

Commentary

Enzyme Replacement Therapies and Immunogenicity in Lysosomal Storage Diseases: Is There a Pattern?

Paul Harmatz, MD

UCSF Benioff Children's Hospital Oakland, Oakland, California

ABSTRACT

Lysosomal storage diseases arise because of genetic mutations that result in nonfunctioning or dysfunctional lysosomal enzymes responsible for breaking down molecules such as glycosaminoglycans or glycogen. Many of these storage diseases, such as the mucopolysaccharidosis (MPS) disorders and Pompe disease, can now be treated with infusion therapies to replace the dysfunctional protein with active enzyme. Although these therapies are effective, in at least one condition, infantile-onset Pompe disease, antibodies that develop against the drug significantly reduce its efficacy. However, this influence on efficacy does not appear to manifest across all enzyme replacement therapies. An example is MPS IVA, or Morquio A syndrome, in which the glycosaminoglycans keratan sulfate and chondroitin-6-sulfate accumulate in tissues as a result of *N*-acetylgalactosamine-6-sulfatase deficiency. The current approved treatment for MPS IVA is elosulfase alfa, a recombinant human enzyme replacement therapy. Although all patients receiving elosulfase alfa treatment develop antidrug antibodies and most develop neutralizing antibodies, clinical data to date show no effect on drug efficacy or safety. Overall, the relevance of antidrug antibodies specific to enzyme replacement therapies for the lysosomal storage diseases remains a mixed picture that will require time and continued clinical follow-up to resolve for each specific condition and treatment. (*Clin Ther.* 2015;37:2130–2134) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: antidrug antibody, elosulfase alfa, enzyme replacement therapy, immunogenicity, Morquio A syndrome, mucopolysaccharidosis.

BACKGROUND

Lysosomal storage diseases are characterized by failure of function of 1 or more lysosomal enzymes.^{1,2}

The result of the lost function is accumulation in tissues of the enzyme's target molecule, and these conditions present with a broad spectrum of manifestations depending on the severity of the mutation, specific target molecule, and tissues most affected. Most of these diseases are inherited in an autosomal recessive manner with some exceptions, such as Fabry disease (X linked)³ and one of the mucopolysaccharidosis (MPS) disorders, MPS II (Hunter syndrome; OMIM 309900; also X linked). Eleven lysosomal enzyme deficiencies are classified as MPS disorders,² including MPS IVA (Morquio A syndrome; OMIM 253000).

In MPS IVA, a deficiency in the enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS) leads to lysosomal accumulation of its target molecules, the glycosaminoglycans keratan sulfate and chondroitin-6-sulfate.^{4,5} This accumulation affects a variety of organ systems, including bone, respiratory, cardiovascular, visual, auditory, and hepatic tissues.⁶

Individuals with MPS IVA do not usually show signs of the condition at birth but eventually present with progressive disease. They typically have severe skeletal dysplasia characterized by dwarfism, hip and spine abnormalities, and joint instability and hypermobility as a result of the lax ligaments that distinguish this condition from other mucopolysaccharide diseases. Progression of skeletal disease can lead to neurological impairments from compression myelopathy, but the central nervous system is generally considered to be unaffected, in contrast to all other MPS disorders except for MPS VI.^{6,7}

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In the absence of treatment, death usually occurs in the second or third decade for MPS IVA patients who experience rapid disease progression, which is characterized by rapidly worsening dysostosis multiplex, limited growth, and high urinary keratan sulfate (uKS) values.⁸ In patients with a slower disease progression, the various system manifestations, including skeletal, develop less rapidly but eventually do arise, and life expectancy for this group is usually no greater than the sixth decade.⁹ MPS IVA, which follows an autosomal recessive pattern of inheritance, occurs in ~1 in 76,000 to 640,000 live births globally.¹⁰

ENZYM REPLACEMENT THERAPY WITH ELOSULFASE ALFA

Efficacy and Safety

The current treatment for MPS IVA is infusion with replacement enzyme in the form of recombinant human GALNS (elosulfase alfa^{*}). This drug, which received approval from the US Food and Drug Administration in February 2014, is administered once weekly (2 mg/kg infusion; VIMIZIM prescribing information¹¹). Clinical trials have demonstrated the effectiveness of weekly elosulfase alfa infusion in increasing endurance, as measured by the 6-minute walk test (6MWT), the primary efficacy measure in the Phase III trial (MOR-004). The Phase III randomized, placebo-controlled trial also demonstrated the effect of weekly elosulfase alfa in reducing uKS values,^{10,12} one of the secondary outcomes; higher levels of uKS have been associated with more severe impairment.⁹ The 3-minute stair climb, the trial's other secondary outcome, remained unaffected by treatment.

Based on findings from the Phase III trial, elosulfase alfa has an acceptable safety profile, with the most frequent adverse events being rated as mild to moderate infusion-associated reactions.¹² In MOR-004 (the pivotal Phase III study), hypersensitivity reactions occurred in about one fifth of patients and were usually mild to moderate,¹² but only 10% of patients in this trial tested positive for immunoglobulin E.¹³

Earlier multicenter, open-label dose-escalation trials (MOR-002) showed similar improvements in the 6MWT, which were sustained during almost 3 years of follow-up in the MOR-100 extension study.¹⁴ This maintenance of endurance over a period of years is clinically relevant for a patient population that, without treatment, would experience decline.^{9,15}

Although these longer term findings are promising, further analysis is needed to investigate the effect of antidrug antibodies (ADAs) and neutralizing antibodies on long-term treatment efficacy and safety.¹⁶

Enzyme Replacement Therapy and Immunogenicity

Describing the relationship between efficacy and antibodies is relevant in the context of enzyme replacement because of the lessons learned from enzyme replacement therapy (ERT) for infantile-onset Pompe disease.¹⁷ Pompe disease is also a lysosomal storage disorder, arising from a deficiency in acid-alpha glucosidase, one of the enzymes responsible for breaking down glycogen. The result is a buildup of the carbohydrate in the heart and skeletal muscles. The disease occurs in 3 forms, including infantile onset, which is characterized by relatively rapid progression and usually death by the age of 2 years. The ERT for this condition, alglucosidase alfa[†], has proved effective in extending ventilator-free survival in this patient population, but a drug-specific antibody response has been associated with a critical loss of efficacy.^{18,19}

The impact on efficacy of the drug-specific antibody response to alglucosidase alfa has specifically been linked to the presence or absence of endogenous immune-reactive material in the form of incomplete or nonfunctional protein, known as cross-reactive immunological material (CRIM).¹⁸ Among the lysosomal storage diseases, CRIM status has been noted as a determining factor of clinical outcome for a subset of Pompe patients, those with infantile-onset Pompe who are CRIM negative. CRIM-negative patients with infantile-onset Pompe would be expected to lack endogenous protein and are reported to be more likely to develop high, lasting antibody titers and have a worse clinical outcome compared with their CRIM-positive counterparts.^{17,18,20} The hypothesis is that the presence of even limited acid-alpha glucosidase material from birth in CRIM-positive individuals could prime the immune system to recognize the infused alglucosidase alfa as “self” and not mount a response; in the absence of these priming molecules, the replacement enzyme triggers antibody production.

This interpretation has, however, been brought into question by findings of high ADA titers in some CRIM-positive patients²¹ and low¹⁹ or moderate²² titers in

^{*}VIMIZIM, BioMarin Pharmaceutical Inc. (Novato, California).

[†]Myozyme® (Genzyme Corp., Boston, Massachusetts).

some CRIM-negative patients. In a recent study of 11 children with infantile-onset Pompe,¹⁹ ADA titers did not correlate with CRIM status. In addition, the 4 patients in that study who were CRIM negative died before 4 years of age regardless of their antibody titers, implicating some other factor related to CRIM status. These authors suggest that an early start to therapy, before 2 months of age, played a role in lower antibody titers in their patient group. Another report described an adult patient who was CRIM positive with a high antibody titer and who experienced reduced alglucosidase alfa efficacy.¹⁹ Current practice in Pompe disease involves treatment with immunosuppressant drugs to induce tolerance to the ERT in CRIM-negative/antibody-positive patients.^{18,23}

The type of mutation may be relevant to the antibody story in some other lysosomal storage disorders. In Fabry disease, for example, patients who have nonsense mutations are more likely than those with missense mutations to develop ADAs.²⁴ In a study of 36 MPS II (Hunter syndrome) patients receiving idursulfase ERT, Barbier et al.²⁵ found that those with nonsense or frameshift mutations were more likely to develop antibodies and show a reduced urinary glycosaminoglycan response compared to their counterparts with missense mutations. Nevertheless, antibody response was not related to 6MWT improvement, liver and spleen volume change, or improvements in respiratory measures in their patients receiving ERT. These authors suggested that the antibodies do not shape clinical outcomes but might serve as a marker of genotype (ie, nonsense/frameshift versus missense). Antibodies to idursulfase developed in about half of the MPS II patients in that study.

In contrast, for MPS IVA patients, any correlation between genotype and antibody titer requires further exploration, in part because genotype has not been systematically determined in clinical trials and CRIM status has not been addressed for this population. However, unlike CRIM-negative patients with infantile-onset Pompe, most of whom have a nonsense or frameshift mutation,²⁶ many mutations identified in MPS IVA involve missense-related changes, implying the presence of some translated protein.²⁷

Regarding early treatment as a possible way to evade antibody-related complications, as has been suggested for Pompe disease, early intervention with ERT is beginning to be evaluated in MPS, with trials ongoing for patients younger than 5 years of age. Results of

studies in which a younger sibling begins ERT earlier than an older sibling so far suggest improved outcomes overall with earlier intervention.^{28,29}

Elosulfase Alfa: Immunogenicity and Pharmacokinetics/Pharmacodynamics and Efficacy

The CRIM status findings in infantile-onset Pompe disease, in which high or sustained antibody titers may interfere with ERT efficacy, has focused attention on other ERTs and how antibody titers might influence their effectiveness. Schweighardt et al.¹³ evaluated the immunogenicity of elosulfase alfa in MPS IVA patients participating in the MOR-004 Phase III trial. As they describe in their paper, the outcome thus far differs from that of infantile-onset Pompe disease and alglucosidase alfa. Schweighardt et al. report that in the Phase III trial, ADAs developed in all patients on elosulfase alfa treatment, and antibodies developed in most of them (96.6% on the every-other-week dosing regimen and 98.3% on the weekly regimen) that could interfere with *in vitro* binding to a target receptor (ie, neutralizing antibodies). However, antibody titers did not correlate with worsening 6MWT values or with increased uKS. These authors also found no link between antibody titers and hypersensitivity reactions, and no pattern related to the presence of ADA immunoglobulin E and hypersensitivity, anaphylaxis, or treatment withdrawal. They note that monitoring of immunogenicity and potential effects on safety and efficacy will continue in the postapproval setting.

A further analysis of the pharmacokinetics of the drug during this Phase III trial³⁰ indicated that total antibody titers had no effect on drug clearance but that NAb positivity was associated with a reduced clearance rate and longer plasma half-life in patients receiving a weekly dose. The implications of this effect on clearance are unknown.

The reason for these very different outcomes with ERT for different lysosomal storage disorders is unclear, but one possible explanation in the case of elosulfase alfa arises from its short half-life, which can be as little as 7 minutes at week 1 and peaks at only 35 minutes in plasma by week 22 of treatment, once antibody is present. Schweighardt et al.¹³ hypothesize that during infusion, elosulfase alfa may saturate available antibody, leaving the remaining drug free to bind the receptor and enter the cell via rapid clearance through the target receptor. The presence of the drug

and the antibody together in the plasma for only a short amount of time additionally might reduce the opportunity for immune complex formation.

Elosulfase alfa is not the only ERT that shows a pattern of antibody positivity combined with continued drug efficacy. The lack of an association between efficacy and the presence of ADAs has also been reported for ERT treatment for MPS I,³¹ MPS VI,³² and Fabry disease.³³ However, one study that included 30 men being treated with one of the ERTs for Fabry disease for up to 10 years suggested some reduced efficacy in those who were antibody positive.³⁴ Deegan,³⁵ in a review from the same year, notes interpretation difficulties related to the heterogeneity of both the disease presentation in Fabry disease and therapeutic response. Gaining a clear picture of the antibody–efficacy interaction is difficult, even within a single condition.

FUTURE PERSPECTIVES

In the setting of lysosomal storage disorders, antibody measures have been associated with a risk of reduced ERT efficacy in Pompe disease, a mixed set of outcomes in Fabry disease, and no influence to date on the efficacy in MPS I or MPS VI. Joining the last group is elosulfase alfa for MPS IVA. In all patients on elosulfase alfa treatment, antibodies to the drug develop, but antibody titers thus far show no correlation with efficacy or safety. With this latest contribution to the growing literature on antibodies and end points in the ERT context, we see a continued heterogeneity of antibody-related findings that reflects the heterogeneity across these lysosomal storage disorders and an overall difficulty in correlating antibody levels and outcomes. As data continue to accumulate over the long term, the underlying cause of this variability across disorders may become clearer. Meanwhile, some limited evidence suggests that a focus on early treatment—and thus early diagnosis—might be beneficial not only in terms of clinical outcomes but also for preempting the antibody question altogether.

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CONFLICTS OF INTEREST

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Address correspondence to: Paul Harmatz, MD, Pediatric GI and Nutrition, UCSF Benioff Children’s Hospital Oakland, 747 52nd Street, Oakland, CA 94609. E-mail: pharmatz@mail.cho.org