Immunogenicity of Elosulfase Alfa, an Enzyme Replacement Therapy in Patients With Morquio A Syndrome: Results From MOR-004, a Phase III Trial

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ABSTRACT

Purpose: Morquio A syndrome (mucopolysaccharidosis IVA [MPS IVA]) is a lysosomal storage disorder caused by deficiency of the enzyme *N*-acetylgalactosamine-6-sulfatase, which is required to degrade the glycosaminoglycan keratan sulfate. Morquio A is associated with extensive morbidity and early mortality. Elosulfase alfa is an enzyme replacement therapy that provides a treatment option for patients with Morquio A. We examined the immunogenicity profile of elosulfase alfa, assessing any correlations between antidrug antibodies and the efficacy and safety outcomes in 176 patients with Morquio A from a 24-week international Phase III trial.

Methods: Patients were randomized to placebo (n = 59) or elosulfase alfa 2.0 mg/kg administered weekly (n = 58) or every other week (n = 59) as an ~4-hour infusion. Blood samples were routinely tested to determine drug-specific total antibody titer and neutralizing antibody (NAb) positivity. Drug-specific immunoglobulin E positivity was tested routinely and in response to severe hypersensitivity adverse events (AEs). Antidrug antibody positivity and titer were compared with efficacy and safety metrics to assess possible correlations.

Findings: The 176 patients in the trial were 54% female, with a mean age of 11.9 years. In all patients treated with elosulfase alfa antidrug antibodies developed, and in the majority, antibodies capable of interfering with cation-independent mannose-6-phosphate receptor binding in vitro (NAb) developed. Less than 10% of patients tested positive for drug-specific IgE during the study. Despite the high incidence of anti–elosulfase alfa antibodies, no correlations were detected between higher total antibody titers or NAb positivity and worsened 6-minute walk test results, urine keratin sulfate levels, or hypersensitivity AEs. Drug-specific IgE positivity had no apparent association with the occurrence of anaphylaxis, other hypersensitivity AEs, and/or treatment withdrawal.

Implications: Despite the universal development of antidrug antibodies, elosulfase alfa treatment was both safe and well tolerated and immunogenicity was not associated with reduced treatment effect. ClinicalTrials.gov identifier: NCT01275066. (*Clin Ther*. (*Clin Ther*. 2014;▮:▮▮▮–▮▮▮) © 2014 Published by Elsevier HS Journals, Inc.

Key words: antibody, efficacy, enzyme replacement therapy, immunogenicity, Morquio A, mucopolysaccharidosis IVA.

INTRODUCTION

Morquio A syndrome (mucopolysaccharidosis IVA; OMIM 253000) is an autosomal recessive lysosomal storage disease caused by a deficiency of the enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS; EC 3.1.6.4), which is required for degradation of the glycosaminoglycans chondroitin-6-sulfate and keratan sulfate (KS). Morquio A syndrome is a rare disease with an incidence estimated to range from 1 in 76,000 to 1 in 640,000 live births in different populations.[1–3]

Patients with Morquio A syndrome appear initially healthy at birth but clinical signs due to the accumulation of glycosaminoglycans in multiple cells, tissues, and organs develop.[4] Although the progression of

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Morquio A syndrome and the severity of individual clinical manifestations can vary considerably among patients, generally the burden of disease is severe, and patients have profound unmet medical needs.[5,6] Patients frequently show prominent skeletal and connective tissue abnormalities, most commonly dwarfism with short trunk and neck, spinal abnormalities, genu valgum, pectus carinatum, hip dysplasia, and joint hypermobility and instability due to ligamentous laxity and joint bone deformities.[5] Reduced endurance due to pulmonary and cardiac manifestations is also common, affecting both quality of life and mortality; for patients with Morquio A syndrome, death often results from cardiorespiratory or neurologic complications.[5] Patients with rapidly progressing disease rarely live past their second or third decade, and even patients with more slowly progressing disease rarely live past their sixth decade.[5]

Enzyme replacement therapy (ERT) by infusion of recombinant human GALNS (elosulfase alfa*) is approved by the US Food and Drug Administration and the European Commission for treatment of patients with Morquio A syndrome. Elosulfase alfa is currently the only approved therapy for Morquio A syndrome. Elosulfase alfa ERT is expected to reduce accumulated KS, which causes the Morquio A clinical manifestations.[7] However, ERTs have the potential to induce antidrug antibodies in treated patients.[8,9] Immune responses to ERTs for other lysosomal storage disorders are highly variable in terms of the incidence of antidrug antibodies and the impact on safety and efficacy.[8–10] Here we report the immunogenicity profile of elosulfase alfa in patients with Morquio A syndrome during a 24-week Phase III clinical study (MOR-004) and examine the relationship between immunogenicity and patient outcomes and safety.

METHODS

Study Design and Patients

MOR-004 was a 24-week, randomized, double-blind, placebo-controlled Phase III study of elosulfase alfa in patients with Morquio A syndrome, conducted at 33 study centers in 17 countries from February 2011 to August 2012. After screening, 176 eligible patients who completed baseline assessments were randomized to placebo (59 patients), elosulfase alfa 2.0 mg/kg/week (QW; n = 58) or elosulfase alfa 2.0 mg/kg/every other week (QOW; n = 59), administered in an infusion of ~4 hours; 1 patient from the QW group discontinued the study due to voluntary withdrawal of consent. The primary safety and efficacy outcomes of the MOR-004 trial have been reported.[11] In brief, the primary trial endpoint was the distance traveled during a 6-minute walk test (6MWT), a test of patient endurance and ambulation that was performed in accordance with American Thoracic Society guidelines.[12] To assess elosulfase alfa immunogenicity, antibody positivity and titer were assessed throughout the trial. The study protocol was approved by an institutional review board, independent ethics committee, or research ethics board at each participating clinical site. Each participant or his or her legally authorized representative provided written informed consent before entering the study. Patients, investigators, and site personnel were all blinded to treatment assignments until completion of final analyses.

Study participants had a documented clinical diagnosis of Morquio A syndrome based on clinical signs and symptoms, together with either a documented decrease in GALNS enzyme activity as assayed in fibroblasts or leukocytes or a genetic test confirming the Morquio A diagnosis according to the laboratory processes and procedures.[13] Other inclusion criteria included an average 6MWT distance of 30 to 325 m during screening, anticipated ability to comply with the treatment schedule, and willingness to use an acceptable method of contraception. Exclusion criteria included undergoing a hematopoietic stem cell transplantation and major surgery within 3 months of study entry.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2000. Each participant or his or her legally authorized representative provided written informed consent before entering the study in compliance with applicable local regulations.

Administration of Elosulfase Alfa

Patients received premedication with an antihistamine ~30 to 60 minutes before the start of the elosulfase alfa infusion. At the discretion of the investigator, patients with risk factors for

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