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;▮:▮▮▮–▮▮▮) © 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]

Accepted for publication June 1, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.06.004
0149-2918/$ - see front matter

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]

ENZYME 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 information[11]). 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 patients[21] and low[19] or moderate[22] titers in

*VIMIZIM, BioMarin Pharmaceutical Inc. (Novato, California).

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