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Laronidase

Treatment of Mucopolysaccharidosis I

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Alronidase
BM-101
Aldurazyme™

Recombinant α-L-iduronidase
8-L-Histidine-α-L-iduronidase (human)

CAS: 210589-09-6

EN: 273813

Abstract

Mucopolysaccharidosis I (MPS I) is a rare, inherited lysosomal storage disease caused by deficiency of α-L-iduronidase. The disease has a wide spectrum of clinical severity and constitutes 3 syndromes, of which Hurler's syndrome is the most severe. Enzyme replacement therapy has been investigated in the treatment of MPS I and the cloning of complementary DNA encoding α-L-iduronidase has enabled the production of recombinant human α-L-iduronidase (laronidase). Phase II and III clinical trials have confirmed the safety and efficacy of laronidase in the treatment of MPS I. The drug was launched in the U.S. in May 2003 and marketing approval by the European Commission is expected soon.

Introduction

Mucopolysaccharidosis I (MPS I) is a rare, inherited lysosomal storage disease caused by deficiency of α-L-iduronidase. It affects approximately 3,000 to 4,000 people worldwide, including approximately 1,000 in the U.S. (1). The deficiency blocks the degradation of the glycosaminoglycans heparan sulfate and dermatan sulfate, which accumulate in lysosomes. Mucopolysaccharidosis I has a wide spectrum of clinical severity and constitutes three syndromes: Hurler's syndrome (severe), Hurler-Scheie syndrome (intermediate) and Scheie's syndrome (mild). The clinical manifestations of Hurler's syndrome include progressive developmental delay, corneal clouding, airways obstruction, cardiovascular disease, hepatosplenomegaly and severe joint restriction. Most patients die by the age of 10 years. Patients with the less severe syndromes have a longer life expectancy. Those with Hurler-Scheie syndrome may live into their second or third decade, while those with Scheie's syndrome have a potentially normal life span. The difference in severity is due primarily to the effect of various mutations which permit residual enzyme activity (2).

Bone marrow transplantation is an effective treatment for patients with Hurler's syndrome. However, the mortality and morbidity associated with this procedure and the limitations of donor availability mean that its use is not widespread. Enzyme replacement therapy has been successfully used in other lysosomal storage diseases and has been investigated in the treatment of mucopolysaccharidosis I. The cloning of complementary DNA encoding α-L-iduronidase has enabled the production of recombinant human α-L-iduronidase (laronidase, Aldurazyme™).

Pharmacological Actions

Laronidase was produced by overexpression in a Chinese hamster ovary (CHO) cell line in sufficient quantities for use in biochemical studies and animal models (3).

In a study of MPS I using the feline model, laronidase was administered intravenously to cats on a weekly basis for 3 or 6 months (doses of 25,000 or 125,000 U/kg). Biochemical studies showed that the liver and spleen contained the highest enzyme activities and glycosaminoglycan storage was correspondingly decreased in these tissues. However, clinical effects were only observed in 1 cat. No consistent differences in enzyme activities or glycosaminoglycan storage between cats treated with low and high doses were observed. The duration of therapy did not significantly alter the distribution of enzyme activity (4). An earlier study in a canine model also showed normal levels of enzyme in the liver and spleen after weekly administration of laronidase

J.A. McIntyre. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

(~1 mg) to dogs for 3 months. Histological examination of tissues showed normalization of lysosomal storage in liver, spleen and kidney glomeruli (5).

Long-term and high-dose trials of laronidase in the canine model demonstrated uptake of the drug and decreased lysosomal storage in the liver, kidney, spleen, lymph nodes, synovium, adrenals and lungs. In these trials, 1 dog was treated for 13 months and 2 dogs received a high dose (approximately 0.5 mg/kg) 5 times over 10 days. The long-term treatment resulted in weight gain, increased activity and an improvement in joint stiffness in the MPS I dog compared with the untreated littermate. The treated dog gained 6.1 kg compared with only 1.4 kg in the untreated dog (6).

Clinical Studies

In the initial phase II study, 10 patients with MPS I were treated with laronidase intravenously at a dose of 125,000 U/kg once weekly for 52 weeks. Patients were aged 5-22 years on entry to the study, the majority with Hurler-Scheie syndrome. The diagnosis was confirmed by the biochemical determination of laronidase deficiency in leukocytes. The patients were evaluated at baseline, and after 6, 12, 26 and 52 weeks. Urinary glycosaminoglycan excretion declined rapidly to 60-80% below baseline values after 8-12 weeks of treatment. Hepatosplenomegaly decreased significantly in all patients; the size of the liver was normal for body weight and age in 8 patients by 26 weeks. The rate of growth in height and weight had increased significantly at 52 weeks by a mean of 85% and 131%, respectively, in the 6 prepubertal patients. Joint mobility improved and all patients reported improved endurance and fewer limitations in their ability to perform daily activities. Airways function improved in the 7 patients with apnea and hypopnea at baseline. The number of episodes of apnea and hypopnea during sleep decreased by 61%. New York Heart Association functional class improved by 1 or 2 classes in all patients. There was no evidence of improvement in corneal clouding. The most frequent adverse effect was recurrent urticaria related to infusion (2).

A pivotal, international, phase III study was conducted as a randomized, double-blind, placebo-controlled trial. Forty-five patients received laronidase 0.58 mg/kg body weight or matching placebo once weekly for 26 weeks. The primary endpoints were pulmonary function and endurance. There was a mean change in percent predicted forced vital capacity (FVC) of +4.0% and a +38.0-m change in the 6-min walk test in laronidase-treated patients compared with placebo. These differences were statistically significant after adjustment for baseline differences between patients. Reductions in liver size and in urinary glycosaminoglycan excretion were also observed. The safety profile was comparable between treatment groups. The most common adverse events associated with laronidase were upper respiratory tract infection, rash and injection site reaction. The most common adverse events requiring intervention were infusion-related hypersensitivity reactions, including flushing, fever, headache and rash. There were no serious drug-related adverse events reported (1).

In an open-label extension of this study, all patients received laronidase. In the 22 patients who had received the active treatment during the double-blind phase, there was a mean FVC change of +5.4% and a +40.0-m change in the 6-min walk test after 62 weeks of treatment compared with pretreatment baseline values. These changes were statistically significant. Patients from the placebo group (n=23) demonstrated a mean FVC change of +2.6% and a +32.4-m change in the 6-min walk test after 24 weeks of treatment with laronidase. During the extension phase (to 36 weeks), the safety profile of the drug was comparable to the double-blind phase, but 1 patient had a serious anaphylactoid reaction (urticaria and airways obstruction requiring tracheostomy) during an infusion (1, 7).

Ongoing clinical studies include an evaluation of the safety and pharmacokinetics of laronidase in patients under 5 years of age and an open-label dose optimization study in approximately 32 patients. More than 70 patients continue to receive treatment with laronidase in the ongoing extension studies and the expanded access program. As of April 2003, patients from the first clinical study (2) had been receiving weekly infusions of the drug for more than 4 years (1).

The U.S. FDA granted marketing approval for Aldurazyme™ in April 2003 and the drug was launched in the U.S. in May 2003. The drug is indicated for patients with Hurler's syndrome, Hurler-Scheie syndrome and for Scheie's syndrome patients with moderate to severe symptoms. As the first drug ever approved for MPS I, Aldurazyme™ has been granted orphan drrug status in the U.S., which confers seven years of market exclusivity. Applications to market the drug are also pending in the European Union, Canada and Australia. In Europe, the Committee for Proprietary Medicinal Products has issued a positive opinion on Aldurazyme™, typically the final step prior to marketing clearance for a drug in the 15 countries in the European Union. A decision is expected by the European Commission in the second quarter of 2003, and by Canada and Australia in the fourth quarter of 2003 or first quarter of 2004 (1).

Conclusions

The results of the phase II and III studies in 10 and 45 patients, respectively, with MPS I have confirmed the safety and efficacy of laronidase in the treatment of this progressive and debilitating hereditary disease. The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted unanimously that the phase III, double-blind trial showed a meaningful treatment effect in both primary endpoints. The FDA has granted marketing approval for the drug and a decision by the European Commission is expected imminently.

Source

BioMarin/Genzyme LLC (US).

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