

Enzyme therapy in Fabry disease: severe adverse events associated with anti-agalsidase cross-reactive IgG antibodies

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Fabry disease is an X-linked lysosomal storage disorder related to α -galactosidase A deficiency.
- Two enzyme replacement therapies were approved by the European Medicines Agency in 2001: agalsidase-alfa and agalsidase-beta.
- Patients with Fabry disease and treated with agalsidase-alfa or -beta can develop antibodies against the protein infused.
- IgG antibodies against agalsidase-alfa and IgG and IgE antibodies against agalsidase-beta were previously described.

WHAT THIS STUDY ADDS

- Despite two successive treatments with agalsidase in our patient, kidney function declined.
- Cross-reactivity between the two enzymes could be demonstrated.
- Negative IgE antibodies and skin tests results do not necessarily equate with safety and the ability to continue with enzyme replacement therapies.

AIMS

To report a severe adverse event related to enzyme replacement therapy with agalsidase in an hemizygous male patient treated for Fabry disease.

METHODS

Retrospective analysis of clinical, radiological and biochemical data in a patient who suffered adverse events related to both agalsidase alfa and agalsidase beta treatments.

RESULTS

A hemizygous male patient was first treated for Fabry disease with agalsidase alfa. After more than 1 year of therapy, infusion-related symptoms necessitated systemic steroids and antihistaminic therapy. Decline in kidney function prompted a switch for agalsidase beta. Anaphylactoid shock occurred after the second infusion. No serum IgE antibodies were disclosed. Skin-test reactivity to agalsidase beta was negative. Following a published rechallenge infusion protocol, agalsidase beta was reintroduced, leading to a second anaphylactoid shock episode. Enzyme replacement therapy was stopped and the patient was treated with symptomatic therapy only. This case was referred to the pharmacovigilance department.

CONCLUSION

The negativity of immunological tests (specific anti-agalsidase IgE antibodies and skin tests) does not rule out the risk of repeated anaphylactoid shock following agalsidase infusion.

Fabry disease (FD) (OMIM 301 500) is an X-linked metabolic disorder characterized by a defect in the degradation of glycosphingolipids with terminal α -galactose residues that leads to progressive intralysosomal accumulation of globotriaosylceramide (GL-3) in various tissues [1]. The underlying cause is a mutation in the gene encoding the lysosomal enzyme α -galactosidase A (alphaGAL). Manifestations of the disease occur mostly in affected hemizygous men but also in heterozygous (carrier) women [2–4]. Severe morbidity is caused by heart failure, arrhythmias, stroke or end-stage renal disease. In the absence of enzyme replacement therapy (ERT), life expectancy is about 50 years for men and 70 years for women.

Case report

A 40-year-old male patient was referred in 2004 because of left foot oedema. He had experienced acroparaesthesia and hypohidrosis from the age of eight. Physical examination showed distal limb lymphoedema, angiokeratoma and telangiectasies. Blood pressure was normal. Because of such symptoms and familial history – a brother also affected – FD was suspected.

Ophthalmological examination revealed cornea verticillata. Echocardiography revealed left ventricular hypertrophy with no diastolic dysfunction. Brain magnetic resonance imaging revealed high signal on T₂-weighted

images in the posterior part of both thalami (pulvinar), a typical finding of FD [5]. Measured glomerular filtration rate (GFR) by lohexol method was 63 ml min⁻¹ 1.73 m⁻² and the daily proteinuria level was 1 g. A renal biopsy was not performed. Chest X-ray revealed two dorsal vertebral fractures. Dual energy X-ray absorptiometry confirmed osteoporosis with a T score below –4 SD in both lumbar and femoral sites. FD was confirmed by a leucocyte-specific activity of α -galactosidase A of 2 nmol h⁻¹ mg⁻¹ of protein (normal range 25–55). The missense mutation D266E in exon 5 of α -galactosidase A gene has been identified. Successive GFR measurements, daily proteinuria and titres of antibodies against ERT are summarized in Figure 1.

Ramipril 1.25 mg day⁻¹ was started. Enzyme replacement therapy was initiated in May 2005. The patient received an agalsidase-alfa infusion of 0.2 mg kg⁻¹, biweekly. In July 2005, during the fifth infusion, the patient had an acute reaction with bronchial spasm, which was treated with intravenous (i.v.) corticosteroids and antihistaminic therapy. The patient then received premedication therapy with 60 mg of i.v. methylprednisolone and 5 mg of i.v. dexchlorpheniramine before the following infusions and tolerance was good. In June 2006, GFR was unchanged at 60 ml min⁻¹ 1.73 m⁻². Antibodies against agalsidase-alfa were negative. ERT was pursued with premedication therapy, but the patient suffered sweats, asthenia, dysaesthesia in hands, and peripheral vasoconstriction at the end of each infusion.

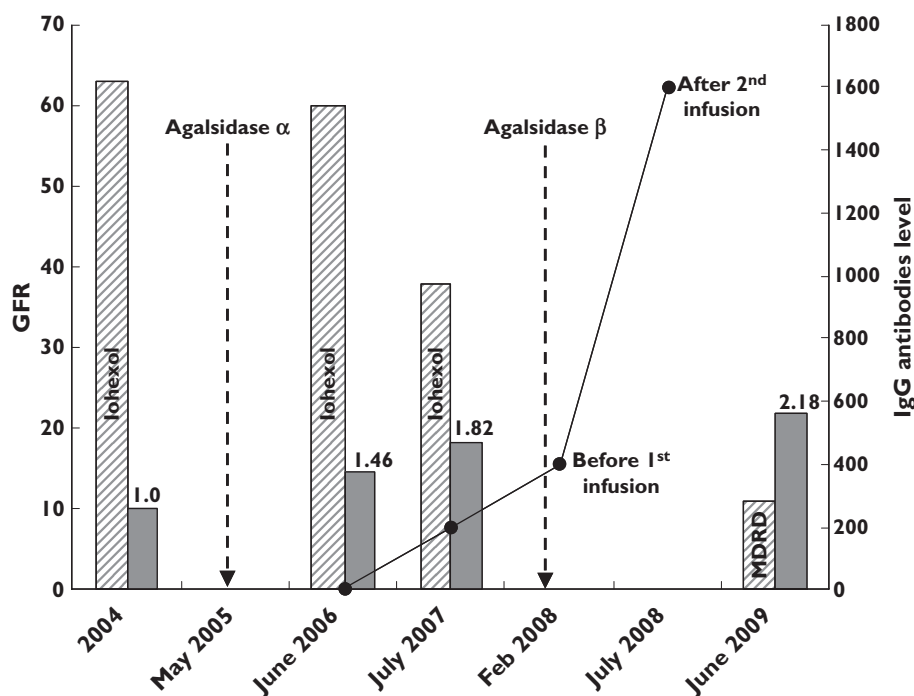


Figure 1

Successive glomerular filtration rate (GFR) measurements, daily proteinuria and titres of antibodies. GFR (ml/min/1.73 m²) (▨); Proteinuria (g/day) (■); IgG Antibodies level (titre) (—●—)

In July 2007, serum IgG antibodies against agalsidase- α were positive (titre 200; average < 100). Agalsidase- α infusions were continued biweekly and infusion duration was increased to 3 h. The GFR had decreased to $38 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ (iohexol method) and daily proteinuria level was 1.82 g. Blood pressure was 106/66 mmHg.

In February 2008, because of the decline of kidney function, the patient was switched to agalsidase- β 1 mg kg^{-1} biweekly. He received premedication therapy with 60 mg of i.v. methylprednisolone and 5 mg of i.v. dexchlorpheniramine before the first infusion, which was administered in 4 h. Tolerance was excellent except for acroparaesthesia during the infusion. Because of a well-defined osteoporosis that could be a specific feature of FD [6, 7], steroid therapy was considered deleterious. Premedication therapy before the second infusion was then given without steroids. One hour after the infusion had started, the patient was pale with cold extremities and a diffuse malaise. He also had nausea and vomited. Blood pressure was normal with heart rate 87 bpm compared with 50 at rest. Agalsidase- β was immediately stopped. After 1 h, the patient had recovered. Total IgE level in serum was 590 IU ml^{-1} (average < 20 IU ml^{-1}). An indirect enzyme-linked immunosorbent assay test was used to detect IgG and IgE antibodies against agalsidase- β . Specificity was confirmed in a radioimmunoprecipitation assay. Before the first agalsidase- β infusion, IgG antibodies were at a titre of 400 (average < 100), which increased to 1600 immediately after the second infusion. No anti-agalsidase IgE antibodies were present. In May 2008, skin testing was conducted using agalsidase- β . Both prick tests and intradermal testing were negative. Because skin test results were negative, the patient was carefully rechallenged with ERT.

In July 2008, following a published challenge infusion protocol, agalsidase- β was administered at a dose of 0.5 mg kg^{-1} (half the standard dose) for the first infusion [8]. The infusion was initiated at a rate of 0.01 mg min^{-1} for the first 30 min (1/25 of the standard recommended initial rate). Administration of preinfusion prophylactic medication was not allowed for the first infusion to permit early recognition of acute systemic reactions. In our patient, after 2 h of infusion and 6.45 mg of agalsidase- β , the patient presented hyperkinetic shock with paleness, coldness of extremities, oxygen saturation 80%, blood pressure about 155/80 mmHg and heart rate 67 bpm without disorder of consciousness. Agalsidase- β was immediately stopped. NaCl 0.9% infusion (1000 ml) and i.v. dexchlorpheniramine were administered. Two hours later, the patient had recovered. Total IgE level in serum was 1130 IU ml^{-1} (average < 20 IU ml^{-1}). Serial levels of urinary GL-3 were not performed under ERT.

From September 2008, the patient was treated with only symptomatic therapy including aspirin 75 mg day^{-1} , ramipril 7.5 mg day^{-1} , atorvastatin 10 mg day^{-1} , sertraline 50 mg day^{-1} , alendronate 70 mg week^{-1} and calcium and vitamin D supplementation.

In June 2009, the plasma level of creatinine was $512 \mu\text{mol l}^{-1}$ and GFR had decreased to $11 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ (Modification of the Diet in Renal Disease method). Daily proteinuria level was 2.18 g. Arteriovenous shunt was performed and dialysis will begin in the next weeks.

Discussion

We report here a severe adverse event following ERT with agalsidase- β in an hemizygous male patient treated for FD. This patient had first been treated with agalsidase- α , with infusion-associated reactions (IAR) that necessitated corticosteroids and antihistaminic therapy. IgG antibodies against agalsidase- β were detected before the first agalsidase- β infusion, which demonstrates the cross-reaction between the two species. Even if the patient had no IgE antibodies and negative skin tests, the severity of IAR was considered as an anaphylactoid reaction.

Introduction of ERT represents an important milestone in the management of patients with FD. Without such treatment, quality of life and life expectancy are severely compromised in both hemizygous men and heterozygous women. Currently two different enzyme preparations are available in the EU: agalsidase- α (ReplagalTM; Shire, Wayne, PA, USA) and agalsidase- β (FabrazymeTM; Genzyme, Cambridge, MA, USA), produced by expression of the α -galactosidase A gene in modified human cells derived from fibroblasts and Chinese hamster ovary cells, respectively. Patients are usually treated with the established protocols: agalsidase- α at 0.2 mg kg^{-1} and agalsidase- β at 1.0 mg kg^{-1} , every 2 weeks. However, comparison between the two enzymes is difficult, mainly because in the Phase III pivotal studies, evaluation of agalsidase- α was based predominantly on clinical end-points [9], whereas evaluation of agalsidase- β focused mainly on histological primary end-points [10]. From available data, ERT at European Medicines Agency-authorized dosages may stabilize kidney function at an early stage of the disease [11–14]. Both drugs have common antigenic determinants [15]. Factors that may influence the therapeutic response are incompletely understood. In our case, the rapid and severe decrease of GFR can be explained, at least in part, by the high level of daily proteinuria [14]. Irreversible damage in organs probably plays a role, but differences in uptake of the enzyme or the occurrence of neutralizing antibodies may also influence the outcome. Pivotal studies have reported the emergence of IgG antibodies in 56 and 88% of patients treated by agalsidase- α and agalsidase- β , respectively [9, 10]. There has been no detection of IgE antibodies in patients under agalsidase- α until now [11], whereas patients treated with agalsidase- β could develop IgE antibodies or skin-test reactivity [8]. Additional reports have shown these anti-

bodies to have potential neutralizing capacities as shown by urinary GL-3 excretion [11, 15, 16]. In the presence of persistent antibodies, a higher treatment dose seems more effective in further reducing GL-3 levels [17]. Even if urinary clearance of GL-3 was found to correlate negatively with persistent IgG antibodies against agalsidase, urinary GL-3 was not monitored in our patient mainly because it is not a reliable biomarker [18]. Of note, although in heterozygous female patients antibodies against agalsidase usually do not develop, serious adverse events may complicate the treatment [19]. The study by Vedder *et al.* showed that high titres of antibodies persisted in men who were switched from 0.2 mg kg⁻¹ agalsidase-alfa to 1.0 mg kg⁻¹ agalsidase-beta [17]. The occurrence of antibodies was not associated with low residual alphaGAL activity in leucocytes, nor with the presence of a missense or nonsense mutation. Hence, the type of mutation on the α -galactosidase gene does not seem to correlate anti-agalsidase antibodies occurrence [17, 20]. Of note, anti-agalsidase IgE and IgG antibody testing is performed only by pharmaceutical firms involved in agalsidase production and marketing. Considering the additive mixed with the enzyme, which was NaCl 0.9%, we estimated that it played no role in our case.

A protocol has been designed for rechallenge with agalsidase-beta in patients with IARs under agalsidase-beta [8]. First, the initial doses of agalsidase-beta and infusion rates were much lower than the standard recommended regimen and were progressively titrated upward in accordance with the patient's tolerance. Second, careful monitoring of the patient and flexible tailoring of dosage regimens and infusion rates were key elements. Third, preinfusion medications were prohibited to permit early recognition of acute systemic reactions. In our patient, reinstitution of agalsidase-beta therapy was a failure. However, serum IgE antibodies against agalsidase-beta and skin-test reactivity to agalsidase-beta were both negative. Nevertheless, total IgE antibodies in serum were highly elevated after the two agalsidase-beta infusions. There was no evidence of mast-cell degranulation as assessed by serum tryptase level, which was undetectable immediately after the two anaphylactoid reactions. Notably, in Bodensteiner's study the six patients were male with very low or undetectable levels of endogenous alphaGAL activity and all developed IgG antibodies [8]. During clinical trials, it has been observed that IARs occur more often in patients who are IgG-positive, but that the frequency and severity of IARs diminish over time in most patients due to infusion rate optimization, preinfusion medication, and, possibly, increased tolerance to the exogenous protein since antibody titres often decline with time [13, 14]. However, a small number of patients experience severe and/or recurrent IARs that sometimes lead to discontinuation of ERT, as in our patient.

Switching a patient with FD from one agalsidase to the other may be followed by severe anaphylactoid

hypersensitivity-like reaction. Concordance between IgE antibodies against medication and skin tests does not always exist [21]. Of note, we did not determine if total IgE antibodies of our patient were directed towards agalsidase-beta epitopes. Because such tests are not highly sensitive, the fact that anti-agalsidase IgE antibodies and skin reaction tests were negative does not rule out true hypersensitivity to agalsidase-beta in our patient. One explanation could be that Fabry patients often have a low reaction to insect bites, probably part of an autonomic dysfunction [22]. The immunological response to ERT may also be modulated by mannose-6-phosphate receptors or Fc receptors, or both. Considering that some patients exhibit inhibition of enzyme, animal models were developed. For example, in models of Hurler's disease, which is another lysosomal storage disorder linked to α -glucosidase deficiency, tolerant dogs were found not to inhibit uptake of enzyme when treated with ciclosporin A or azathioprine associated with low-dose infusions. The next step will be to assess the efficacy of such adjunctive therapies in preventing an immune response [23].

Conclusion

Our case has demonstrated that negative IgE antibodies and skin tests results do not necessarily equate with safety and the ability to continue with ERT. For the physician prescribing ERT, the clinical challenge is to find the treatment that will achieve and sustain the optimal clinical benefit of therapy for each patient. Rechallenging ERT in a patient with such IARs is highly debatable and should include efficacy/tolerance considerations, such as the decline of kidney function, the amount of time without dialysis saved for the patient, risks of anaphylaxis or anaphylactoid reaction, and potential adverse effects of adjuvant therapy such as corticosteroid therapy in our patient with osteoporosis.

Competing interests

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