



Case Report

Development of high sustained anti-drug antibody titers and corresponding clinical decline in a late-onset Pompe disease patient after 11+ years on enzyme replacement therapy

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ABSTRACT

A late-onset Pompe disease patient developed high sustained antibody titers (HSAT) of $\geq 51,200$ after 11+ years on alglucosidase alfa and previous tolerance. There was a corresponding worsening of motor function and rise in urinary glucose tetrasaccharide (Glc₄). Following immunomodulation therapy, HSAT were eliminated with improved clinical outcomes and biomarker trends. This report highlights the importance of continued surveillance of antibody titers and biomarkers, the negative impact of HSAT, and improved outcomes with immunomodulation therapy.

1. Introduction

Pompe disease (OMIM #232300), also referred to as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid α -glucosidase (GAA, EC 3.2.1.20). The condition is characterized by progressive myopathy and respiratory disease. The presence or absence of cardiomyopathy in the first year of life defines two broad phenotypes: infantile Pompe disease (IPD) and late-onset Pompe disease (LOPD). Patients with IPD present with cardiomyopathy while those with the late-onset form present with progressive limb-girdle and respiratory muscle weakness without cardiomyopathy. Enzyme replacement therapy (ERT) with recombinant human acid α -glucosidase (rhGAA), alglucosidase alfa, became available in 2006 with a recommended dose of 20 mg/kg every other week. In the past several years, higher doses of alglucosidase alfa have been proven to be well tolerated and can lead to improved clinical outcomes in some Pompe disease patients [1–3].

Even on treatment, improvement of clinical symptoms is impacted by factors such as cross-reactive immunologic material (CRIM) status, presence of high sustained antibody titers (HSAT; defined as titers of $\geq 12,800$), stage of disease at start of treatment, and extent of muscle

fiber damage [4,5]. The development of anti-drug antibody (ADA), the negative impact of ADA, and the success of immunomodulation therapy in IPD have been well recognized [5–9]. In contrast, there is no clear consensus on the challenges of immunogenicity in LOPD. Some studies have shown that LOPD patients who developed HSAT had deterioration in clinical status, whereas others have proposed that ADA does not affect the efficacy of ERT in LOPD patients [10–14].

2. Case report

An adolescent patient with LOPD developed HSAT and clinical decline after 11+ years of alglucosidase alfa treatment. The diagnosis of Pompe disease was confirmed at age 9 months by muscle biopsy, enzyme analysis, and GAA sequence analysis, revealing compound heterozygosity for c.525delT and c.-32-13T >G, predictive of LOPD. There was absence of cardiomyopathy in the first year of life. At age 20 months, the patient began ERT with alglucosidase alfa at 20 mg/kg IV every other week (EOW) due to worsening muscle weakness and motor delay. Treatment was well tolerated with no infusion-associated reactions (IARs). Anti-rhGAA IgG antibody titers collected intermittently were negative or very low <1:800. At age 30 months, the patient began taking

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a few independent steps with a broad-based gait and exaggerated lumbar lordosis. At age 40 months, the ERT dose was increased to 40 mg/kg IV EOW. Significant clinical improvement and decline in urinary glucotetrasaccharide (Glc₄) levels were observed without change in ADA titers. At 10 years of age, ERT was adjusted to 40 mg/kg IV weekly due to persistence of muscle weakness. There were no IARs and the patient experienced improvements in ambulation and endurance. Anti-rhGAA antibody titers remained low at <3200 (Fig. 1).

At 12.4 years of age, the patient underwent spinal fusion with rod insertion due to significant scoliosis impairing quality of life. The patient experienced a CSF leak post-operatively but recovered after bed rest and had no change in clinical status. At age 13.8 years, the patient experienced a steady rise of ADA titers from 6400 to 51,200 with a corresponding rise in urinary Glc₄ levels (Fig. 1). Despite HSAT, the patient continued to receive alglucosidase alfa at 40 mg/kg weekly without infusion-associated reactions. A small increase in CK levels from 1400 U/L to 1700 U/L was also observed around the time of HSAT development. At age 14.7 years, the family reported a clinical plateau progressing to a clinical decline. The patient experienced a plateau in weight gain and gastrointestinal symptoms of intermittent diarrhea and feeling of bladder and bowel urgency after eating. Worsening gait and balance, decreased endurance, and increased weakness were observed in clinic. A six minute walk test (6MWT) obtained at 14.7 years noted a very unsteady gait with shoulders and arms flailing and a fall at 1 min and 45 s into the test. Prior 6MWT at age 14.1 years was completed with gait typical of LOPD patients but without stopping or falls. While no significant change in total distance walked was recorded on the two 6MWTs; the patient reported a decline in walking ability in daily life and a deterioration in his ability to climb stairs (Table 1).

At age 15.3 years, the family reported that the patient's gait was wider and that quadriceps strength was declining. On tests of motor

abilities, the patient had stable to very slightly decreased performance. On the Gait, Stairs, Gower, Chair (GSGC) scale, total score worsened from 14 to 16 due to decreased performance on stair climb assessment. A small decline in performance on the Standing and Walking/Running/Jumping dimensions of the Gross Motor Function Measure (GMFM) from 87.18% to 84.62% and 94.44% to 91.67%, respectively, was observed. There was slight decline in the 6MWT distance from 526.1 m at age 14.7 years to 512.6 m at age 15.3 years and in the percent predicted from 64.1% to 63.1% (Table 1 and Supplementary Figs. 1 and 2).

Pulmonary function tests (PFTs) noted a steady decline of FVC from 87% predicted at 12.4 years to 77% predicted at 13.9 years, 74% predicted at 14.2 years, and 61% predicted at 15.8 years (Table 1). Despite the decline in FVC values, the patient reported no clinical symptoms and denied any difficulty in respiration with physical activity.

Immunomodulation therapy was initiated at age 14.9 years with bortezomib, rituximab, methotrexate, and IVIG based on a protocol previously published by Banugaria et al. (2013) (Fig. 1) [7]. Bortezomib was added to the immune modulation protocol due to its effectiveness in eliminating long lived plasma cells [7]. The patient continued weekly rhGAA at 40 mg/kg. Laboratory monitoring included CBC with differential, comprehensive metabolic profile, creatine kinase isoenzymes, lymphocyte subpopulation counts (CD3, CD4, CD8, CD19), immunoglobulin panel (IgG, IgA, IgM, IgE), urinary Glc₄, and anti-rhGAA IgG antibody titers.

With the implementation of immune tolerance induction (ITI), the patient had a slow decrease of anti-rhGAA IgG antibody titer level to 3200, with fluctuation of levels between 12,800 and 3200 (Fig. 1). Given the lack of a sustained low ADA titer and minimal decline in urine Glc₄ levels, a second course of bortezomib was administered with maintenance of rituximab, methotrexate, and IVIG. Prior experience of HSAT in patients with Pompe disease and mucopolysaccharidosis (MPS) II who

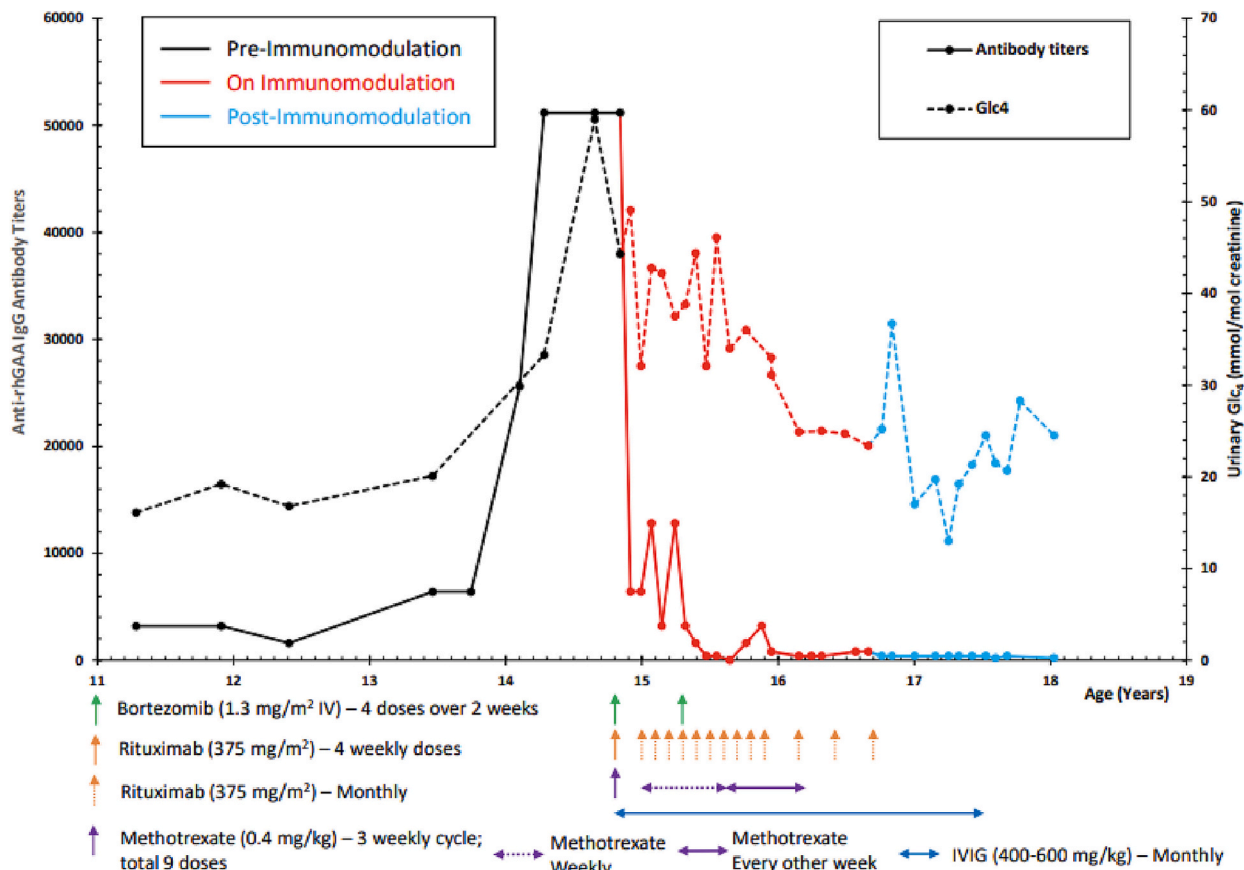


Fig. 1. Anti-rhGAA IgG antibody level, urinary Glc₄ levels and timing of immunomodulation therapy.

Table 1
FVCs and PT outcomes.

Age (years)	FVC % Predicted	6MWT (Meters)	6MWT % predicted	GSGC (total)	QMFT	GMFM (Standing) %	GMFM (Walk/Run/Jump) %
8.1		368.5	49.5	12		84.62	87.5
9.6		401.2	54.7	10		89.74	81.94
10.2		458.0	59.7	10		87.18	94.44
12.1	87	502.9	68.2				
12.4	87						
13.7	74						
13.9	77	511.8	62.6				
14.1		511.0	64.1	14	41		
14.2	74						
14.7		526.1	64.1				
15.3		512.6	63.1	16	44	84.62	91.67
15.8	61						
17.1		480.0	59.2				
17.5	57						
18.6	65	508.0	62.3	13	47	89.7	95.8

Table 1 footnotes: pre-immunomodulation: <14.9 years, on immunomodulation: 14.9–17.4 years, post-immunomodulation: >17.4 years. Functional capacity for walking was measured using the Six Minute Walk Test (6MWT) conducted during clinical visits in accordance with American Thoracic Society guidelines [16]. The percent of normal distance walked was calculated using published formulas [17,18]. The Gait, Stairs, Gowers, Chair Test (GSGC) was used to measure motor function as previously described [19,20]; scores range from 4 to 27 with a score of 4 indicating normal function. The Quick Motor Function Test (QMFT) has scores ranging from 0 to 64 (score of 64 indicates normal function) and was developed to measure motor function in patients with Pompe disease [21]. The Gross Motor Function Measure (GMFM-88) is a test for motor skills, with scores ranging from 0 to 100%, with 100% indicating normal function [22].

underwent immunomodulation therapy suggested that an intensified regimen is needed to eliminate the long lived plasma cells secreting antibodies to therapeutic proteins [15]. At 8 weeks following the second course of bortezomib (age 15.6 years), the patient's ADA titers decreased to pre-HSAT levels, and have remained below 800 (Fig. 1). Since ITI treatment week 64 (age 16.1 years), urine Glc₄ levels have declined to levels observed prior to development of HSAT (Fig. 1). Rituximab was administered at reduced intervals until week 94 (age 16.8 years). Methotrexate was administered weekly on day of ERT until treatment week 35 (age 15.6 years), and then every other week until week 70 (age 16.2 years). Immunoglobulin therapy was administered at reduced intervals until week 142 (age 17.4 years), when complete recovery of lymphocyte subpopulation counts, specifically CD19, was observed. The patient continued to maintain adequate humoral response to routine vaccines. No long-term side effects related to immunomodulation were observed. Based on low ADA titers in absence of immunosuppressive agents, a complete reconstitution of B cells, and adequate humoral response to vaccines, the patient was considered immune tolerant to alglucosidase alfa.

With elimination of HSAT, the patient reported that gait and endurance had returned to baseline or possibly slightly better than prior to HSAT, and that strength overall had improved. Gastrointestinal symptoms had resolved with noted weight gain. The patient had slightly improved measurement on several motor function tests, including the GSGC and GMFM-88 (Table 1). On the QMFT, the patient's score improved from 44 to 47 points, largely due to ability to lift his head off of the mat in supine and ascend stairs without a rail. On the GMFM, standing dimension improved from 84.6% to 89.7%, and Walking/Running/Jumping dimension improved from 91.7 to 95.8% (Table 1, Supplementary Figs. 1 and 2). On 6MWTs performed at 17.1 years and 18.6 years, total distance improved from 480 m to 508 m, with percent predicted increasing from 59.2% to 62.3%. On PFT, FVC continued to decline from 74% predicted at 14.2 years to 57% predicted at 17.5 years, then increased to 65% predicted at 18.7 years.

3. Discussion and conclusion

We report the case of a patient with LOPD who developed HSAT after 11+ years on ERT. This patient had previously never mounted a significant ADA response and was considered immune tolerant to alglucosidase alfa. His ADA titers remained low with 3+ years of treatment on rhGAA dose of 40 mg/kg weekly. Immunomodulation with bortezomib, rituximab, methotrexate, and IVIG was successful in

eliminating HSAT and inducing tolerance to alglucosidase alfa. Clinical improvement was noted with restitution of endurance and gait to pre-HSAT levels, and improvements in objective measures such as GSGC, GMFM, QMFT, and PFTs. Reduction in urinary Glc₄ biomarker levels was observed with successful reduction of drug antibody titers. Our LOPD patient required a prolonged duration of immunomodulation treatment similar to what has been noted for other LOPD patients and reported on an MPS II patient with HSAT to idursulfase who had been on ERT for several years prior to ITI [15]. Thus it appears that patients who develop HSAT after long-term ERT may require a longer duration of immunomodulation for successful elimination of high titer antibodies than those treated early in the course of therapy [15].

This case illustrates the importance of continued surveillance of anti-rhGAA IgG antibodies and monitoring of biomarkers for Pompe disease patients on rhGAA treatment. In recent years, high-dose of ERT and long-term exposure have been suggested as pathways for immune tolerance in patients with LOPD [10,11]. The long duration and higher dose of ERT did not tolerate our patient, emphasizing the need for continued regular antibody titer and biomarker monitoring. High sustained antibody titers can impact the efficacy of ERT in LOPD patients. Our patient experienced decline in motor function with rising titer levels, with subtle changes in 6MWT, GSGC, and GMFM scores. Quantitative motor assessments at regular intervals may be needed to better capture the subtle changes in clinical progression of LOPD patients.

The factors leading to development of an immune-mediated response to alglucosidase alfa remain unclear and require further investigation. The only significant occurrence in the patient's medical history was scoliosis repair approximately 12 months prior to the rise of ADA titers. The patient otherwise remained healthy with no history of frequent infections and no history suggestive of an autoimmune process. Further studies are needed to better understand the immunogenicity in LOPD and assess the factors that may lead to a break in immune tolerance. Pompe disease patients who develop HSAT can have successful reduction of anti-drug IgG titers with immunomodulation therapy and remain on high dose rhGAA for continued clinical benefit.

Declaration of Competing Interest

None.

Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgmr.2023.100981>.

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