Severe Infusion Reactions to Fabry Enzyme Replacement Therapy: Rechallenge After Tracheostomy

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Received: 02 June 2011 / Revised: 27 July 2011 / Accepted: 17 October 2011 / Published online: 11 December 2011
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Abstract A 34-year-old male patient with Fabry disease (OMIM 301500) commenced enzyme replacement therapy (ERT) with Agalsidase alfa, with positive clinical response. Infusion reactions, initially mild and easily managed, commenced during his 13th infusion, and continued over the next 3 years. Severity of reactions subsequently increased despite very slow infusion, extended prophylactic medication and attempted desensitisation, requiring regular intensive care unit (ICU) admissions. Facial oedema and flushing, throat tightness, headache and joint pain typically occurred 4–36 h after completion of most infusions, responding rapidly to subcutaneous adrenaline. Low titre specific IgG seroconversion was noted at 12 months, with subsequent reversion to negative after 5 years, despite persistence of infusion reactions. Specific IgE and skin testing was negative. Trial of ERT product switch to Agalsidase-beta resulted in no improvement in reactions. At 5 years, ERT was ceased in the face of recurrent ICU readmissions. In the face of progressive clinical deterioration, he underwent tracheostomy to allow recommencement

of ERT. Two years later, he has clinically improved on regular attenuated dose Agalsidase-beta, administered by slow infusion in a local hospital setting.

Case Report

Diagnosed in early childhood following proband identification, the patient endured severe disabling neuropathic pain and diarrhoea during childhood and adolescence, truncating his educational and employment opportunities. Serum and WBC α -Galactosidase (GLA) levels were measured as 0.03 nmol/min/mg (normal range 0.4–2.0), and genotype was identified as G128E. At the time of enzyme replacement therapy (ERT) commencement at age 34, his BMI was 20.1 kg/m². His baseline pain was partially controlled on phenytoin, but frequent exacerbations occurred with infections and weather changes, sometimes requiring hospitalisation and narcotics. Diarrhoea was intractable, depression was significant, exercise capacity was limited to getting through his workday, and proteinuria had reached 800 mg/day, although Cr-EDTA GFR, ECG and echocardiogram were normal.

The first 12 infusions of ERT (Agalsidase alfa 0.2 mg/kg/fortnight over 40 min) were uneventful. The 13th infusion, delayed for 3 months for logistic reasons, was complicated by facial flushing and subjective throat tightness, without change in temperature or blood pressure. Symptoms resolved rapidly with cessation of infusion, intravenous hydrocortisone and promethazine.

All subsequent infusions were given under prophylaxis with hydrocortisone, combined variably with antihistamine (promethazine or cetirizine), oral prednisolone and paracetamol. Over the next 3 years, reactions were occasional and mild, but accelerated in severity and frequency throughout

Communicated by: Robert J Desnick.

Competing interests: None declared.

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the fourth and fifth years of ERT, against a variety of attempted interventions. These included dose reduction, extended infusion times, and pre-treatment with various dose combinations of steroids, antihistamine, paracetamol, pethidine, transhexamic acid and danazol. Several attempts at desensitisation failed. Reactions requiring adrenaline treatment were induced with doses of Agalsidase alfa below 50 µg.

Reactions typically comprised facial oedema, throat tightness, headache, with variable flushing and joint pain. They were commonly delayed 4–36 h after completion of the infusion, and responded to the addition of adrenaline to steroid and antihistamine.

Baseline testing for IgG against GLA was negative, but seroconversion was first noted at low titre (maximum 1:100) at 12 months, with subsequent titres stable until 5 years after ERT initiation, when IgG reverted to negative. Specific testing revealed no evidence of IgE antibodies, mast cell or complement activation, or C1 esterase inhibitor deficiency, either during or after reactions. Skin tests were negative. During and after reactions, BP, oxygen saturation remained normal. Serial spirometry performed before, during, after and independent of ERT showed similar results – airway obstruction was minimal and bronchodilator response was negligible. Inhaled bronchodilator at the time of reactions did not help.

Specialist fibre-optic airway examination revealed no obvious structural cause for the symptoms experienced during ERT, but a narrow oropharynx with (Mallampati score IV) and large nasal polyps. Polysomnography revealed severe obstructive sleep apnoea (apnoea: hypnoea index of 45 events per hour increasing to 93 events per hour in REM associated with significant oxygen desaturation ($\text{PaO}_2 = 76\%$) and sleep fragmentation).

Other than Fabry disease, no other risk factors for obstructive sleep apnoea were present. BMI had decreased slightly to 19.2 kg/m². The patient was very keen to proceed with ERT. His response had been subjectively positive, and ongoing daily diaries documented fewer and less severe pain exacerbations, less diarrhoea, and increased active life participation compared with his pre-ERT status. GFR was stable, and proteinuria reduced on renin–angiotensin blockade to 300–500 mg/day; however, the frequency and severity of reactions were clearly of major concern.

From Infusion 120 (5 years), ERT was changed to half-dose (0.5 mg/kg) Agalsidase-beta, which was initially well tolerated but induced a severe reaction on the second administration.

The dose was then further reduced from 35 to 10 mg, and infused over 10 h. When two consecutive treatments (Infusions 128 and 129) induced severe delayed reactions

requiring ICU readmission 24–48 h post-infusion, ERT was ceased, against the patient's expressed wishes, but in the interests of safety. Over the 2 years after cessation of ERT, the patient's pain worsened despite increased prophylactic therapy with maximal doses of multiple agents under advice from a pain management team, exercise tolerance decreased, sweating ceased and depression recurred. His ability to discern warmth in his distal lower limbs regressed to pre-ERT levels. Prior to ERT commencement, he was consistently unable to detect temperature sensation below the knees, but this had improved after 2 years of ERT, to the level of the mid metatarsals. Depression became increasingly significant, but medication was ineffective. Plasma Gb3 had increased from 3.9 nmol/ml at 5 years post ERT initiation, at which time he had been receiving only very low Agalsidase alpha dose (<0.1 mg/kg/fortnight) for the previous 6 months, to 7.3. In consultation with a multidisciplinary team, he elected to undergo tracheostomy to increase the safety margin to resume ERT, as well as to alleviate his sleep apnoea and upper airway obstruction.

Subsequently, 2.5 years after completely ceasing ERT and 7.5 years after his first ERT infusion, he underwent Agalsidase-beta rechallenge within a high-dependency setting, at a fortnightly dose of 10 mg over 12 h, under prophylaxis with hydrocortisone, cetirizine and alprazolam). Mild to moderate reactions repeatedly occurred 1–12 h after completion of infusions. Premedication was changed from hydrocortisone to dexamethasone (to exclude the unlikely scenario that allergy was to vehicle), with empirical addition of chromoglycate, ranitidine, symbicort, monteleukast and prolongation of the protection period pre-infusion. We have no evidence of efficacy of any of these, but he has incrementally advanced to routine ward admissions for infusions, dose increase to 20 mg (0.3 mg/kg) Agalsidase-beta over 12 h, and administration of more convenient 36-h admissions at his local hospital each fortnight. He typically requires 1–3 doses of subcutaneous adrenaline (0.3 mg) for the reactions which characteristically occur 6–12 h after completion of most infusions.

Currently, he has been back on ERT for 2 years, has resumed sweating, is again coping with full-time work, and pain is controlled. Echocardiogram and GFR remain normal, and proteinuria is stable at 200 mg/day on ancillary therapy. Antibody testing remains negative for both IgG and IgE. Despite his ERT dose still being well below the approved dose of 1 mg/kg/fortnight, he has improved since infusions resumed. We plan to very slowly increase dose to standard levels, but will need to continue our empiric compromise between possible benefit of this, against extended infusion time, patient inconvenience and reaction risk.

Discussion

The male phenotype of Anderson–Fabry disease, although often clinically severe, is probably modified by ERT. In many countries, including the UK, North America, Europe and Australia, most affected patients can access ERT as part of their comprehensive medical care. Recombinant human GLA is commercially available in two forms, Agalsidase alfa (Replagal, Shire Human Genetic Therapies), and Agalsidase-beta (Fabrazyme, Genzyme)), both administered intravenously. Each can induce infusion reactions, but excellent safety profiles in placebo controlled trials and open-label use are well documented (Eng et al. 2001a, b; Ramaswami et al. 2005; Barbey and Livio 2006). Reactions are generally easily manageable, reduce with time, and rarely interfere with ongoing ERT, although prophylaxis may be required (Wilcox et al. 2004; Barbey and Livio 2006). Agalsidase alfa infusion reactions are less common (approximately 13%) than those induced by Agalsidase-beta, possibly related to the lower protein dose administered in standard ERT (0.2 mg/kg vs. 1.0 mg/kg). Reactions are less common in patients with missense mutations, in whom low levels of endogenous enzyme can usually be detected.

Reactions very rarely necessitate ERT withdrawal. The typical pattern of Agalsidase-beta infusions were prospectively documented in Phase 3 and 4 trials undertaken in 58 patients over 30–36 months (Wilcox et al. 2004). IgG seroconversion occurred in 90% of patients at a median time of 6 weeks, and coincided in 70% of these with the onset of clinical infusion reactions. Reactions were typically mild, managed by infusion rate reduction with or without medication, and comprised various combinations of rigours, feeling cold or warm, fever, nausea, headache, and nasal congestion. Over time, infusion reactions decreased, as did antibody titre in most patients. Specific serum IgE or positive skin tests were found in three patients, all of whom were successfully rechallenged. Evidence of treatment efficacy was present independent of seroconversion, although subsequently Linthorst et al. (2004) reported failure of standard dose ERT to reduce urinary globotriaosylceramide in a subset of reacting patients with neutralising antibodies. In this study, IgG antibodies cross-reacted in vitro similarly with both recombinant enzymes, indicating that product switch is unlikely to be clinically useful.

Registry data from the Fabry Outcome Study (FOS) documented an incidence of reactions to Agalsidase alfa of 13% of all patients: 17% in males and 6% in females – representing 1% of total infusions over 900 patient years of infusions in 400 patients (Barbey and Livio 2006). Similar to Agalsidase beta, infusion reactions occurred in most affected patients soon after treatment initiation were easily

managed by premedication (paracetamol, antihistamines and corticosteroids) and slowing of the infusion rate, and disappeared after the next few infusions. Reactions were severe in only 6% of patients experiencing reactions, and in only one patient was withdrawal from ERT required. No IgE antibodies were detected. IgG antibodies typically developed at approximately 3 months, but after 12–18 months of therapy 83% of patients treated with Agalsidase alfa were antibody free, and about 30% of antibody positive patients had developed immunological tolerance.

While ERT infusion reactions typically occur in male Fabry patients with a null mutation and specific IgG antibodies, their pathogenesis remains undefined. While the absolute protein infusion dose may explain the different rate of antibody formation between Agalsidase alpha and beta, their different glycosylation pattern may also be relevant (Schellekens 2002).

Our patient has a missense mutation, had only low titre IgG reverting to negative after desensitisation, and his delayed, atypical infusion reactions seem to be unrelated to antibody. It is interesting that none of five other family members have reacted to either form of long-term ERT. It is possible that his congenitally narrow airway and probable Fabry-related OSA exacerbated the ERT reactions, but the severity of reactions is unique in our experience. Stopping then resuming ERT is recognised as a risk factor for infusion reactions, and was possibly relevant to his reaction to his 13th infusion, occurring after a break of 3 months.

The unfortunate combination of rare, life-threatening disease and intractable ERT reactions promised him a progressive debilitating course, poor quality of life, ultimate organ failure and premature death. Demonstrating extraordinary determination to pursue treatment, he is again accessing ERT at a dose that has objective efficacy, albeit below “standard” dose. His currently tolerated fortnightly 0.3 mg/kg dose of Agalsidase- β will hopefully produce benefit worthy of his considerable efforts. To some extent, dosing of ERT is empiric – dose-finding and dose-comparator studies are very limited. Both forms of Fabry ERT have been shown – at their different “standard” doses – to have clinical efficacy. While their manufacturing processes, glycosylation patterns and individual organ uptakes are different, they have identical amino acid sequences, suggesting that – at least in some patients – there may be latitude for dose reduction of Agalsidase-beta.

We report our first patient in whom severe reactions to recombinant GLA necessitated treatment withdrawal. Subsequent clinical deterioration stimulated the trial of multiple therapeutic strategies, including successful challenge after tracheostomy.

Acknowledgements The authors gratefully acknowledge the persistence and courage of the patient and his family, the assistance of nursing and medical staff of the Nephrology, Otolaryngology, Intensive Care and Medical Day Units of the Royal Melbourne and the patient's regional hospitals, and the provision of Gb3 levels and antibody testing from the laboratories of Shire and Genzyme.

Synopsis

Tracheostomy allowed reinstitution of enzyme replacement therapy in a male Fabry patient, after withdrawal due to severe atypical infusion reactions despite extensive prophylaxis.

COI Disclosure

Dr Nicholls has received research and travel support from Genzyme and Shire HGT.

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