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The relationship between anti-idursulfase antibody status and safety and efficacy outcomes in attenuated mucopolysaccharidosis II patients aged 5 years and older treated with intravenous idursulfase☆,☆☆

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ABSTRACT

In the pivotal phase II/III trial of idursulfase administered intravenously to treat mucopolysaccharidosis II, approximately half of the patients developed antibodies to idursulfase. This post-hoc analysis of data from the phase II/III trial and extension study examined the relationship between antibody status and outcomes. A total of 63 treatment-naïve patients received 0.5 mg/kg of intravenous idursulfase weekly for two years. Thirty-two patients (51%) were positive for anti-idursulfase IgG antibodies, 23 of whom (37%) became persistently positive. All patients who developed an antibody response did so by their scheduled Week 27 study visit. Positive antibody status appeared to have no statistically significant effect upon changes in six-minute walk test distance, percent predicted forced vital capacity, or liver and spleen volume. All patients showed significant decreases in urinary GAG levels, although the antibody positive group maintained somewhat higher urinary GAG levels than their antibody-negative counterparts at the end of study (138.7 vs. 94.7 μg/mg creatinine, $p = 0.001$). Antibody positivity was not associated with a higher event rate for serious adverse events. Among patients who had no prior infusion-related reactions, antibody positive patients were 2.3 times more likely to have a first infusion-related reaction than those who would remain negative ($p = 0.017$); the risk increased to 2.5 times more likely for those who were persistently positive ($p = 0.009$). These differences in risk disappeared among patients with a previous infusion-related reaction, likely because of preventive measures. A genotype analysis for the 36 patients with available data found that patients with nonsense or frameshift mutations may be more likely to develop antibodies, to experience infusion-related reactions, and to have a reduced uGAG response than those with missense mutations, suggesting the possibility that antibodies are not a driver of clinical outcomes but rather a marker for genotype.

1. Introduction

Mucopolysaccharidosis II (MPS II or Hunter syndrome; OMIM 309900) is a lysosomal storage disorder caused by the accumulation of the glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate within lysosomes due to a deficiency in the enzyme iduronate-2-sulfatase [1,2]. MPS II is a progressive disease in which patients appear normal at birth but develop characteristic signs and symptoms beginning during childhood, leading to significant morbidity throughout life and early mortality [3,4]. Somatic signs and symptoms can include coarse facial features, macroglossia, hearing loss, recurrent upper respiratory and ear infections, airway obstruction, impaired pulmonary function, cardiac valve disease, skeletal abnormalities, short stature, joint stiffness and contractures, hepatosplenomegaly, hernia, chronic diarrhea, and a characteristic pebbly skin rash [5]. Approximately two-thirds of patients experience progressive cognitive impairment in addition to somatic signs and symptoms [6].

Enzyme replacement therapy with idursulfase, a recombinant human iduronate-2-sulfatase (Elaprase®, Shire Human Genetic Therapies, Lexington, Massachusetts, USA), was approved in 2006 in the United States and in 2007 in Europe at the recommended dose of 0.5 mg/kg weekly. It is currently available in 52 countries. The pivotal phase II/III study (NCT00069641) was a randomized, double-blind, placebo-controlled, multicenter, international trial enrolling 96 patients without cognitive impairment (attenuated phenotype) aged

Abbreviations: %FVC, percent predicted forced vital capacity; 6MWT, six-minute walk test; Ab+, antibody positive; Ab−, antibody negative; AEs, adverse events; CSA, conformation-specific antibody assay; ELISA, enzyme-linked immunosorbent assay; FVC, forced vital capacity; GAG, glycosaminoglycan; IRAE, infusion-related adverse events; MPS, mucopolysaccharidosis; NAb+, neutralizing antibody positive; NAb−, neutralizing antibody negative; PAb+, persistently antibody positive; PNAb+, persistently neutralizing antibody positive; RIP, radioimmunoprecipitation; SAE, serious adverse event; TEAE, treatment emergent adverse event; uGAG, urinary glycosaminoglycan.

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5.0 to 30.9 years [7]. Patients received either infusions of idursulfase (0.5 mg/kg every week or every other week), or placebo for 53 weeks. Patients in both idursulfase arms demonstrated statistically significant improvements in the primary efficacy endpoint, a two-component score generated by summing the rank scores for change from baseline in the six-minute walk test (6MWT) distance and percent predicted forced vital capacity (%FVC). All patients who completed the phase II/III study enrolled in the open-label extension study (NCT00630747) and were treated with intravenous idursulfase 0.5 mg/kg weekly for an additional 24 months [8]. In the extension study, significant improvements in change from baseline in 6MWT distance, a primary endpoint, were seen at all time points except one. Significant improvements in %FVC were seen only at one time point; however, absolute FVC showed sustained improvement throughout the study.

As previously published, IgG antibodies to idursulfase were detected in 46.9% of the patients in the weekly treatment group of the phase II/III trial [7] and in 50% of the patients over the course of the entire phase II/III trial plus extension [8], with unknown long-term effects on the efficacy and safety of idursulfase. IgE antibodies were not detected in any patients in the phase II/III study or extension. The concern with IgG antibodies is that the clinical efficacy of idursulfase may be reduced when an immune response neutralizes enzyme activity, either by direct inactivation of the enzyme's catalytic activity, or by affecting its biodistribution and/or cellular uptake. Additionally, there is a concern that the presence of a humoral immune response may contribute to the development of infusion-related hypersensitivity reactions [9]. Here, we present results from a post-hoc analysis of data from the phase II/III study and extension study in order to examine the association between anti-idursulfase antibody status and the efficacy and safety of idursulfase in an attenuated, treatment-naïve population of patients 5 years of age and older.

2. Methods

2.1. Patients

The phase II/III study enrolled patients between the ages of 5 and 31 years with a clinically and biochemically confirmed diagnosis of MPS II [7]. All patients were cognitively intact and are, therefore, considered to be representative of the attenuated phenotype of MPS II. Patients were required to reproducibly perform pulmonary function testing with a demonstrated FVC of <80% of predicted. Exclusion criteria included tracheostomy, bone marrow transplant, or cord blood transplant. Upon completion of the phase II/III study, patients were enrolled into the extension study [8].

The original phase II/III trial and extension study were conducted in compliance with international guidelines and appropriate local country regulations [7,8]. Written informed consent for these studies was given by adult patients or the parents/guardians of patients under the age of 18 years. The protocol and informed consent documents were approved by the institutional review board (IRB) and/or independent ethics committee at each site conducting the studies. The work described in this manuscript represents new statistical analyses of immunogenicity (antibody) test results that were generated during these trials. No new blood samples were obtained in order to perform the current analyses, and no existing blood samples were re-analyzed for antibody titer.

The primary population for the post-hoc analysis was comprised of two subgroups of treatment-naïve patients who had received weekly infusions of idursulfase 0.5 mg/kg for a total of 105 weeks. Subgroup 1 received 0.5 mg/kg idursulfase weekly in the phase II/III trial for 53 weeks then continued on the same dose and schedule in the extension study. Only the first 53 weeks' worth of extension data was included in the immunogenicity analysis, for a total of 105 weeks of treatment. Subgroup 2 received placebo during the phase II/III study then switched to weekly idursulfase 0.5 mg/kg infusions during the extension study for 105 weeks, for a total of 105 weeks of treatment. Data from both subgroups have been combined and analyzed together in this report.

2.2. Antibody measurements

As described previously, blood samples were screened for the detection of serum idursulfase IgG antibodies using the conformation-specific antibody (CSA) or enzyme-linked immunosorbent (ELISA) assays [7]. All samples meeting the CSA or ELISA cut points were confirmed by a radioimmunoprecipitation (RIP) assay. If a sample was confirmed by the RIP assay, then the sample was reported as positive with the titer determined by either the CSA or ELISA assay. The titer was reported as a whole number. If the sample was negative by the RIP assay, the sample was reported as antibody negative. All antibody-positive samples were analyzed for neutralizing antibodies with both an in vitro activity-neutralizing antibody assay [10] and a cell-based internalization antibody assay [11]. Antibody testing was performed at baseline and at the following scheduled Study Week visits: 5, 9, 18, 27, 36, 45, 53, 79, and 105. Note that Study Week visits in which idursulfase infusions were administered and safety and efficacy assessments were made were scheduled to occur at 7 day intervals; however, variations of ± 3 days were permitted for actual visit dates. Therefore, a Study Week visit of a certain number (e.g. Week 27) for a given patient may not have occurred at precisely the corresponding number of calendar weeks after treatment start.

2.3. Antibody status

The following definitions were used for antibody status:

- Antibody Positive (Ab+): At least one serum specimen had measurable antibody by either CSA or ELISA, confirmed by RIP, regardless of the antibody status at any subsequent visits. A patient was considered to be Ab+ at a given scheduled study visit if, by this time point, the patient had at least one visit at which there were measurable IgG antibodies.
- Persistently Antibody Positive (PAb+): There were three or more consecutive scheduled study visits at which the patient was Ab+, regardless of the antibody status at any subsequent visits. A patient was considered to be PAb+ at a given scheduled study visit if, by this time point, the patient had the first of three or more consecutive visits at which there were measurable IgG antibodies.
- Neutralizing Antibody Positive (NAb+): At least one serum specimen was positive at any time during the study on either an activity-neutralizing antibody assay or a cell-based internalization antibody assay, regardless of the antibody status at any subsequent visits. A patient was considered to be NAb+ at a given week if, by this time point, the patient had at least one scheduled study visit at which there were measurable neutralizing antibodies measured by either assay.
- Persistently Neutralizing Antibody Positive (PNAb+): There were three or more consecutive scheduled study visits at which the patient was NAb+, regardless of NAb status at subsequent visits. A patient was considered to be PNAb+ at a given week if, by this time point, the patient had the first of three or more consecutive visits at which there were measurable neutralizing antibodies by either assay.
- Antibody Negative (Ab−): All antibody tests were negative throughout the treatment period.
- Not Persistently Antibody Positive (Not PAb+): Patients did not meet the criteria to be PAb+ at any time. Note that these patients could be Ab−, Ab+ or NAb+.
- Neutralizing Antibody Negative (NAb−): No positive serum specimen during the study on either an activity-neutralizing antibody assay or a cell-based internalization antibody assay. Note that these patients could be Ab−, Ab+, or PAb+.