Nephrotic Syndrome Complicating α-Glucosidase Replacement Therapy for Pompe Disease

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ABSTRACT. We report a patient with Pompe disease who developed reversible nephrotic syndrome during prolonged, high-dose, experimental, enzyme replacement therapy with recombinant human acid α-glucosidase (rhGAA). Because of the development of antibodies to rhGAA and concomitant clinical decline, escalating doses of rhGAA were administered as part of an experimental immune tolerance regimen. Histologic evaluation of kidney tissue revealed glomerular deposition of immune complexes containing rhGAA itself, in a pattern of membranous nephropathy. To our knowledge, this is the first reported case of nephrotic syndrome occurring during enzyme replacement therapy. The nephrotic syndrome gradually resolved after the rhGAA dose was decreased, indicating that decreasing the antigenic load can ameliorate glomerular immune complex deposition associated with enzyme replacement in a highly sensitized patient. Pediatrics 2004;114:e532–e535. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2003-0988-L. enzyme replacement therapy, glucogen storage disease type II, rhGAA, membranous nephropathy, nephrotic syndrome.

ABBREVIATIONS. rhGAA, recombinant human acid α-glucosidase; C3, complement component 3.

The clinical use of therapeutic proteins has rapidly expanded in the past decade, with the advent of molecular genetic techniques. Enzyme replacement therapy has recently been used for previously untreatable diseases such as Hurler’s syndrome, Anderson-Fabry disease, and Gaucher disease.1–3 Like all exogenous proteins, therapeutic proteins developed for enzyme replacement therapy are potentially immunogenic. Antibodies that develop against replacement enzymes may be without clinical significance or may lead to hypersensitivity reactions, decreased bioavailability, or decreased efficacy of the therapeutic proteins.4,5 In a recent trial of enzyme replacement therapy for Anderson-Fabry disease, seroconversion occurred for 90% of patients but was not linked to any decrease in efficacy.6 Recurrent urticaria was observed for a subset of patients receiving α-l-iduronidase for Hurler’s syndrome, although this problem was manageable with premedication and infusion rate adjustment. Four of 10 participants in that trial developed nonneutralizing antibodies specific for the therapeutic protein, together with subclinical complement activation. However, declines in antibody titers and complement activation were noted with time. In fact, immune tolerance developed for each of those patients during a 2-year period.7 Although the rate of seroconversion has been reported to be much lower for patients receiving replacement enzyme for treatment of Gaucher disease (<20%),8 several patients with Gaucher disease have demonstrated clinical deterioration after the development of neutralizing antibodies. Several strategies to provide replacement enzyme while overcoming deleterious antibody effects have been investigated in this setting, including treatment with cytotoxic agents, plasmapheresis, and increasing the amount or frequency of enzyme infusion.9–10

Enzyme replacement therapy has recently been applied to Pompe disease, i.e., glycogen storage disease type II.11,12 Classic infantile Pompe disease is a metabolic myopathy caused by lack of lysosomal acid α-glucosidase, which results in deposition of lysosomal glycogen, cardiomyopathy, myopathy, hypotonia, and death, often by 1 year of age.13 The 3 infants who were treated with recombinant human acid α-glucosidase (rhGAA) showed steady decreases in heart size and maintenance of normal heart function for >1 year. The later clinical decline observed for 2 of the patients was ascribed to the presence of anti-rhGAA antibodies, given the correlation of antibody appearance and deterioration.11 Most recently, for 4 infants with Pompe disease who were treated with recombinant α-glucosidase from rabbit milk and in whom anti-recombinant α-glucosidase antibodies developed in the early phase of treatment and then declined, survival was prolonged...
past the age of 4 years. We report a patient with Pompe disease with high anti-rhGAA antibody titers during enzyme replacement therapy who developed nephrotic syndrome while receiving prolonged, high-dose, experimental, enzyme replacement therapy to overcome antibody effects.

CASE REPORT

The patient was diagnosed with Pompe disease at 3 months of age, at which time he began twice-weekly intravenous infusions of rhGAA (5 mg/kg body weight; Genzyme Corp, Cambridge, MA) as part of a phase I/II clinical trial. After 1 month of rhGAA treatment, he had detectable antibodies to rhGAA (1:12 800 titer) (Fig 1A). After 15 weeks, the twice-weekly rhGAA dose was increased to 10 mg/kg in an attempt to manage symptoms of clinical decline, concomitant with increasing anti-rhGAA titers. After 24 weeks of rhGAA treatment, the patient became ventilator-dependent. In an effort to reduce antibody titers, he underwent experimental immune tolerance therapy for 10 days, as reported by Brady et al. This therapy consisted of frequent plasmapheresis and intravenous immunoglobulin G administration, with daily infusions of rhGAA (10 mg/kg body weight) and cyclophosphamide. No reduction in anti-rhGAA titers was achieved. Daily oral cyclophosphamide treatment was subsequently administered for 18 weeks, without decreases in antibody titers, and rhGAA infusions were increased to 5 times per week with a dose of 10 mg/kg.

At 27 months of age, after 10 months of 5 rhGAA infusions per week, the patient developed anasarca. His serum albumin and total protein levels had both gradually decreased, to 1.5 g/dL and 5.0 g/dL, respectively (Fig 1B). Dipstick urinalysis showed 4+ proteinuria, confirming nephrotic syndrome, with moderate hematuria (10-20 red blood cells per high-power field, without casts). The urine protein/creatinine ratio was elevated at 7.4 (normal: <0.2). The serum creatinine level was normal at 0.2 mg/dL. Levels of complement component 3 (C3) and component 4 were normal (101 and 36 mg/dL, respectively). Serologic tests for antinuclear antibody, anti-neutrophil cytoplasmic antibody, human immunodeficiency virus, hepatitis B, and hepatitis C were negative. A percutaneous renal biopsy was performed. Light microscopy showed diffusely thickened glomerular basement membranes (Fig 2A). Silver methenamine stain showed diffuse, well-developed, basement membrane spikes and mesangial expansion, diagnostic for membranous nephropathy. No glomerulosclerosis

![Fig 1. Time course of rhGAA administration and nephrotic syndrome. In (A), titers of circulating anti-rhGAA antibody (×1000) are shown by the stippled bars. rhGAA doses are shown by the black bars. In (B), serum albumin levels (g/L) are shown by the solid line and urine protein/creatinine ratios by the interrupted line.](image-url)
Immunofluorescence microscopy revealed diffuse, global, granular, capillary loop and mesangial staining with antibodies to immunoglobulin G, C3, and immunoglobulin M and polyvalent antisera (Fig 2B). No tubular basement membrane staining was present. Electron microscopy showed numerous medium-to-large subepithelial deposits, a few small transmembranous deposits, and medium-size mesangial deposits (Fig 2D). Podocyte foot processes were diffusely effaced. Immunofluorescence microscopy, performed with an antibody specific for rhGAA, showed granular staining along capillary loops and in the mesangium (Fig 2C). No such staining was seen in control renal tissue from a patient with idiopathic membranous nephropathy.

After the renal biopsy, rhGAA infusions were suspended for 3 weeks and then restarted at 10 mg/kg per week. One month later, the patient’s urine protein/creatinine ratio decreased to 3.5, the serum albumin level increased to 2.5 g/dL, and edema resolved. In the subsequent 4 months, proteinuria resolved and serum albumin and total protein levels normalized. Serial echocardiograms after rhGAA dose reduction continued to show some evidence of left ventricular hypertrophy, without additional deterioration in ventricular motion.

**DISCUSSION**

Our patient is the first human patient reported to have developed nephrotic syndrome during enzyme replacement therapy, with heavy urinary protein losses, hypoalbuminemia, and anasarca. The renal biopsy for our patient revealed thickened glomerular basement membranes with subepithelial immune deposits, indicative of membranous nephropathy. The term membranous nephropathy is based on the diffuse thickening of the glomerular basement membrane seen with light microscopy. The characteristic spikes shown with silver methenamine stain represent basement membrane projections between the subepithelial immune deposits. Subepithelial immune complex deposition in our case after immune tolerance regimen requiring frequent, high-dose, exogenous protein (rhGAA) administration recapitulates the immune complex glomerulonephritis observed in early chronic serum sickness studies. In those studies, rabbits undergoing chronic administration of bovine serum albumin developed glomerular subepithelial deposits, glomerular capillary thickening, and proteinuria. Mild proteinuria has also been observed in experimental animals during high-dose treatment with recombinant human.
\(\alpha\)-L-iduronidase.\(^{16}\) The subepithelial immune complexes in our case were shown to contain rhGAA. Glomerular deposition of rhGAA could have resulted from either passive glomerular trapping of circulating immune complexes or in situ complex formation after trapping of rhGAA. C3 Raji cell replacement and complement component 1q enzyme-linked immunosorbent assays revealed no circulating immune complexes at various time points during a 6-month period preceding the development of nephrotic syndrome (data not shown). This suggests either efficient trapping of immune complexes or glomerular trapping of rhGAA as a precipitating event. This contrasts with the pathophysiologic development of idiopathic membranous nephropathy, in which antibody is directed against an endogenous antigen expressed by glomerular epithelial cells that has yet to be identified.\(^{14}\)

Immune tolerance regimens have been widely used in hemophilia to eradicate inhibiting antibodies.\(^{17,18}\) Nephrotic syndrome has been observed for several patients with hemophilia B undergoing immune tolerance therapy for anti-factor IX antibodies.\(^{17–21}\) Renal biopsy in 1 of those cases showed membranous nephropathy, comparable to our case, although factor IX was not demonstrated in the immune deposits.\(^{21}\) Also similar to our case, slow resolution of proteinuria was seen after reduction of the factor IX dose. Despite the greater disease prevalence and higher rate of antibody development for hemophilia A (30–50% vs 1–3% for hemophilia B), nephrotic syndrome has been reported only for hemophilia B.\(^{18,22}\) Explanations for this discrepancy may lie in the lower success rate of immune tolerance induction for hemophilia B, permitting persistence of high antibody levels and necessitating ongoing high-dose antigen treatment to overcome the inhibition.\(^{17,18}\) Moreover, factor IX dose requirements during immune therapy are as high as 500 \(\mu\)g per dose, compared with 10 \(\mu\)g for factor VIII, which may lead to increased risk of immune complex formation.\(^{19}\)

The development of nephrotic syndrome predominantly among patients with hemophilia B for whom immune tolerance therapy is prolonged because of poor response is in complete accord with our patient’s failure to achieve immune tolerance.\(^{18}\)

We report the first case of nephrotic syndrome complicating enzyme replacement therapy, which developed after an immune tolerance regimen with prolonged high doses of enzyme for a patient with high antibody titters. As molecular genetic advances make possible the transition from supportive care to active intervention for numerous genetic disorders, the inventory and use of recombinant enzymes for replacement therapy will likely increase. Development of significant antibody titters and the need for prolonged high doses may increase the risk of nephrotic syndrome, presenting an additional potential side effect of enzyme replacement therapy that may insidiously complicate care. If lower doses of replacement enzyme remain efficacious, however, then resolution of symptoms may be possible as immune complex resorption exceeds formation and glomerular integrity is restored.

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