

Elimination of Antibodies to Recombinant Enzyme in Pompe's Disease

TO THE EDITOR: Infantile Pompe's disease is due to a deficiency of lysosomal acid alpha glucosidase (GAA). In patients in whom GAA is not produced, a status called cross-reacting immunologic material (CRIM)-negative, enzyme-replacement therapy with recombinant human GAA (rhGAA) has uniformly led to high titers of anti-rhGAA antibody, with an ultimately fatal outcome.¹ Previous attempts at eliminating rhGAA antibodies in these patients have failed.¹⁻³ We report the successful induction of immune modulation in a CRIM-negative patient with Pompe's disease who continues to be antibody-free at 24 months of age and continues to gain motor milestones.

A baby boy of African-American descent presented at 5 weeks of age with cardiomyopathy and decreased muscle tone. The diagnosis of Pompe's disease was confirmed by means of enzymatic analysis and molecular evidence of the homozygote R854 stop mutation in the GAA gene. No GAA was detected on a Western blot skin-fibroblast assay, confirming the infant's CRIM-negative status. Enzyme-replacement therapy with rhGAA (Myozyme, Genzyme) was initiated when the patient was 7 weeks of age (Fig. 1).¹ Levels of IgG antibodies against rhGAA, measured with the use of an enzyme-linked immunosorbent assay,¹ increased rapidly, reaching a titer of 1:1600

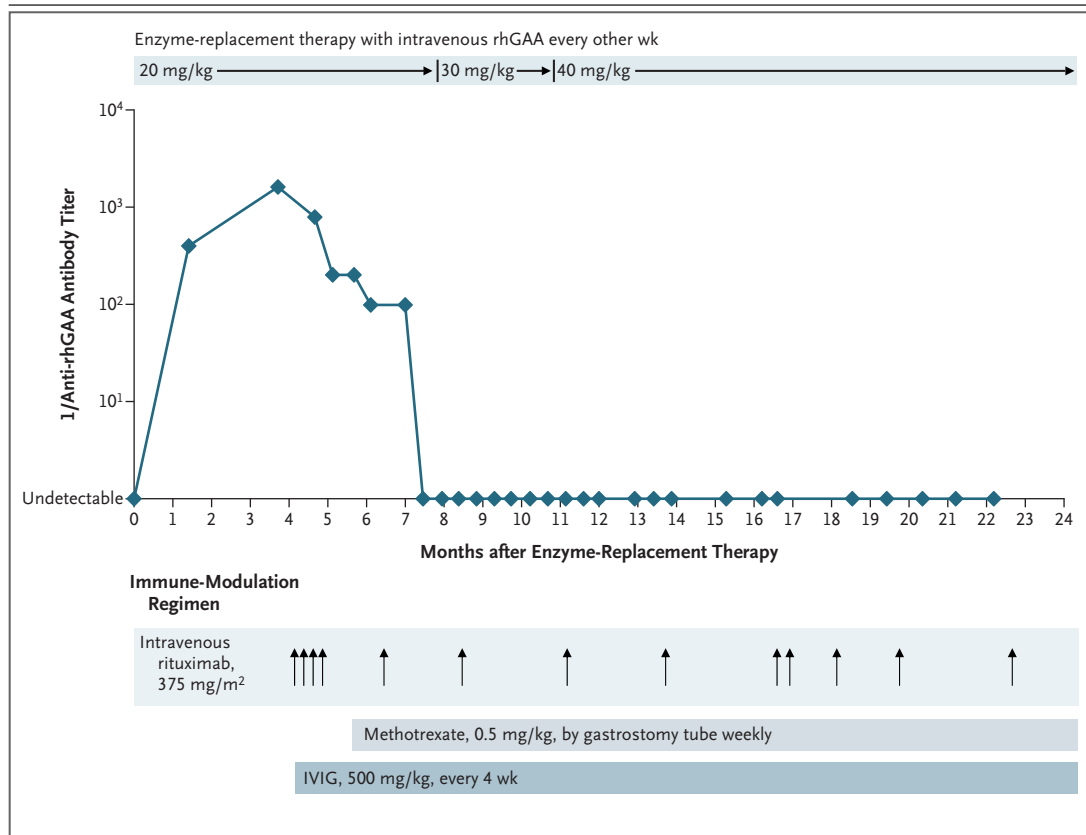


Figure 1. Antibodies against Recombinant Human Acid Alpha Glucosidase (rhGAA) in the Patient.

At 1.4 months after the start of enzyme-replacement therapy, antibody against rhGAA developed, rising to a titer of 1:1600 within less than 4 months after the start of therapy. Immune-modulation therapy was begun, consisting of four weekly doses of rituximab at 375 mg per square meter of body-surface area (arrows), followed by a maintenance dose every 4 to 12 weeks (with an extra dose after month 16). Methotrexate, at a dose of 0.5 mg per kilogram of body weight weekly, was added to the regimen after 7 weeks. Intravenous immune globulin (IVIg) was given, at a dose of 500 mg per kilogram, every 4 weeks. The anti-rhGAA antibody titer declined, becoming negative by 7.5 months after the start of the enzyme-replacement therapy (and within 3.5 months after the start of the full immune-modulation regimen).

at 23 weeks of age. Immune modulation with the anti-CD20 monoclonal antibody rituximab plus methotrexate⁴ and intravenous gamma globulin was initiated at 25 weeks of age, resulting in rapid elimination of the anti-rhGAA antibody (Fig. 1). Intravenous gamma globulin was used as an immune modulator, but since rituximab induces generalized severe B-cell suppression, intravenous gamma globulin was also administered to preserve normal immune function. With this approach, the patient has maintained undetectable antibody titers against rhGAA through 22 months of enzyme-replacement therapy (Fig. 1).

At 13 months of age, persistent carbon dioxide retention developed in the patient, and he became ventilator-dependent and required a tracheostomy. However, his ventilator settings have been stable, and he now tolerates brief periods of ventilator-free time. After the initiation of enzyme-replacement therapy, the patient's cardiomyopathy resolved, and he has shown continued neurologic improvement.

Historically, CRIM-negative patients with Pompe's disease receiving enzyme-replacement therapy fare poorly, and when treated with enzyme-replacement therapy, all have died or were ventilator-dependent, with major motor and cardiac decline. These CRIM-negative patients with Pompe's disease all had early seroconversion; in all, persistent high-titer antibodies developed within 12 months after the start of enzyme-replacement therapy. In contrast, our patient, at 24 months of age, shows ongoing clinical benefit from enzyme-replacement therapy, with undetectable antibody titers. Although the follow-up of this patient is limited to 24 months, previously studied CRIM-negative patients have all died or dramatically declined by this age.

Successful immune modulation permitting rhGAA therapy to be continued in this CRIM-

negative patient with Pompe's disease appears to be a promising approach to the treatment of this refractory disorder. This case suggests that tolerance induction may be achieved. We speculate that this strategy could be applied in patients with other severe deficiency disorders, such as hemophilia A and B, Gaucher's disease, Fabry's disease, and mucopolysaccharidosis type I, in whom the replacement protein elicits robust antibody responses that can interfere with product efficacy.

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Glycemic Control in Patients with Insulinoma Treated with Everolimus

TO THE EDITOR: Management of refractory hypoglycemia due to malignant insulinoma is challenging. Currently available treatments include dietary modification, diazoxide, and, in patients with resistant disease, the use of intravenous dextrose infusion or enteral feedings. Patients

with advanced, unresectable insulinomas often have prolonged hospitalizations and may have fatal complications from this disease.

The mammalian target of rapamycin (mTOR) is a serine-threonine protein kinase that has been implicated in the cellular response to nutrients