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Anti-α-galactosidase A antibody response to agalsidase beta treatment: Data from the Fabry Registry

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ABSTRACT

Agalsidase beta, a form of recombinant human α-galactosidase A (αGAL), is approved for use as enzyme replacement therapy (ERT) for Fabry disease. An immunogenic response against a therapeutic protein could potentially impact its efficacy or safety. The development of anti-αGAL IgG antibodies was evaluated in 571 men and 251 women from the Fabry Registry who were treated with agalsidase beta. Most men developed antibodies (416 of 571, 73%), whereas most women did not (31 of 251, 12%). Women were also significantly more likely to tolerize than men; whereas 18 of 31 women tolerized (58%, 95%CI: 52%–64%), only 47 of 416 men tolerized during the observation period (11%, 95% CI: 8%–15%). Patients who eventually tolerized had lower median peak anti-αGAL IgG antibody titers than patients who remained seropositive at their most recent assessment (400 versus 3200 in men, 200 versus 400 in women, respectively). Patients with nonsense mutations in the *GLA* gene were more likely to develop anti-αGAL IgG antibodies than patients with missense mutations. Approximately 26% of men (151 of 571) reported infusion-associated reactions (IARs), compared to 11% of women (27 of 251). Men who developed anti-αGAL IgG antibodies were more likely to experience IARs compared to those who remained seronegative. Nine percent of seronegative men and women (34 of 375) reported IARs. The majority of IARs occurred during the first 6 to 12 months of agalsidase beta treatment and decreased over time, in both seroconverted and seronegative patients.

1. Introduction

Fabry disease is a rare lysosomal storage disorder caused by a deficiency of the lysosomal enzyme α-galactosidase A (αGAL) and the resulting progressive accumulation of globotriaosylceramide (GL-3) and other glycosphingolipids within various cells and tissues [1,2]. Over time, this accumulation of GL-3 is associated with renal disease progression, cardiovascular disease and strokes [3–8]. Because Fabry disease is X-linked, hemizygous males typically experience the most severe manifestations of Fabry disease [1,2]. However, many heterozygous females also develop substantial signs and symptoms of Fabry disease, including renal failure, cerebrovascular events, and cardiovascular events [4–6,8].

Agalsidase beta, a form of recombinant human αGAL, is approved for use as enzyme replacement therapy (ERT) for treatment of Fabry disease (Fabrazyme®, Genzyme, a Sanofi company, Cambridge, MA). In clinical studies, agalsidase beta was shown to clear microvascular endothelial GL-3 deposits from the kidney, heart, and skin [9,10], and to improve clinical outcomes when initiated before the onset of irreversible organ damage [10,11].

Agalsidase beta is administered via intravenous infusion at the recommended labeled dose of 1.0 mg/kg/2 weeks. Like other therapeutic proteins [12,13], agalsidase beta can cause immunogenicity [14,15], especially if patients have little or no endogenous enzyme. Anti-αGAL IgG antibodies could potentially impact the safety and efficacy of ERT in certain patients, possibly by altering its biodistribution or metabolic clearance [13]. Regular monitoring of serum

Abbreviations: CI, confidence interval; ERT, enzyme replacement therapy; αGAL, α-galactosidase A; GPS&RM, Genzyme Global Patient Safety & Risk Management; IAR, infusion-associated reaction.

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samples for the presence of anti-αGAL IgG antibodies is recommended as part of the routine care for patients who receive ERT.

The formation of anti-αGAL IgG antibodies was monitored in patients treated with agalsidase beta in placebo-controlled Phase 3 and Phase 4 clinical studies [9–11]. A more detailed retrospective analysis of data from these clinical trials and their corresponding open-label extension studies evaluated the impact of anti-αGAL IgG antibodies on efficacy [14]. However, randomized clinical trials of agalsidase beta included relatively limited numbers of subjects and most were men. In a prospective study by Vedder et al. [15], the immunogenicity and safety profile of agalsidase beta was found to be similar to that of agalsidase alfa (another form of recombinant human αGAL, Shire Human Genetic Therapies, Inc., Cambridge, MA), when administered at 0.2 mg/kg/2 weeks.

The Fabry Registry is an observational database that compiles clinical and laboratory data from both treated and untreated patients; it was established to further investigate the long-term effects of ERT and the natural progression of Fabry disease in a larger and more diverse population. The objective of the present analysis was to evaluate the development of anti-αGAL IgG antibodies in Fabry Registry men and women who were treated with agalsidase beta.

2. Methods

The Fabry Registry began enrolling treated and untreated patients in April 2001. As of 02 April 2010, it included 3552 patients (1760 men and 1792 women). All patients with Fabry disease are eligible to enroll in the Fabry Registry, regardless of age, gender, symptoms, or whether they are receiving ERT from any commercial source. Patient and physician participation is voluntary. Patients provide informed consent through local Institutional Review Boards/Ethics Committees and may decline to participate or withdraw consent at any time.

To be included in the current analyses, patients must have received agalsidase beta as their only source of ERT and must have reported at least 1 post-baseline anti-αGAL IgG assessment. Anti-αGAL IgG antibody titers were assessed in diluted serum samples by enzyme-linked immunoabsorbent assay at the Genzyme Clinical Specialty Laboratory (Framingham, MA, US), which has been used in clinical trials with agalsidase beta, as described in detail by Benichou et al. [14]. Anti-αGAL IgG titers are reported as the reciprocal of the maximum dilution that yielded a positive result above the assay cut-point. Patients were designated as *seronegative* if they tested negative for anti-αGAL IgG antibodies each time they were tested. Patients were designated as *seroconverted, then tolerized* if they had 1 or more negative anti-αGAL IgG tests after previously testing positive and whose most recent assessment was negative. Patients were designated as *seroconverted, not tolerized* if they had at least 1 positive anti-αGAL IgG test and their most recent assessment was positive. The Fabry Registry recommends that treating physicians collect serum samples for IgG antibody testing from all patients prior to the first agalsidase beta infusion (baseline), every 3 months thereafter for the first 18 months of treatment, then every 6 months until 2 consecutive negative results are confirmed (tolerization). However, treating physicians determine the actual frequency of assessments according to individual patients' needs.

Plasma GL-3 levels were measured by tandem mass spectrometry [16] at the Genzyme Clinical Specialty Laboratory. The Fabry Registry Board of Advisors recommends that the treating physician collect plasma for GL-3 levels to be assessed prior to the first infusion, then every 3 months for the first 18 months of treatment, then every 6 months thereafter.

The Genzyme Global Patient Safety & Risk Management (GPS&RM) pharmacovigilance database was searched for any infusion-associated reactions (IARs), defined as any related adverse event occurring during or after an agalsidase beta infusion on the day of the infusion among the patients in this cohort.

Statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc., Cary, NC). The binomial proportion Fisher's exact test was used to determine the 95% lower and upper confidence intervals (CI) of the percentage of patients who tolerized. Student's two-sided tests were used to perform statistical significance testing of plasma GL-3 levels between seronegative and seroconverted patients (a p-value cut-point of an alpha-level of 0.05). The Chi-square test was used to perform statistical significance testing of the percentage of seronegative versus seroconverted men who reported IARs; the Chi-square exact test was used to perform statistical significance testing of the percentage of seronegative versus seroconverted women who reported IARs (a p-value cut-point of an alpha-level of 0.05).

3. Results

As of 02 April 2010, a total of 822 Fabry Registry patients (571 men and 251 women) had reported post-baseline IgG titer data to the Fabry Registry. As shown in Fig. 1, 416 of 571 men (73%) reported

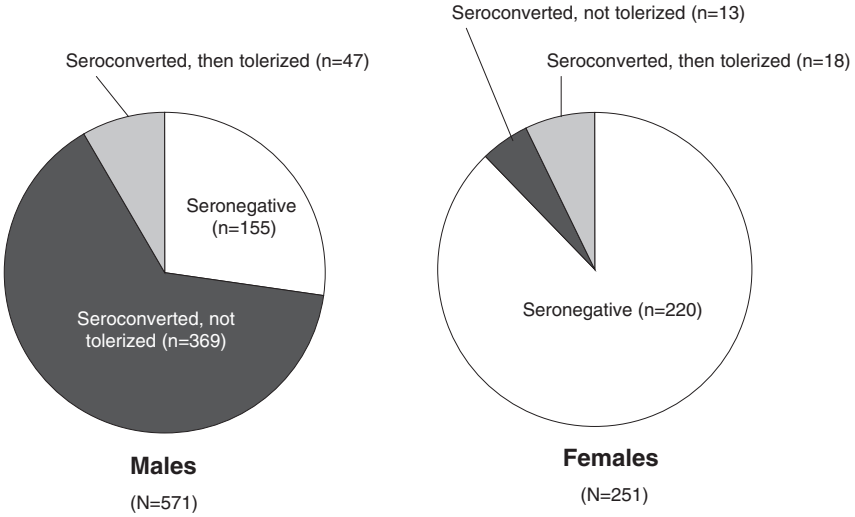

Fig. 1. Most males, but few females develop anti-aGAL IgG antibodies after treatment with agalsidase beta. Seroconversion status is shown for Fabry Registry males and females. Patients designated as *Seronegative* tested negative for anti-αGAL IgG antibodies each time they were tested. Patients designated as *Seroconverted, not Tolerized* had at least 1 positive anti-αGAL IgG test, but did not tolerize. Patients designated as *Seroconverted, then Tolerized* had 1 or more negative anti-αGAL IgG tests after previously testing positive and whose most recent test was negative.