

For reprint orders, please contact reprints@expert-reviews.com

Immune modulation in Pompe disease treated with enzyme replacement therapy

Expert Rev. Clin. Immunol. 8(6), 497–499 (2012)



Suhrad G Banugaria

Division of Medical Genetics,
Department of Pediatrics,
Duke University Medical Center,
Durham, NC, USA



Trusha T Patel

Division of Medical Genetics,
Department of Pediatrics,
Duke University Medical Center,
Durham, NC, USA



Priya S Kishnani

Author for correspondence:
Division of Medical Genetics,
Department of Pediatrics, Duke
University Medical Center,
Durham, NC, USA
Tel.: +1 919 684 2036
Fax: +1 919 684 8944
kishn001@dm.duke.edu

“The development of an immune response with resultant loss of therapeutic efficacy of enzyme replacement therapy remains a significant issue in Pompe disease, most notably in the infantile form.”

Pompe disease is a lysosomal storage disease characterized by massive glycogen deposition in skeletal, cardiac and smooth muscle secondary to the deficiency of acid α -glucosidase (GAA) [1]. Once rapidly fatal, it has become a treatable condition since the development of enzyme replacement therapy (ERT) with α -glucosidase α (recombinant human GAA [rhGAA], Myozyme[®]/Lumizyme[®] Genzyme Corp. Cambridge, MA, USA) [1]. However, while this treatment has proven to be efficacious in both infantile and late-onset Pompe patients [2,3], many challenges remain. The development of an immune response with resultant loss of therapeutic efficacy of ERT remains a significant issue in Pompe disease, most notably in the infantile form. Similar obstacles have been faced in other conditions treated with therapeutic proteins, including hemophilia, diabetes and multiple sclerosis, as well as lysosomal storage diseases like Fabry disease, Gaucher disease and the mucopolysaccharidoses [4,5].

In addition to the human burden, hundreds of millions of dollars are wasted in the use of therapeutic proteins in patients who are not responding to the treatment because of antibodies developed against them [6]. Therefore, the identification of patients at risk of developing an immune response and the investigation of novel immunomodulatory strategies to preclude or reverse immune responses and to induce immune tolerance is of paramount importance, not only for improving the functional status of individual patients,

but also for minimizing wasteful financial expenditures.

The development of high, sustained anti-rhGAA IgG antibody titers is associated with decreased overall and ventilator-free survival and diminished cardiac and motor outcomes in infantile Pompe disease (IPD) treated with ERT [7–9]. Earlier studies in Pompe disease treated with ERT have demonstrated that the cross-reactive immunologic material (CRIM) status can be used to predict treatment response, with CRIM-negative status portending the development of high, sustained antibody titers and poor treatment outcomes [7,8]. However, later work in IPD revealed that a subset of CRIM-positive patients may also develop high, sustained antibody titers and correspondingly poor treatment outcomes [9]. Recently, the development of high antibody titers that adversely impact treatment outcomes has been noted in late-onset Pompe disease as well [10,11].

Similar challenges have been faced in the murine Pompe model, in which ERT administration is complicated by antibody formation and infusion-associated reactions. This murine Pompe model is analogous to the CRIM-negative patients in that there is a complete absence of endogenous GAA, prompting the immune system to mount a robust immune response to exogenous enzyme. Preclinical work in this model prevented an increase in anti-rhGAA antibody titers in the ERT-naive setting with the use of methotrexate, while response to mycophenolate and cyclosporin A/azathioprine was variable. This protocol

KEYWORDS: antibodies • immune modulation • Pompe disease

EXPERT
REVIEWS

was successful with the administration of methotrexate within the first 24 h of ERT. Since there was an increase in peritoneal B1 B cells within the first 24 h of ERT administration, it is believed that the reduction of this B1 B-cell response may be part of the complex mechanism of action of methotrexate-induced immune tolerance [12]. Methotrexate also targets rapidly dividing B and T cells, which reduces overall antibody production. Tissue-specific adeno-associated virus vector-mediated gene therapy has also been investigated in the murine Pompe model and appears to induce immune tolerance to rhGAA due to the upregulation of regulatory T cells [13]. A monoclonal nondepleting anti-CD4 antibody has previously been used to suppress the immune response to equine IgG in nonhuman primates [14], prompting its consideration for use in Pompe disease. This antibody appears to block T-cell activation and prevent T-cell help to antigen-activated B cells, while upregulating regulatory T cells. The utility of this anti-CD4 antibody in counteracting the immune response to ERT is currently being explored in the murine Pompe model with early success [15].

In addition to these studies in the murine Pompe model, the clinical setting of IPD has served as an excellent model for the understanding of the impact of antibody responses to therapeutic protein and demonstrating the potential clinical applications of immunomodulation to optimize therapeutic efficacy. Various combinations of rituximab (anti-CD20 monoclonal antibody), plasmapheresis, intravenous immunoglobulin (IVIg), cyclophosphamide, methotrexate and increased-dose ERT have been used to try to prevent the development of or eliminate antibodies against ERT in the IPD setting [16–19]. Of these, the combination of rituximab and methotrexate \pm intravenous γ globulin has been able to successfully tolerize IPD patients to rhGAA in the naive or early ERT setting [16,17]. Although the exact mechanism by which this immunomodulatory regimen counteracts the immune response has not been elucidated, a basic understanding may be developed based on the proposed mechanisms of the individual agents. While methotrexate targets both B and T cells, rituximab targets CD20-positive B cells, which are responsible for the initiation and propagation of an immune response. IVIg downregulates antibody responses by binding to inhibitory FcR and also protects against infectious agents in immune suppressed conditions. It is believed that the suppression of B- and T-cell populations responsible for antibody formation, with simultaneous upregulation of regulatory T cells, is important for the success of this immunomodulatory regimen in diminishing the immune response to rhGAA.

While the aforementioned immunomodulatory protocol has been used successfully in the naive setting, various protocols tried in the setting of an entrenched immune response, in which high antibody titers have already been formed, have been unsuccessful. The combination of cyclophosphamide, IVIg, plasmapheresis and increased doses of rhGAA \pm rituximab has failed to induce immune tolerance in the setting of an established immune response in CRIM-negative IPD patients [18,19]. To date, no immunomodulatory regimen has been successful in combating the entrenched immune response, thus underscoring the need for

new therapies that target plasma cells, which are the main source of antibody production once the humoral immune response is well established [18,19]. Bortezomib (Velcade[®], Millenium Pharmaceuticals, Inc., MA, USA), a proteasome inhibitor, is one such agent that targets mature antibody-producing plasma cells. A multipronged approach using bortezomib to target plasma cells and rituximab, methotrexate and IVIg to target B and T cells appears to be a viable option for immunomodulation in the setting of an entrenched immune response. Indeed, this combination of agents has been able to lead to sustained reduction in antibody titers with simultaneous clinical benefits in several IPD patients [20]. These data support the rationale that using agents that act at different levels of the humoral immune response pathway is critical in achieving long-term immune tolerance induction.

While successful, currently available immunomodulatory protocols are nonspecific to the therapeutic protein (Myozyme and ERT), often require prolonged administration or repeated dosing and may lead to generalized immune suppression and interfere with vaccination schedules in the IPD setting. Frequent methotrexate administration has been associated with bone marrow and gastrointestinal toxicities. Rituximab, on the other hand, is associated with infection, infusion-associated reactions and serious side effects such as progressive multifocal leukoencephalopathy and reactivation of hepatitis B infection. Bortezomib is associated with peripheral neuropathy, neutropenia, thrombocytopenia and gastrointestinal and cardiac side effects. Given these and other significant side effects of the currently used agents, great consideration must be taken when initiating immunomodulatory protocols in Pompe patients. As the field of immunomodulation in Pompe disease progresses, there is much yet to accomplish.

Considering the limitations of current immunomodulatory protocols, which include significant side effects, prolonged administration and immune suppression, it seems that more efficacious immunomodulatory agents must be identified. The ideal regimen for immunomodulation in Pompe disease treated with ERT would consist of agent(s) that allow for brief administration, prolonged rhGAA-specific tolerance and limited side effects.

In addition to the need for the development of more effective immunomodulatory regimens, it is also imperative to gain a better understanding of how, when and in which patients one should appropriately intervene with these regimens. CRIM-negative status can be determined rapidly by western blot and immunomodulatory treatments can be started in the ERT-naive setting for a better response to ERT. However, given the difficulty of identifying which CRIM-positive patients are at risk for developing high antibody titers, it is important to continuously monitor antibody response to ERT in all patients and thus immunomodulatory treatment can be started early if titers are showing an upward trend. Attempts have been made to identify those CRIM-positive patients at risk for developing high antibody titers by identifying specific immunogenic B- and T-cell epitopes based on patient genotype. However, even the combination of CRIM status and B- and T-cell epitope identification cannot always predict which patients will or will not develop high antibody titers. Identification of patients at

risk of developing high, sustained antibody titers will require an understanding of the interplay of genotype, phenotype, protein structure, immunogenicity, clinical status and other host and environmental factors. Only once these factors are better understood will it be possible to predict which patients will likely benefit from immunomodulatory therapies and thus develop treatment algorithms for immunomodulation in Pompe disease or any other disease treated with therapeutic proteins.

Financial & competing interests disclosure

PS Kishnani has received research/grant support and honoraria from Genzyme Corporation and is a member of the Pompe and Gaucher Disease Registry Advisory Board for Genzyme Corporation. Alglucosidase α rhGAA, in the form of Genzyme's product alglucosidase α (Myozyme®/Lumizyme®)

has been approved by the US FDA and the European Union as therapy for Pompe disease. Duke University and the inventors of the method of treatment and precursors of the cell lines used to generate the enzyme (rhGAA) used commercially have received royalties pursuant to the university's policy on inventions, patents and technology transfer. This potential conflict for Duke University has been resolved through monetization. SG Banugaria and PS Kishnani are listed as inventors on a Duke University pending patent application for the use of bortezomib in diseases treated with therapeutic proteins. TT Patel has no financial or proprietary interest in the materials presented herein. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- Hirschhorn R, Reuser AJJ. Glycogen storage disease Type II: acid α -glucosidase (acid maltase) deficiency. In: *Scriver's OMMBID the Online Metabolic & Molecular Bases of Inherited Disease*. Valle D, Scriver CR (Eds). McGraw-Hill, NY, USA (2009).
- Nicolino M, Byrne B, Wraith JE *et al*. Clinical outcomes after long-term treatment with alglucosidase α in infants and children with advanced Pompe disease. *Genet. Med.* 11(3), 210–219 (2009).
- van der Ploeg AT, Clemens PR, Corzo D *et al*. A randomized study of alglucosidase α in late-onset Pompe's disease. *N. Engl. J. Med.* 362(15), 1396–1406 (2010).
- Porter S. Human immune response to recombinant human proteins. *J. Pharm. Sci.* 90(1), 1–11 (2001).
- Wang J, Lozier J, Johnson G *et al*. Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention and treatment. *Nat. Biotechnol.* 26(8), 901–908 (2008).
- Schellekens H. The immunogenicity of therapeutic proteins. *Discov. Med.* 9(49), 560–564 (2010).
- Amalfitano A, Bengur AR, Morse RP *et al*. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a Phase I/II clinical trial. *Genet. Med.* 3(2), 132–138 (2001).
- Kishnani PS, Goldenberg PC, DeArmy SL *et al*. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. *Mol. Genet. Metab.* 99(1), 26–33 (2010).
- Banugaria SG, Prater SN, Ng YK *et al*. The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease. *Genet. Med.* 13(8), 729–736 (2011).
- de Vries JM, van der Beek NA, Kroos MA *et al*. High antibody titer in an adult with Pompe disease affects treatment with alglucosidase α . *Mol. Genet. Metab.* 101(4), 338–345 (2010).
- Patel TT, Banugaria SG, Case LE, Wenninger S, Schoser B, Kishnani PS. The impact of antibodies in late-onset Pompe disease: a case series and literature review. *Mol. Genet. Metab.* 106(3), 301–309 (2012).
- Joseph A, Munroe K, Housman M, Garman R, Richards S. Immune tolerance induction to enzyme-replacement therapy by co-administration of short-term, low-dose methotrexate in a murine Pompe disease model. *Clin. Exp. Immunol.* 152(1), 138–146 (2008).
- Sun B, Kulis MD, Young SP *et al*. Immunomodulatory gene therapy prevents antibody formation and lethal hypersensitivity reactions in murine pompe disease. *Mol. Ther.* 18(2), 353–360 (2010).
- Winsor-Hines D, Merrill C, O'Mahony M *et al*. Induction of immunological tolerance/hyporesponsiveness in baboons with a nondepleting CD4 antibody. *J. Immunol.* 173(7), 4715–4723 (2004).
- Banugaria SG, Patel TT, Prater SN *et al*. The use of non-depleting anti-CD4 monoclonal antibody for immune tolerance induction in Pompe disease (abstract). *Mol. Genet. Metab.* 105(3), 290 (2012).
- Messenger YH, Mendelsohn NJ, Rhead W *et al*. Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. *Genet. Med.* 14(1), 135–142 (2012).
- Mendelsohn NJ, Messenger YH, Rosenberg AS, Kishnani PS. Elimination of antibodies to recombinant enzyme in Pompe's disease. *N. Engl. J. Med.* 360(2), 194–195 (2009).
- Hunley TE, Corzo D, Dudek M *et al*. Nephrotic syndrome complicating alpha-glucosidase replacement therapy for Pompe disease. *Pediatrics* 114(4), e532–e535 (2004).
- Banugaria SG, Patel TT, Mackey J *et al*. Persistence of high sustained antibodies to enzyme replacement therapy despite extensive immunomodulatory therapy in an infant with Pompe disease: need for agents to target antibody-secreting plasma cells. *Mol. Genet. Metab.* 105(4), 677–680 (2012).
- Banugaria SG, Prater SN, Nampoothiri S *et al*. Novel application of bortezomib in abrogating antibodies against ERT in Pompe disease: a strategy for broad clinical application in diseases treated with therapeutic proteins (abstract). *Mol. Genet. Metab.* 102(3), 245–246 (2011).