administered enzyme is not expected to treat or prevent neurological deterioration. As MPS I patients suffer from spinal cord compression due in part to thickened spinal meninges, we undertook a phase I clinical trial of lumbar intrathecal laronidase in MPS I subjects age 8 years and older with symptomatic (primarily cervical) spinal cord compression. The study faced significant challenges, including a heterogeneous patient population, difficulty recruiting subjects despite an international collaborative effort, and an inability to include a placebo-controlled design due to ethical concerns. Nine serious adverse events occurred in the subjects. All subjects reported improvement in symptomatology and showed improved neurological examinations, but objective outcome measures did not demonstrate change. Despite limitations, we demonstrated the safety of this approach to treating neurological disease due to MPS I.

1. Introduction

Mucopolysaccharidosis I (MPS I) is caused by deficiency of the enzyme alpha-L-iduronidase (EC 3.2.1.76), a soluble lysosomal hydrolase that is involved in catabolism of heparan sulfate and dermatan sulfate glycosaminoglycans. Like other lysosomal storage diseases, MPS I causes progressive disability and death due to abnormal accumulation of substrate inside cells. Both systemic and neurological diseases occur in the condition. Systemic manifestations can be treated with enzyme replacement therapy using the recombinant form of alpha-L-iduronidase, laronidase, administered by weekly intravenous injections. Several recombinant enzyme treatments are approved for use in human patients with lysosomal storage diseases [1–7].

The challenge for neurological disease due to MPS I is to deliver the enzyme into the central nervous system. The cerebrospinal fluid naturally circulates throughout the neuraxis, providing potentially broad distribution from a single injection point. Injection into the cerebrospinal fluid is used to deliver chemotherapeutic agents, narcotic analgesics and the muscle relaxant baclofen clinically in patients. Injecting the enzyme into the cerebrospinal fluid is also less invasive than injecting directly into the brain parenchyma, and more suitable for chronic use than osmotic opening of the blood–brain barrier. Preclinical studies of recombinant lysosomal enzymes injected into the cerebrospinal fluid of large animals (dogs, cats and monkeys) have shown, somewhat surprisingly, that they can penetrate into deep brain structures such as the white matter, hippocampus, basal ganglia and thalamus [8–11].

We performed a phase I clinical trial of laronidase administered intrathecally via lumbar spinal tap for patients with MPS I. For this initial safety study, we elected to study MPS-related spinal cord compression. MPS I patients often develop meningeal thickening due to lysosomal storage [12], and we reasoned that this may be more likely to be reversible than disease in the brain. In addition, our preclinical studies in MPS I dogs showed that we could achieve extremely high enzyme concentrations and substantial reduction of lysosomal storage in the spinal meninges, even in adult animals [8,13,14]. We present the results of this study, along with a discussion of the challenges facing clinical trials of therapies for rare neurodegenerative diseases.

* Corresponding author.
E-mail address: pdickson@ucla.edu (P.I. Dickson).

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2. Materials and methods

2.1. Subjects

All study procedures were reviewed and approved by the John Wolf Human Subjects Committee at the Los Angeles Biomedical Research Institute and at institutional review boards at UCSF Benioff Children's Hospital Oakland and the Helsinki University Children's Hospital. The study was conducted in the United States under a Food and Drug Administration Investigational New Drug (IND) application and in Europe under a European Medicines Agency (Eudra) registration. Studies were listed on www.clinicaltrials.gov (National Clinical Trials (NCT) numbers NCT00215527 and NCT00786968). Enrollment into the research studies took place between November 2005 and March 2010, accruing 5 subjects. In order to be eligible for the study, subjects had to have symptomatic spinal cord compression that did not require urgent surgical intervention. A neurologist and neuroradiologist were required to assess each subject for evidence of cord compression. Our studies included subjects 8 years old or older with MPS I (Scheie, Hurler–Scheie, and Hurler syndromes) with symptomatic cervical spinal cord compression. All study participants had been on intravenous enzyme replacement therapy with laronidase (commercially available recombinant alpha-L-iduronidase) for many years prior to the study entry and otherwise were without severe concurrent illness precluding them from undergoing study treatments. The majority of subjects resided in the United States; however, because MPS I is a rare disease, we also established an international site in Finland to allow enrollment of eligible participants outside the US. Eligibility for the extension study was limited to subjects who exhibited a "good response" to intrathecal laronidase, defined as improvement or stabilization of spinal cord compression as determined by spinal magnetic resonance imaging (MRI), neurologic examination, subjective assessment score, Japanese Orthopedic Association score, Functional Independence Measure score, or six-minute walk test.

2.2. Study design

These were phase I open label interventional studies. The studies included a pilot phase and an extension phase. Participants of the pilot phase received 4 monthly doses of 1.74 mg laronidase diluted in Elliott's B (Ben Venue Laboratories) artificial cerebrospinal fluid (1 part laronidase to 2 parts Elliott's B by volume; total volume 9 mL) administered intrathecally (via alumbar spinal injection) 30 days apart. Those showing improvement during the pilot phase were given an opportunity to enroll into the extension phase of the study and receive additional intrathecal treatments (same dose and volume) every 30 to 90 days based on clinical condition. One subject (subject 2) received prophylaxis with oral prednisone prior to intrathecal laronidase after the subject developed a cellular and IgG antibody response in the cerebrospinal fluid. Some participants required that treatments be administered under fluoroscopic guidance and with anesthesia.

2.3. Measures of safety

To evaluate the possible adverse effects of the study treatments, participants had physical and neurologic examinations before and after each study treatment. Blood samples were collected for routine safety testing. All new physical complaints were evaluated and recorded including their severity and attribution to study treatments. The cerebrospinal fluid was evaluated for signs of inflammation, infection, and immune response. We measured visual acuity via Snellen test.

2.4. Objective measures of efficacy

Response to treatment was assessed using a combination of subjective and objective measures. Functional Independence Measure (FIM) score, 6-minute walk test, and Japanese Orthopedic Association (JOA) score measures were used to assess any changes in functional status and myelopathy. Scoring criteria for JOA and FIM are given in the supplemental materials (data files 2 and 3 of reference [15]). Cerebrospinal fluid glycosaminoglycans were measured at Seattle Children's Hospital using a clinically-available test. The laboratory uses a dimethylene blue dye-binding assay to quantitate total glycosaminoglycans [16]. MRI of the brain and spinal cord was obtained to assess the degree of cord compression and measurement of meningeal thickness. MRI was performed using a 1.5-Tesla GE LX9.1. Brain imaging included sagittal T1-weighted, axial FLAIR, axial T2-weighted and axial diffusion-weighted images. Sagittal T1- and T2-weighted images of the whole spine and axial T1-weighted images of the cervical spine were obtained. Axial T1-weighted studies of the cervical spine were used to score spinal cord compression according to the methods of Houten and Cooper [17]. Brain images were evaluated for abnormal signal intensity in T2, enlargement of perivascular spaces, and ventricular size as per Matheus et al. [18]. The grading systems that were used to indicate the severity of spinal cord compression and brain imaging findings are given in the supplemental materials (data file 4 of reference [15]). Cerebrospinal fluid opening pressure was measured before administration of each treatment and served as an indication of the effects of therapy on hydrocephalus. Hydrocephalus in MPS I subjects is communicating and thought to be due to inadequate reabsorption of the cerebrospinal fluid via glycosaminoglycan-clogged arachnoid granulations. We evaluated somatosensory evoked potentials in the upper and lower extremities as per [19]. Subjects enrolled in the extension study also underwent pulmonary function testing using spirometry.

2.5. Subjective measures of efficacy

Subjects were asked at baseline to report the five most troubling symptoms related to spinal cord compression. At each visit, they were asked to rate these from baseline as 0 = no change, +1 = slightly better, +2 = moderately better, +3 = much better, −1 = slightly worse, −2 = moderately worse, or −3 = much worse. The investigator was also asked to record whether the subject was better, worse, or unchanged from baseline as an overall ("global") assessment using the same scale.

2.6. Data analysis

The safety set included all enrolled subjects who received at least one dose of intrathecal laronidase. The efficacy set was defined in the 4-month pilot study as all subjects who completed the CSF glycosaminoglycan analysis at 90 days and the MRI spinal cord compression score at 120 days. The planned study size was 10 subjects, which would provide 80% power to detect an adverse event that occurred at a rate of 15%. We had initially planned to evaluate the adverse events by frequency across visits, but due to the low subject accrual we instead listed all adverse events (Table 1 of reference [15]). We evaluated the efficacy variables for intrasubject change over time, using mean, standard deviation, and 95% confidence intervals. We averaged the baseline and day 0 results for efficacy variables from the pilot study, as both occurred pre-treatment. We defined a change as significant if the 95% confidence interval did not contain zero.

3. Results

3.1. Study population and characteristics

Subject characteristics are shown in Table 1. The clinical trial design included an initial pilot study of four monthly intrathecal injections of laronidase. Subjects with a "good response" defined as improvement or stabilization of spinal cord compression were eligible for a 1-year extension study, in which treatments were administered at 30 or 90 day

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