

Immune modulation in a patient with Morquio syndrome treated with enzyme replacement therapy

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Clinical Implications

- In patients with Morquio A syndrome, immune tolerance induction may reduce antibody production and improve clinical response to enzyme replacement therapy in those patients with severe mutations such as a large deletion. Hypersensitivity reactions appear to correlate with antibody titers.

TO THE EDITOR:

Morquio A syndrome or mucopolysaccharidosis type IVA (MPS IVA) is a lysosomal storage disorder caused by mutations in *GALNS*, which encodes N-acetylgalactosamine-6-sulfatase, an enzyme necessary for the degradation of keratan sulfate (KS) and chondroitin-6-sulfate. Clinical features include skeletal deformities and corneal clouding. Recombinant human N-acetylgalactosamine-6-sulfatase (rhGALNS), or elosulfase alfa, is the standard of treatment for MPS IVA.

Immunogenicity to enzyme replacement therapy (ERT) has been reported in several lysosomal storage diseases.¹ Antibody production can reduce efficacy of ERT and cause hypersensitivity reactions. Immune modulation has been used in lysosomal storage disorders, most notably Pompe disease.¹ The Duke University immune tolerance induction protocol was shown to improve clinical course and disease biomarkers in Pompe patients compared with nontolerized counterparts.²

Here we report the first patient with MPS IVA treated with immune modulation before starting ERT.

The proband presented for clinical evaluation of short stature at 2.75 years. He had pectus carinatum, genu valgum, shortened forearms, and ulnar deviation of the wrists. N-Acetylgalactosamine-6-sulfatase activity was 2.08 nmol/17 h/mg (normal 76.1-255.1). Genetic testing identified a homozygous 20 Kb deletion of exons 3-14 of *GALNS*, confirming the diagnosis of MPS IVA.

Because of the patient's large gene deletion and predicted lack of endogenous protein, there was concern for antibody production to ERT. Given the success of immune modulation in Pompe disease, the decision was made to use a modified version of Duke University's protocol for our patient.¹ The protocol consisted of rituximab intravenous infusions (12.5 mg/kg) on day -1, elosulfase alfa infusions (2 mg/kg) on day 0, and methotrexate subcutaneous injection or intravenous infusion (0.4 mg/kg) on days 0, 1, and 2. This cycle was repeated weekly for 4 weeks.

The patient developed vomiting and urticarial rash with the first rituximab infusion. He was treated with epinephrine,

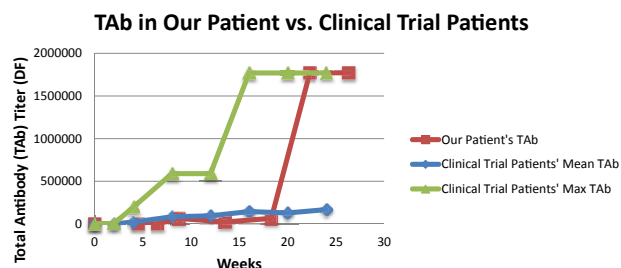


FIGURE 1. Total antibody (TAB) levels. Comparison of TAB levels in our patient and those in the clinical trial. Note the delayed peak in our patient. DF, Dilution factor.

diphenhydramine, methylprednisolone, and a normal saline bolus. Before the next infusion, he underwent a desensitization protocol using acetaminophen, diphenhydramine, methylprednisolone, and ranitidine. All subsequent rituximab infusions were well tolerated. The immune tolerance induction protocol was then carried out without adverse events. Although the Duke University protocol for Pompe disease calls for intravenous immunoglobulin (IVIG) at 4-week intervals, our patient did not develop hypogammaglobulinemia. Therefore, IVIG was not given.

Between weeks 22 and 26 of treatment, the patient developed hives and vomiting with each infusion. His symptoms were managed with ondansetron, acetaminophen, diphenhydramine, dilution of the drug, and slower infusion rate. He continues to receive this regimen, which allows him to tolerate his infusions.

Total anti-rhGALNS antibodies (TAB) and neutralizing antibodies (NAB) were monitored regularly.

Our patient's baseline TAB was 90 DF (dilution factor) (Figure 1). This level remained low for over 20 weeks. Beginning around week 22, TAB increased to 1,771,470 DF. This sudden and marked rise corresponded to the patient's hypersensitivity reactions. TAB level remained stably elevated at 1,771,470 thereafter. NAB were 21.41 DF at baseline and increased to 964.29 DF between weeks 22 and 26. Urine KS decreased from 66 µg/mg Cr (normal 0-9.6) at baseline to a nadir of 22.16 µg/mg at 13 weeks (Figure 2). Concurrent with the upsurge in TAB, urine KS trended up, reaching 38.77 µg/mg. Clinically, the patient's endurance and ambulation have improved and he maintains age-appropriate growth velocity.

Only approximately 14% of patients with MPS IVA have deletions, and most of these are compound heterozygous.³ Our patient has a large, homozygous deletion that has not been reported in mutation databases^{4,5} or the Morquio A patient registry.⁶ A similar large, homozygous deletion was reported in one instance but the breakpoints of the deletion are unclear.⁷ Because our patient's deletion abolishes most of the mRNA transcript, it is predicted to result in minimal to no protein production and, from a clinical standpoint, greater risk of developing antibodies to ERT.

All patients in the rhGALNS clinical trial developed anti-rhGALNS antibodies by week 4 (Figure 1). TAB peaked on average at 16 weeks at 1,770,000 DF. In comparison, our patient's

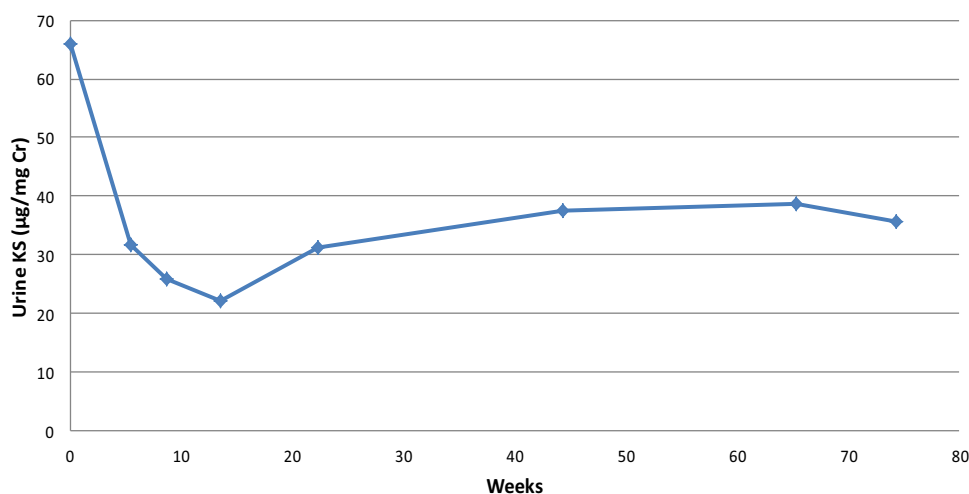


FIGURE 2. Urine KS excretion. KS levels decreased after initiation of ERT, then increased corresponding to the development of hypersensitivity. ERT, Enzyme replacement therapy; KS, keratan sulfate.

TAb peaked at 22.5 weeks at 1,771,470 DF (Figure 1). At the end of the clinical trial, mean TAb was 167,737 DF and max TAb was 1,771,700 DF. Although our patient's antibody level was above the mean observed in the clinical trial, his response was delayed compared with those who produced similar high levels.

Our patient developed symptoms possibly consistent with a type I hypersensitivity reaction during his elosulfase alfa infusions between weeks 22 and 26. These symptoms corresponded to a significant increase in TAb level, which we believe to be related to the reaction. Unfortunately, specific anti-elosulfase alfa IgE levels were not available at the time to corroborate this hypothesis. In hindsight, we would have performed another cycle of immune modulation, but because of delay in receiving results from the laboratory, this significant increase was noted several weeks after the fact. In the clinical trial, 19% of patients developed hypersensitivity reactions despite premedication with an antihistamine.⁸ No correlation was found between hypersensitivity reactions and antibody titers.⁸ However, we hypothesize that such a relationship exists given the time association between rise in TAb and infusion-related reactions in our patient. NAb remained low in proportion to TAb and was therefore thought not to have a significant effect.

Urinary KS level is a useful biomarker in MPS IV. In the clinical trial, the average decrease in KS from baseline in all patients was roughly 40% at 24 weeks.⁸ In those patients with the highest TAb levels, the average decrease from baseline was approximately 35%. In comparison, our patient's urine KS level was 53% lower than baseline at 24 weeks (Figure 2). This difference suggests an improved response to ERT in our patient due to immune modulation. Around 22 weeks, his urine KS began to rise, corresponding to the period during which he developed hives and rapid rise in TAb. This change implies lower efficacy of ERT due to high antibody titers.

Despite infusion reactions and high antibody levels, our patient responded well clinically. Similarly, patients in the clinical trial showed improvement. The positive outcomes may be due to

the low proportion of NAb or the short half-life of elosulfase alfa in plasma and its rapid uptake into tissue, allowing it to escape binding by anti-rhGALNS antibodies.⁸

In our patient with MPS IVA, immune modulation blunted immune response, resulting in greater reduction of urine KS compared with clinical trial patients. Immune tolerance induction in patients with MPS IVA may enhance clinical outcome in patients with severe mutations, such as a large deletion. We hypothesize a relationship between antibody titers, hypersensitivity, and response to ERT. The long-term clinical significance of immune modulation in MPS IVA remains to be determined.

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