Agalsidase Alfa and Kidney Dysfunction in Fabry Disease

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ABSTRACT

In male patients with Fabry disease, an X-linked disorder of glycosphingolipid metabolism caused by deficient activity of the lysosomal enzyme α-galactosidase A (α-Gal A), kidney dysfunction becomes apparent by the third decade of life and invariably progresses to ESRD without treatment. Here, we summarize the effects of agalsidase alfa on kidney function from three prospective, randomized, placebo-controlled trials and their open-label extension studies involving 108 adult male patients. The mean baseline GFR among 54 nonhypertensive patients (measured GFR(135 ml/min per 1.73 m²) treated with placebo was 85.4 ± 29.6 ml/min per 1.73 m²; during 6 mo of placebo, the mean annualized rate of change in GFR was −7.0 ± 32.9 ml/min per 1.73 m². Among 85 nonhypertensive patients treated with agalsidase alfa, the annualized rate of change was −2.9 ± 8.7 ml/min per 1.73 m². Treatment with agalsidase alfa did not affect proteinuria. Multivariate analysis revealed that GFR and proteinuria category (<1 or ≥1 g/d) at baseline significantly predicted the rate of decline of GFR during treatment. This summary represents the largest group of male patients who had Fabry disease and for whom the effects of enzyme replacement therapy on kidney function have been studied. These data suggest that agalsidase alfa may stabilize kidney function in these patients.


Fabry disease is an X-linked disorder of glycosphingolipid metabolism caused by deficiency of the activity of the lysosomal enzyme α-galactosidase A (α-Gal A), resulting from one of many mutations of the gene GLA located at the Xq22.1. The disease occurs with an incidence of approximately 1 in 117,000 live male births, although recent surveys suggest that the incidence may be much higher. Fabry disease primarily affects male individuals; female heterozygotes are reported to experience all of the signs and symptoms of Fabry disease but with a later onset and a more variable phenotype than is seen in men. The signs and symptoms of Fabry disease are thought to be due to progressive accumulation of globotriaosylceramide (Gb₃) within tissues and organs. Among other signs and symp-
toms, progressive kidney dysfunction is nearly universal in male individuals with Fabry disease. The initial sign of decline in kidney function is proteinuria or microalbuminuria, which has been reported in affected male individuals as young as 16 yr and is present in half of male individuals by age 35 yr. Gb₃ accumulation within the glomeruli results in mesangial widening and glomerular sclerosis, with a resultant loss of filtering capacity. Chronic renal insufficiency (defined as serum creatinine levels ≥1.5 mg/dl) has an onset in the third decade of life and progresses rapidly to ESRD, with a reported average rate of decline in filtering capacity of 12.2 ml/min per yr (range 3.3 to 33.7 ml/min per yr) once chronic renal insufficiency has been reached. The average age at initiation of dialysis for ESRD in male patients with Fabry disease ranged between 36.7 and 42.0 yr. Kidney dysfunction in female patients with Fabry disease is less prevalent than and usually not as severe as that in male patients but does progress to ESRD in some cases.

Enzyme replacement therapy (ERT) with human α-Gal A was approved for treatment of Fabry disease in 2001 and has been reported to alleviate neuropathic pain, result in regression of hypertrophic cardiomyopathy, improve sweat function, reduce plasma and urine sediment Gb₃ levels, and reduce microvascular endothelial Gb₃ deposits. In one long-term (up to 4.5 yr) study of 25 male individuals with Fabry disease, agalsidase alfa, α-Gal A produced by gene activation in a human cell line, was reported to stabilize kidney function in patients with stage 1 or 2 chronic kidney disease at baseline and to slow the progression of renal dysfunction in adult male patients with stage 3 chronic kidney disease compared with historical control subjects. Observational studies of the patients enrolled in the Fabry Outcome Survey (FOS) suggested a similar renoprotective effect of agalsidase alfa. The results of a recent, double-blind, placebo-controlled trial suggested that agalsidase beta, a recombinant form of α-Gal A produced in Chinese hamster ovary cells, slowed the progression of major clinical events in patients with Fabry disease and mild to moderate kidney disease, with the benefit being greater in patients with estimated GFR (eGFR) >55 ml/min per 1.73 m² at baseline than in those with baseline eGFR ≤55 ml/min per 1.73 m². In this report, we present a summary of the effects of agalsidase alfa on kidney function in all of the adult male patients who were enrolled in prospective, randomized, placebo-controlled clinical studies of agalsidase alfa and their open-label extension studies and who were treated for at least 12 mo.

RESULTS

Patients, Demographics, Concomitant Renoprotective Treatment, and Treatment Time

Of the 121 adult male patients who had Fabry disease and were enrolled in these three studies, 108 had sufficient GFR measurements for inclusion in this analysis. The number of patients who had GFR measured before and after placebo, before and during agalsidase alfa, or before and during both placebo and agalsidase alfa is illustrated in Figure 1. The average age of these 108 patients at baseline was 34.2 ± 9.3 yr (range 18 to 54 yr). Average systolic blood pressure (BP) was 126.5 ± 14.5, and diastolic BP was 71.6 ± 10.9 mmHg. At baseline, 18 (16.7%) patients were reported as having hypertension. During the 6-mo placebo period, angiotensin-converting enzyme inhibitors (ACEIs) and/or selective angiotensin II receptor blockers (ARBs) were administered to nine (16.1%) of 56 patients. During the active treatment phase of the study, ACEIs and/or ARBs were administered to 26 (30.0%) of the 93 patients. The average mean agalsidase alfa treatment duration for patients in this pooled analysis was 2.0 ± 1.0 yr (median 1.6 yr). Six patients had their final GFR measurement recorded after a total of 4.5 yr of agalsidase alfa therapy; and 5, 8, 11, 10, 26, and 27 patients had their final GFR measurement made after 4.0, 3.0, 2.5, 2.0, 1.5, and 1.0 yr of therapy, respectively.

Renal Function

Progression of Renal Function during the Placebo Period.

The mean baseline GFR measured before the placebo period was 88.9 ± 32.5 ml/min per 1.73 m² (median 92.3 ml/min per 1.73 m²; range 12.7 to 160 ml/min per 1.73 m²; n = 57). After 6 mo of placebo, mean GFR had declined to 85.0 ± 37.6 ml/min per 1.73 m² (median 83.3 ml/min per 1.73 m²; range 12.5 to 184.0 ml/min per 1.73 m²), representing an average annualized rate of change of −7.7 ± 38.0 ml/min per 1.73 m²/yr (P = 0.14, paired t test). Three patients had renal hyperfiltration (i.e., baseline GFR >135 ml/min per 1.73 m²). When these three patients were removed from the analysis, the baseline GFR was 85.4 ± 29.6 and the GFR after 6 mo was 81.9 ± 34.8, representing an average annualized rate of change of −7.0 ± 32.9 ml/min per 1.73 m² in this subgroup (P = 0.12, paired t test).

Renal Function during Treatment.

Before the initiation of agalsidase alfa therapy, GFR ranged from 25 to 184 ml/min per 1.73 m² and averaged 90.3 ± 31.2 ml/min per 1.73 m² (median 87.4 ml/min per 1.73 m²; n = 93). Two patients had GFR between 15 and <30 ml/min per 1.73 m² at baseline. No patient had GFR <15 ml/min per 1.73 m². GFR measurements at baseline and during agalsidase alfa therapy are presented in Figure 2, and the rates of change of GFR...
The rate of change of GFR in male patients with Fabry disease during 12 to 54 mo of ERT with agalsidase alfa was estimated by measuring GFR both before and after a 6-mo placebo period. The rate of decline in GFR was $-0.10 \pm 12.88$ ml/min per 1.73 m$^2$/yr during the 12 mo of agalsidase alfa ($P = 0.097$, paired $t$ test). A similar statistically not significant (NS) effect was seen when this analysis was confined to the 18 patients with baseline GFR between 30 and $<90$ ml/min per 1.73 m$^2$ at baseline (Figure 3).

The two patients with GFR $<30$ ml/min per 1.73 m$^2$ at baseline progressed to ESRD during treatment after 12 mo of agalsidase alfa therapy. In addition, three other patients who had received $<12$ mo of agalsidase alfa treatment also progressed to ESRD. Before starting agalsidase alfa therapy, two of these three patients had GFR between 15 and $<30$ ml/min per 1.73 m$^2$ and one had GFR $<15$ ml/min per 1.73 m$^2$.

### Responder Analyses

Table 2 presents the responder analyses. The response rate was better in patients with preserved kidney function at baseline regardless of whether GFR or the level of proteinuria was used to categorize baseline kidney function. Importantly, only five of 36 patients with GFR between 60 and $<90$ ml/min per 1.73 m$^2$ at baseline progressed to the next, more severe category during the study.

### Proteinuria

No significant change in urinary protein excretion was observed with 1 or 2 yr of agalsidase alfa treatment. At baseline, mean urine protein excretion was $1.030 \pm 0.40$ g/d (median $0.006$ to 10.550 g/d; $n = 80$). After 1 yr of agalsidase alfa therapy, mean urine protein excretion was $0.970 \pm 0.520$ g/d (median $0.420$ g/d; range $0.040$ to 8.660 g/d; $n = 76$), and after 2 yr of treatment, mean urine protein excretion was $0.970 \pm 1.140$ g/d (median $0.610$ g/d; range $0.036$ to 4.680 g/d; $n = 34$).

In the 80 patients with quantitative baseline proteinuria measurements and at least 1 yr of therapy with agalsidase alfa, multivariate analysis revealed that baseline GFR ($P = 0.005$) and proteinuria category ($<1$ or $\geq 1$ g/d; $P = 0.002$) were significant factors in predicting the rate of decline in GFR. The average rate of decline of GFR in the 58 patients with proteinuria $<1$ g/d was $2.1 \pm 8.8$ ml/min per 1.73 m$^2$/yr, whereas the rate of decline in the 22 patients with baseline proteinuria $\geq 1$ g/d was $-6.4 \pm 5.8$ ml/min per 1.73 m$^2$/yr.

### Table 1. The rate of change of GFR in male patients with Fabry disease during 12 to 54 mo of ERT with agalsidase alfa

<table>
<thead>
<tr>
<th>Baseline GFR Range (ml/min per 1.73 m$^2$)</th>
<th>Age (yr; Mean ± SD)</th>
<th>$n$</th>
<th>Treatment Time (mo; Mean ± SD)</th>
<th>Baseline Proteinuria (mg/24 h; Median [Min, Max]) $^a$</th>
<th>Baseline GFR (ml/min per 1.73 m$^2$; Mean ± SD)</th>
<th>Rate of Change in GFR (ml/min per 1.73 m$^2$/yr; Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 135$</td>
<td>35.0 ± 8.8</td>
<td>8</td>
<td>1.2 ± 0.2</td>
<td>1236 (n = 1)</td>
<td>151.9 ± 16.4</td>
<td>$-24.5 \pm 9.0$</td>
</tr>
<tr>
<td>90 to $&lt;135$</td>
<td>28.5 ± 7.8</td>
<td>36</td>
<td>2.0 ± 1.0</td>
<td>207 (6, 912; n = 29)</td>
<td>109.6 ± 13.4</td>
<td>$-2.2 \pm 9.3$</td>
</tr>
<tr>
<td>60 to $&lt;90$</td>
<td>36.5 ± 7.8</td>
<td>36</td>
<td>2.2 ± 1.2</td>
<td>500 (611, 5382; n = 36)</td>
<td>78.1 ± 8.4</td>
<td>$-3.2 \pm 6.7$</td>
</tr>
<tr>
<td>30 to $&lt;60$</td>
<td>41.3 ± 7.8</td>
<td>14</td>
<td>2.1 ± 0.9</td>
<td>1192 (228, 7980; n = 13)</td>
<td>50.1 ± 8.2</td>
<td>$-2.9 \pm 11.8$</td>
</tr>
<tr>
<td>15 to $&lt;30$</td>
<td>41.5 ± 6.4</td>
<td>2</td>
<td>1.0</td>
<td>10,545 (n = 1)</td>
<td>26.7</td>
<td>$-9.5$</td>
</tr>
<tr>
<td>Total</td>
<td>34.4 ± 9.0</td>
<td>85</td>
<td>2.1 ± 1.1</td>
<td>388 (6, 10,545; n = 79)</td>
<td>84.5 ± 25.5</td>
<td>$-2.9 \pm 8.7$</td>
</tr>
</tbody>
</table>

$^a$n = the number of patients who had quantitative assessment of baseline proteinuria.

$^b$Excluding patients with a baseline GFR $>135$ ml/min per 1.73 m$^2$. 

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**Figure 2.** GFR during treatment with agalsidase alfa in male patients with Fabry disease, divided into subgroups according to baseline GFR.

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**Table 2.** The rate of change of GFR in male patients with Fabry disease during 12 to 54 mo of ERT with agalsidase alfa.
The study presented here represents the largest group of male patients who have Fabry disease and who have had repeated measurements of GFR either before or during treatment with ERT. While treated with placebo, GFR declined at a mean rate of 7.7 ml/min per 1.73 m²/yr. Although this placebo observation period was short, the observed rate of change in GFR was similar to that reported by others.8,19 During treatment with agalsidase alfa in this study, the rate of loss of GFR in patients with baseline GFR from 30 to 135 ml/min per 1.73 m² was numerically less than that seen during the placebo period, suggesting that renal function was stabilized in male patients with Fabry disease for periods between 1.0 and 4.5 yr (Table 1); however, these observed differences were not statistically significantly different, likely as a result of the large variation in the rate of change of GFR during either the placebo or the agalsidase alfa treatment period. An important observation was that the magnitude of proteinuria at baseline was a strong predictor of the rate of loss of GFR during ERT.

The results from the 6-mo placebo period of this study provides some insight into the natural history of kidney function in untreated Fabry disease, particularly because GFR was measured rather than estimated. Hyperfiltration (GFR ≥135 ml/min per 1.73 m²) was common; it was observed in three placebo patients at enrollment and developed in three additional patients during the placebo period. That it developed during these studies suggests that it may be an initial indication of kidney dysfunction in Fabry disease, as has been postulated by Barbey et al.22 In patients with hyperfiltration, a fall in GFR toward normal could represent either a positive result of a treatment or continued disease progression. The wide range of the rate of change in GFR during the placebo period suggests that 6 mo may be too short an observation period to describe accurately the progression of kidney disease in non–ERT-treated patients with Fabry disease.

The advent of ERT has raised the possibility of positively affecting the progression of kidney disease in patients with Fabry disease. Two different forms of α-Gal A are available: Agalsidase alfa11 and agalsidase beta.14 Agalsidase beta has been approved in >40 countries, including the United States, for
dosing at 1.0 mg/kg every other week.\textsuperscript{25} Both proteins reduce plasma and urine sediment Gb\textsubscript{3} levels,\textsuperscript{11,14} and both are reported to stabilize kidney function in long-term, open-label studies.\textsuperscript{16,24,25} The stabilization of kidney function by agalsidase alfa in the present study (Figures 2 and 3, Table 1) is nearly identical to that reported by Germain \textit{et al.}\textsuperscript{25} with long-term use of agalsidase beta; however, neither of these studies included a long-term, concurrently followed placebo group, and thus the conclusion that ERT stabilized kidney function must remain somewhat speculative.

Proteinuria has emerged as an important risk factor for the decline in kidney function while receiving ERT. In this study, baseline proteinuria \( \geq 1 \) g/d was strongly and statistically significantly associated with a greater rate of decline in GFR during ERT. This observation is similar to those reported for two long-term studies of agalsidase beta.\textsuperscript{20,25} In both of those studies, renal events were significantly more frequent in patients with baseline proteinuria \( > 1 \) g/d. The influence of proteinuria at baseline on the average rate of decline of GFR during ERT is illustrated in Figure 5, which shows that ERT with either agalsidase alfa or agalsidase beta seems to slow the rate of decline of kidney function to an equivalent degree when compared with the expected loss of filtering capacity in untreated or placebo-treated patients but that this benefit is experienced only by patients with proteinuria \(< 1 \) g/24 h. Because of the progressive nature of kidney dysfunction in Fabry disease, it may be unreasonable to think that ERT will quickly stop or reverse renal damage. Even in those without Fabry disease, GFR declines by approximately 1 ml/min per 1.73 m\textsuperscript{2}/yr after the age of 30 yr.\textsuperscript{26}

Further evidence supporting the importance of proteinuria in influencing the response to ERT is provided by Tahir \textit{et al.},\textsuperscript{27} who reported that aggressive antiproteinuric therapy with ACEIs or ARBs combined with agalsidase beta (1 mg/kg every other week) stabilized kidney function in male and female patients with Fabry disease during a median 30 mo of treatment. Our study was started before the antiproteinuric effect of ACEIs or ARBs in Fabry disease was appreciated (e.g., Brenner \textit{et al.}\textsuperscript{28}), and the fraction of patients treated with these agents increased during the study period. For example, 16.1\% of the patients reported use of an ACEI or ARB during the placebo period, and 29.2\% reported their use during the treatment period. The study was not designed to evaluate the effect of ACEIs or ARBs in a controlled setting; therefore, the failure of the multivariate analysis to identify a significant benefit associated with these agents may reflect their uncontrolled use and less than optimal dosing and should not be considered as evidence against their importance in treating kidney disease in patients with Fabry disease.

We and others have chosen to use proteinuria of 1 g/d as a threshold for analysis of the influence of urinary protein excretion on the response to ERT\textsuperscript{20,25}; however, on the basis of the informal responder analysis presented in Table 2, it seems likely that the negative influence of proteinuria extends to as low as 0.3 g/d. This observation, coupled with the fact that the response rate to agalsidase alfa was higher in patients with preserved baseline GFR (Table 2), emphasizes the importance of early treatment.

\textbf{Study Limitations}

This report has summarized the results of three separate clinical trials that were conducted at different times and at different study sites. Although the studies specifically excluded patients who had reached ESRD, no other renal-related entry criteria were used. Thus, the inclusion of a large fraction of patients with relatively normal baseline kidney function (GFR \( \geq 90 \) ml/min per 1.73 m\textsuperscript{2}), who would not be expected to demonstrate substantial loss of GFR, may have reduced the power to detect statistically significant effects. Too few patients participated in both the placebo and the active treatment periods for a robust statistical analysis to be performed. On the basis of the results of the 42 patients who participated in both the placebo period and the subsequent open-label treatment period, a prospective study would require approximately 186 patients to study.
have an 80% chance of detecting an improvement of slope of GFR of 5.1 ml/min per 1.73 m²/yr at the 5% significance level. Finally, because the prevalence of uncontrolled hypertension was low in this study, no meaningful analysis of the influence of BP on the renal response to ERT could be performed.

CONCLUSIONS

This summary represents the largest group of male patients who have Fabry and in whom the effects of ERT on renal function have been determined by monitoring changes in measured GFR, the gold standard for evaluating kidney function. In patients with renal dysfunction (i.e., GFR < 90 ml/min per 1.73 m²), eGFR overestimated renal function in the higher range. The results of this analysis suggest that agalsidase alfa may stabilize kidney function in male patients with Fabry disease and are nearly identical to results reported for agalsidase beta in a similar long-term, open-label study. Elevated proteinuria at baseline was a significant predictor of loss of GFR during this study, with an apparent threshold of 1 g/d. Formal confirmation of these preliminary observations will be challenging, because, ideally, it would require a large, long-term, placebo-controlled study. Further observational data from the Fabry Outcome Survey may be useful in evaluating the effect of agalsidase alfa on kidney function in Fabry disease.

CONCISE METHODS

Study Design

Three separate prospective studies of agalsidase alfa (Replagal; Shire Human Genetic Therapies, Cambridge, MA) for the treatment of Fabry disease in male hemizygotes have been conducted. Male adults (≥ 18 yr old) with laboratory and clinical evidence of Fabry disease were eligible for enrollment in these studies. Each study was supported by Shire HGT and began as a 6-mo, randomized, double-blind, placebo-controlled trial, and each was continued as an open-label extension during which all enrolled patients were treated with agalsidase alfa for an additional 12 to 48 mo. Agalsidase alfa was administered at a dosage of 0.2 mg/kg infused over 40 min every other week in each study. In the first study, 26 adult male patients with chronic neuropathic pain were enrolled, and the effect of treatment on pain was assessed using the Brief Pain Index. A second study of 15 adult men with left ventricular hypertrophy was conducted in which the effect of agalsidase alfa on left ventricular mass was evaluated with magnetic resonance imaging. In the third study, 80 adult male patients with chronic neuropathic pain were enrolled, and the effect of treatment on pain was followed with the Brief Pain Index. No specific guidelines were predefined per protocol with regard to potential confounders (e.g., BP management and concomitant renoprotective medication such as ACEIs and ARB). All patients who participated in these studies gave their written informed consent before enrolling in the double-blind and open-label extension phases of each study. The institutional review board or ethics committee reviewed and approved each individual protocol at each study site.

Although none of the three studies had a specific requirement for the presence of renal dysfunction at baseline, the effect of agalsidase alfa on GFR was assessed by measuring GFR at baseline and after 6 mo during the double-blind studies and every 6 or 12 mo in the open-label extension studies. This report describes a secondary, pooled analysis of the effects of long-term treatment with agalsidase alfa on renal function in adult male patients who had Fabry disease and were enrolled in these studies. Results from 108 of 121 enrolled patients who had GFR measured by inulin, technetium-DTPA, or chromium-EDTA before and after the placebo period or before and after ≥ 12 mo of agalsidase alfa therapy were included in this study. Patients were excluded from analysis when they had fewer than two GFR measurements per study period (placebo, active treatment).

Agalsidase Alfa

Agalsidase alfa is a form of human α-Gal A, manufactured in a genetically modified continuous human cell line by methods previously described. The enzyme has the same amino acid sequence as the native human enzyme and has a similar glycosylation pattern. Agalsidase alfa is approved in > 40 countries at a dosage of 0.2 mg/kg infused intravenously every other week, but has not yet been approved in the United States. Each patient received agalsidase alfa (0.2 mg/kg) every other week administered intravenously in 100 ml of physiologic saline infused over approximately 40 min. Premedications were not administered prophylactically unless a patient had experienced a previous infusion reaction. In those cases, patients were premedicated with oral H1 and H2 histamine antagonists, nonsteroidal anti-inflammatory drugs, and/or oral corticosteroids before subsequent infusions. These premedications were subsequently withdrawn without sequelae in the majority of patients.

Renal Function

GFR was measured using inulin, technetium DTPA, or chromium-EDTA (non-US sites) and was expressed as ml/min per 1.73 m² body surface area. In addition, GFR was estimated using the modified Modification of Diet in Renal Disease (MDRD) equation. Patients were categorized as to their baseline GFR as follows: GFR ≥ 135 ml/min per 1.73 m² (defined as hyperfiltration), GFR 90 to < 135 ml/min per 1.73 m², GFR 60 to < 90 ml/min per 1.73 m², GFR 30 to < 60 ml/min per 1.73 m², GFR 15 to < 30 ml/min per 1.73 m², and GFR < 15 ml/min per 1.73 m² or on dialysis. Twenty-four-hour urinary protein excretion was quantitatively determined by the local clinical laboratory.

Statistical Analysis

Baseline GFR was defined as the last value measured before beginning therapy with agalsidase alfa or placebo. The rate of change in GFR during the initial 12 to 54 mo of ERT was calculated for each patient individually by subtracting the baseline value from the final value and dividing by treatment duration. A responder analysis was performed using three different definitions of a responder: (1) Rate of loss of GFR no greater than 5 ml/min per 1.73 m²/yr, (2) less than a 20% decrease in GFR from baseline to final measurement, and (3) no shift to a more severe GFR category. To investigate the influence of baseline factors on the rate of change of GFR during treatment with agalsidase alfa, we fitted a multivariate model. In this model, rate of change in GFR was the outcome measure, and baseline age, baseline GFR, base-
line proteinuria category (<1 or ≥1 g/d), and ACEI/ARB status were explanatory variables. Only patients who had quantitative baseline proteinuria measurements were included in this analysis. A patient who reported the use of an ACEI and/or ARB at any time during the active treatment period was considered positive for ACEI/ARB status. The correlation between simultaneously measured GFR and eGFR was analyzed by linear regression for the entire range of GFR measurements as well as for the subgroup of GFR measurements <90 ml/min per 1.73 m². All analyses were two-tailed, and statistical significance was defined as P < 0.05. All values are expressed as means ± SD.

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