



Enzyme replacement therapy for Fabry disease: A systematic review and meta-analysis

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Abstract

The specific treatment available for Fabry disease (FD) is enzyme replacement therapy (ERT) with agalsidase alfa or beta. A systematic review and meta-analysis was conducted to assess the efficacy and safety of ERT for FD. Only double-blind, randomized clinical trials (RCTs) comparing agalsidase alfa or beta and placebo were included. ERT with either agalsidase alfa or beta was considered similar for the purposes of analysis. Ten RCTs were identified, which showed improvements in neuropathic pain, in heart abnormalities and in globotriaosylceramide (GL-3) levels. A meta-analysis showed increased odds for fever, rigors, development of IgG antibodies to agalsidase, and no significant association with development of hypertension or reduction in the QRS complex duration on electrocardiogram. The RCTs included in this comparison enrolled few patients, were highly heterogeneous, and were focused mainly on surrogate endpoints, limiting any conclusions as to the real effect of ERT for FD. The available evidence suggests that response to ERT is variable across patient subgroups and that agalsidase may slow progression of FD, with slight improvement of existing changes. Nevertheless, many uncertainties remain, and further studies are necessary.

Keywords: Fabry disease, Fabry disease/therapy, enzyme replacement therapy, alpha-Galactosidase.

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder characterized by deficient activity of α -galactosidase A (α GAL-A), one of the enzymes involved in glycosphingolipid catabolism. Consequently, patients exhibit progressive storage of globotriaosylceramide (GL-3) throughout the body, and particularly so in vascular endothelium. The incidence of FD hemizyosity is generally estimated as 1 in 40,000 to 50,000 males (Meikle *et al.*, 1999; Desnick *et al.*, 2001); however, recognition of atypical forms of the disease and neonatal screening (Spada *et al.*, 2006) suggest that the actual figure may be much higher.

Unlike most lysosomal disorders, FD mostly afflicts young adults (Wraith, 2004). In the classic form of the disease, clinical manifestations begin at the age of 5. The most common findings include intermittent acroparesthesia

(“Fabry crisis”), with episodes of acute pain lasting from hours to days; angiokeratomas; cornea verticillata; hypohydrosis or anhydrosis; heat, cold and exercise intolerance; mild proteinuria; and gastrointestinal disorders (Eng *et al.*, 2007). Cardiac complications include left ventricular hypertrophy, heart valve disease, coronary artery disease, conduction abnormalities, heart failure, arrhythmias and acute myocardial infarction (Pieroni *et al.*, 2006). Cerebrovascular disease is manifest as white matter lesions, paresthesias, vertigo, early stroke and transient ischemic attacks (Politei and Capizzano, 2006). Glomerular podocyte injury leads to proteinuria and hematuria, which are usually detected during adolescence. Organ and system involvement is progressive, and by the third to fifth decade of life most patients have developed severe kidney and heart disease (Eng *et al.*, 2007). Progressive renal dysfunction eventually requires dialysis and renal transplantation, and is the main cause of death in FD (Desnick *et al.*, 2001; Eng *et al.*, 2007). Atypical forms follow an oligosymptomatic course, with involvement mostly confined to one system (renal disease, for instance). As FD is an X-linked condition, the phe-

notype in females varies widely, ranging from complete absence of symptoms to severe disease (Wilcox *et al.*, 2008; Pinto *et al.*, 2010).

Supportive therapy of FD includes pain management with analgesics, anticonvulsants and non-steroidal anti-inflammatory agents, treatment of cerebrovascular, cardiac and renal comorbidities with antiplatelet and antihypertensive agents, dialysis and, in end-stage renal disease, kidney transplantation. Specific treatment consists of enzyme replacement therapy (ERT) with recombinant α GAL-A (agalsidase). Two agalsidase products are currently available on the market, agalsidase alfa and agalsidase beta. Agalsidase alfa is manufactured by Shire Human Genetic Therapies (Cambridge, MA, USA) from human cell lines and administered every two weeks by intravenous infusion (over 40 min) at a dose of 0.2 mg/kg. Agalsidase beta is manufactured by Genzyme Corporation, which was recently acquired by Sanofi-Aventis (Paris, France), from CHO (Chinese hamster ovary) cells and administered every two weeks by intravenous infusion at a dose of 1 mg/kg at an initial rate of 0.25 mg/min. Both products have been approved for use in the European Union since 2003, but only agalsidase beta has been cleared by the U.S. Food and Drug Administration (FDA) for use in the USA. In Brazil, agalsidase beta and agalsidase alfa received marketing authorization in 2006 and 2009 respectively.

As a multisystem disease requiring lifelong follow-up and clinical monitoring, FD has a substantial impact on healthcare systems, not only due to the high cost of ERT (approximately R\$ 350,000.00 per year per patient), but also due to the morbidity experienced by patients, usually during working age. The present study sought to evaluate, through a systematic review of the literature (SR) and meta-analysis, the efficacy and safety of ERT for treatment of FD.

Methods

In vitro studies suggest that agalsidase alfa and beta share very high biochemical and structural similarity and are indistinguishable in terms of functional effects. Both have identical amino acid sequences, specific activity and stability (Blom *et al.*, 2003), and show only minor differences in glycosylation (Lee *et al.*, 2003) and mannose-6-phosphate receptor mediated cellular uptake (Sakuraba *et al.*, 2006). The only head-to-head comparison of agalsidase alfa and beta, both given at a dose of 0.2 mg/kg biweekly (Vedder *et al.*, 2007), revealed no clinically relevant difference between the enzymes. Therefore, for the purposes of this SR, agalsidase alfa and beta were considered similar pharmaceutical agents, and study results will be presented according to dose (0.2 mg/kg for agalsidase alfa and 1 mg/kg for agalsidase beta) rather than by agent.

Systematic review

The SR was carried out according to the guidelines of the Cochrane Collaboration (Higgins and Green, 2011). Two investigators searched the literature independently, identified articles of interest by scanning titles and abstracts when available, and, after a consensus meeting, compiled a single list of suitable articles, the full text of which was then read by two other investigators. The reference lists of selected articles were also assessed with a view to identification of other studies of interest that might not have been identified by the main search strategy. The methodological quality of the randomized clinical trials (RCTs) was assessed against a modified version of the Jadad scale (Woodroffe *et al.*, 2005), which evaluates each study with regard to randomization, blinding and subject withdrawals and dropouts. Studies with a score of 0 to 2 are considered low quality, 3 to 4 as of moderate and 5 to 6 as of high quality.

The Embase, PUBMED/MEDLINE and LILACS databases were searched for articles published until July 30, 2010 or March 30, 2011 respectively. According to predefined criteria, only double-blind RCTs comparing ERT to other therapies or placebo for treatment of FD were included in the review.

The search strategies were applied as follows in the PUBMED/MEDLINE: ((fabry disease OR fabry's disease) AND (agalsidase beta OR enzyme replacement therapy)) OR ((fabry disease OR fabry's disease) AND (agalsidase alfa OR enzyme replacement therapy)). In Embase the search strategy was: 'Fabry disease' / exp AND 'therapy' / exp; in the LILACS: Fabry [Words] and therapy [words]. "Human studies" and "reviews, meta-analysis, randomized controlled trials" were used as search limits in the PUBMED/MEDLINE and Embase respectively.

During the data extraction process, complementary information not available in the selected articles was also searched in clinical trial registries (<http://www.clinicaltrials.gov>, <http://www.controlled-trials.com>, and the Cochrane Register of Controlled Trials).

When measures of treatment effect were not directly expressed they were calculated from other available data, with WinPepi 10.7 software. Relative risk and difference between means were calculated for dichotomous and continuous data respectively, both with a 95% confidence interval (CI). When data were expressed with standard error (SE) measurements, the latter were converted to standard deviations (SD) by multiplying the SE by the square root of the number of patients n ($SD = SE \times \sqrt{n}$).

Meta-analysis

For continuous variables, within-study variances were estimated using a t distribution. Meta-analyses were carried out using both fixed and random effects models, represented by the Peto (Bradburn *et al.*, 2007) and DerSimonian-Laird (DerSimonian and Laird, 1986) methods respectively. The Peto method is a fixed effects model-based

approach that has demonstrably superior statistical properties under scenarios with rare events (Bradburn *et al.*, 2007). Statistical heterogeneity was tested using the Cochran Q test and quantified using the I^2 index. $p < 0.05$ was considered significant evidence of treatment effect. For the Q statistic, which is a test with relatively low power in most scenarios, a significance level of $p < 0.1$ was chosen. Statistical analyses were carried out in the Stata 11.1 package (Stata Corporation, College Station, TX, USA).

Results

A total of 547 studies were initially identified, but only 10 were double-blind, randomized, placebo-controlled trials of agalsidase alfa or beta. No studies comparing ERT to other therapies were found, and no additional information was obtained from the clinical trials registries.

Tables 1 and 2 provide an overview of the main characteristics of the studies included. Among these, five were classified as high quality (Moore *et al.*, 2001, 2002; Schiffmann *et al.*, 2001, 2006; Banikazemi *et al.*, 2007;). Four others received a score of 3 for failing to describe the method of randomization (Eng *et al.*, 2001; Thurberg *et al.*, 2002, 2004; Hughes *et al.*, 2008;). Only one RCT received a score of < 3 points (Bierer *et al.*, 2006).

Agalsidase at 0.2 mg/kg/infusion

This SR included five RCTs of agalsidase given at a dose of 0.2 mg/kg/infusion (Moore *et al.*, 2001, 2002; Schiffmann *et al.*, 2001, 2006; Hughes *et al.*, 2008;.) (Tables 1 and 2). The use of premedication was not reported by the authors.

A total of 41 subjects were included in these studies since the studies by Moore *et al.* (2001, 2002), Schiffmann *et al.* (2001, 2006) evaluated the same patient sample; they

were all males, older than 18 years of age, with neuropathic pain. One patient, allocated in the placebo group, failed to complete all proposed stages after randomization in the cohort evaluated. The study by Hughes *et al.* (2008) conducted on the same sex/age group included subjects with evidence of left ventricular hypertrophy. This study did not report any patients lost to follow-up, but one patient from each group (drug/placebo) was excluded in two subgroup analyses (one patient from the myocardial GL-3 analysis due to the development of an arrhythmia during his baseline cardiac biopsy procedure, and one placebo from MRI left ventricular mass analysis due to claustrophobia).

Agalsidase at 1 mg/kg/infusion

This SR also included five double-blind, randomized, placebo-controlled trials of agalsidase given at a dose of 1 mg/kg/infusion (Eng *et al.*, 2001; Thurberg *et al.*, 2002, 2004; Bierer *et al.*, 2006; Banikazemi *et al.*, 2007) (Tables 1 and 2). The patients were pretreated with acetaminophen or ibuprofen, and some with an antihistamine as well (Eng *et al.*, 2001; Banikazemi *et al.*, 2007).

In all, 146 patients took part in these studies, only 13 of whom were female. Three studies (Eng *et al.*, 2001; Thurberg *et al.*, 2002, 2004) evaluated the same patient sample; they had as criteria for inclusion: age > 16 years, serum creatinine < 2.2 mg/dL, and absence of kidney disease requiring renal replacement therapy (patients on dialysis or awaiting transplant). In one study (Banikazemi *et al.*, 2007), the inclusion criteria were: age > 16 years, evidence of mild to moderate renal failure, with serum creatinine ≥ 1.2 mg/dL and < 3 mg/dL or calculated creatinine clearance < 1.33 mL/s; patients were excluded in case of kidney disease requiring renal replacement therapy or history of transient ischemic attack or ischemic stroke, unstable an-

Table 1 - Overview of the double-blind, randomized, placebo-controlled trials of enzyme replacement therapy with agalsidase for Fabry disease.

Authors	n (M:F)	Intervention group dose of agalsidase (n)	Age in years mean (range)	Duration of the double-blind phase of study (months)	Quality score (modified Jadad scale) ^e
Eng <i>et al.</i> (2001) ^a	58 (56:2)	1 mg/kg (n = 29)	Intervention = 32.0 / Placebo = 28.4 (17-61)	5	5
Thurberg <i>et al.</i> (2002) ^a	58 (56:2)	1 mg/kg (n = 29)	Intervention = 32.0 / Placebo = 28.4 (17-61)	5	5
Thurberg <i>et al.</i> (2004) ^a	58 (56:2)	1 mg/kg (n = 29)	Intervention = 32.0 / Placebo = 28.4 (17-61)	5	5
Schiffmann <i>et al.</i> (2001) ^b	26 (26:0)	0.2 mg/kg (n = 14)	Intervention = 34.0 / Placebo = 34.4 ^c	6	3
Moore <i>et al.</i> (2001) ^b	26 (26:0)	0.2 mg/kg (n = 14)	Intervention = 34.0 / Placebo = 34.4 ^c	6	3
Moore <i>et al.</i> (2002) ^b	26 (26:0)	0.2 mg/kg (n = 14)	Intervention = 34.0 / Placebo = 34.4 ^c	6	3
Schiffmann <i>et al.</i> (2006) ^b	26 (26:0)	0.2 mg/kg (n = 14)	Intervention = 34.0 / Placebo = 34.4 ^c	6	3
Bierer <i>et al.</i> (2006)	6 (5:1)	1 mg/kg (n = 4)	Males = 35 / Females = 42 (20-47)	18	1
Banikazemi <i>et al.</i> (2007) ^d	82 (72:10)	1 mg/kg (n = 51)	Intervention = 46.9 / Placebo = 44.3 ^c	35	3
Hughes <i>et al.</i> (2008)	15 (15:0)	0.2 mg/kg (n = 7)	Intervention = 37.1 / Placebo = 37.3 (23-50)	6	

^aThese studies included the same patient sample. ^bThese studies included the same patient sample. ^cRange not reported. ^dMulticentric study. ^eThe methodological quality was assessed against a modified version of the Jadad scale (Woodroffe *et al.*, 2005). Studies with a score of 0 to 2 are considered low quality, 3 to 4 are considered moderate quality and 5 to 6 are considered high quality.

Table 2 - Summary of the efficacy results of enzyme replacement therapy with agalsidase for Fabry disease

Outcomes	Eng <i>et al.</i> (2001), Thurberg <i>et al.</i> (2002), Thurberg <i>et al.</i> (2004)	Schiffmann <i>et al.</i> (2001), Moore <i>et al.</i> (2001), Moore <i>et al.</i> (2002), Schiffmann <i>et al.</i> (2006)	Bierer <i>et al.</i> (2006)	Banikazemi <i>et al.</i> (2007)	Hughes <i>et al.</i> (2008)
Blood pressure	-	-	NS	-	NS
Cardiovascular performance during exercise	-	-	NS	-	-
Cerebral blood flow (resting)	-	↓	-	-	-
Cerebral blood flow after visual stimulation	-	↓	-	-	-
Death	-	-	-	NS	-
ECG findings	NS	↓ QRS	-	-	NS
Echocardiographic findings	NS	-	-	-	NS
GL-3 clearance in plasma	↓	↓	-	-	↓
GL-3 clearance in urinary sediment	↓	NS	-	-	↓
GL-3 content in heart	↓	-	-	-	NS
GL-3 content in kidney	↓	NS	-	-	-
GL-3 content in skin	↓	-	-	-	-
eGFR	NS	NS	-	NS	NS
LVM (MRI)	-	-	-	-	↓
Intraepidermal nerve fiber density and thermal threshold	-	NS	-	-	-
Neuropathic pain	NS*	↓**	-	-	-
Pain-related QoL	-	↑	-	-	-
QoL (SF-36 questionnaire)	NS	-	-	-	-
Proteinuria	-	NS	-	NS	-
Time to first clinical event #	-	-	-	NS	-

↑ = improvement; ↓ = decrease; - = not evaluated; # Clinical events: renal, cardiac, cerebrovascular or death; * Pain was assessed by the McGill Questionnaire; ** Pain was assessed by the Brief Pain Inventory; eGFR, estimated glomerular filtration rate; GL-3, globotriaosylceramide; NS, not significant; QoL, quality of life; LVM, left ventricular mass; MRI = magnetic resonance imaging.

gina or acute myocardial infarction less than 3 months prior to enrollment. The study by Bierer *et al.* (2006) mentioned no criteria for inclusion other than a diagnosis of FD. Only one study had withdrawals or dropouts (Banikazemi *et al.*, 2007), where three patients left the trial to receive commercial therapy (two in the agalsidase and one in the placebo group), another three patients in the agalsidase group withdrew due to suspected or confirmed IgE-mediated reactions, two (one in each group) left due to unknown reasons (“voluntary”, after the occurrence of a clinically relevant event), and three died (two patients, from the agalsidase group, died of pulmonary emboli and sudden cardiac arrest, respectively; and one patient, from the placebo group, died of cardiac arrest one week after a stroke).

Efficacy and safety assessment

The data on efficacy assessment of ERT for FD is summarized in Table 2. This table describes the outcomes/endpoints evaluated in each trial.

Regarding safety, only one study evaluated adverse effects of ERT when given at a dose of 0.2 mg/kg/infusion (Schiffmann *et al.*, 2001). Mild infusion-related events

(most commonly rigors) were not found in the placebo group, but occurred in eight of 14 patients given agalsidase. Premedication with antihistamines and low-dose corticosteroids reduced these reactions, as did slower infusion rates during subsequent treatment sessions.

Two studies described the adverse effects of the administration of agalsidase at a dose of 1 mg/kg/infusion (Eng *et al.*, 2001; Banikazemi *et al.*, 2007). Fever and rigors were more common in the ERT group than with placebo (Eng *et al.*, 2001; Banikazemi *et al.*, 2007). Without statistical differences between the placebo and agalsidase group were reports on hypertension (Eng *et al.*, 2001; Banikazemi *et al.*, 2007;), headache (Eng *et al.*, 2001), chills (Eng *et al.*, 2001), FD-related pain (Eng *et al.*, 2001), vomiting (Banikazemi *et al.*, 2007), perceived temperature changes (Banikazemi *et al.*, 2007), chest pain (Banikazemi *et al.*, 2007) and fatigue (Banikazemi *et al.*, 2007).

Severe treatment-related adverse effects were described in three out of 51 patients given agalsidase at a dose of 1 mg/kg/infusion, but none were so in the placebo group (Banikazemi *et al.*, 2007). One patient developed severe hypotension, followed by detectable anti-agalsidase IgE

antibodies in serum, one developed urticaria and glottis edema, and the third had urticaria, chills and fever (Banikazemi *et al.*, 2007).

Variables selected for meta-analysis

Data extracted from the SR were pooled for meta-analysis. Some studies shared the same endpoints, but few reported absolute post-treatment measurements, measurement units, or the method used for deriving results. For instance, renal function outcomes (measured by creatinine or inulin clearance) were assessed in four studies (Eng *et al.*, 2001; Schiffmann *et al.*, 2001; Banikazemi *et al.*, 2007; Hughes *et al.*, 2008), but only one provided numerical values (Schiffmann *et al.*, 2001), the other studies only reported it descriptively (function “remained stable”). Another variable affected by this issue was plasma, urinary and tissue clearance of GL-3, for which outcomes were alternatively presented as absolute values, relative percentage change, or change measured against a standardized score, making it impossible to pool results for statistical analysis. Therefore, only the following variables could be included in the meta-analysis: duration of QRS complex (the portion of the electrocardiogram comprising the Q, R and S waves, together representing ventricular depolarization), and the incidence of fever, rigors, hypertension and development of IgG antibodies to agalsidase as adverse events.

Regarding QRS duration, as sample size was small and one study (Hughes *et al.*, 2008) did not report SDs, we calculated the summary effect for each potential alternative SD and found that, regardless of the estimated SD, results were not statistically significant (Figure 1).

Few adverse events were reported in more than one study: hypertension, fever, rigors (Eng *et al.*, 2001; Banikazemi *et al.*, 2007) and development of IgG antibodies to agalsidase (Eng *et al.*, 2001; Schiffmann *et al.*, 2001). Pa-

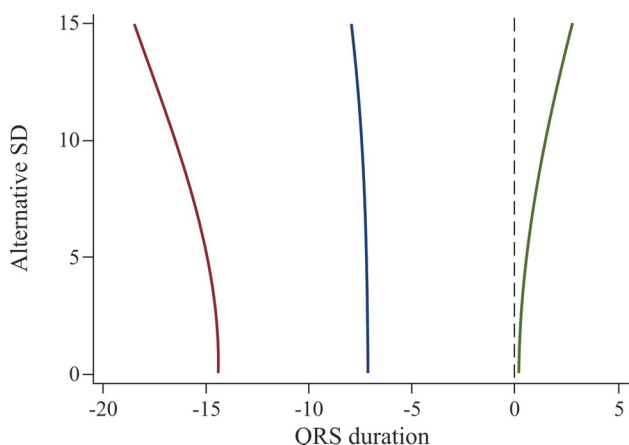


Figure 1 - Summary results under alternative values for the standard deviation for the study by Hughes *et al.* (2008). The blue line depicts the summary, unstandardized mean difference, whereas red and green lines denote lower and upper 95% confidence limits, respectively. Dashed line represents the null effect. Results are based on a random effects model.

tients given ERT were at increased odds for fever (OR, 5.2; 95%CI, 2.1 to 12.8) (Figure 2) and rigors (OR, 6.68; 95%CI, 3.04 to 14.64) when compared to placebo. The risk of hypertension did not reach statistical significance (OR, 3.01; 95%CI, 0.9 to 10.1). The Cochran Q test and the I^2 statistic showed low statistical heterogeneity between these two studies (for fever Q, 0.01; I^2 , 0%, for rigors Q, 0.11; I^2 , 0% and for hypertension Q, 0.49; I^2 , 0%). Development of IgG antibodies occurred in 3/14 patients treated with agalsidase at a dose of 0.2 mg/kg/infusion in the study by Schiffmann *et al.* (2001) and in 3/7 patients in the study by Hughes *et al.* (2008). In patients receiving 1 mg/kg/infusion, the development of antibodies was described only by Eng *et al.* (2001), and included the open-label phase, with 51/58 patients seroconverted.

It was possible to perform the meta-analysis with the patients evaluated in the double-blind phase by Schiffmann *et al.* (2001) and Hughes *et al.* (2008). As expected, there were increased odds for development of IgG to agalsidase (OR, 9.96; 95% CI, 1.81 to 54.80), without heterogeneity between these two studies (Q, 0.05; I^2 0%). However, this immune reaction did not appear to interfere with the efficacy or safety of treatment and did not correlate with the incidence of infusion-related adverse events (Eng *et al.*, 2001; Schiffmann *et al.* 2001).

Discussion

This SR/meta-analysis, designed as a critical assessment of the available literature on ERT for FD, was intended to establish the efficacy and safety of this intervention. Our results are in agreement with previously published SRs on this issue (Connock *et al.*, 2006; Lidove *et al.*, 2007; Schaefer *et al.*, 2009; El Dib and Pastores, 2010), although the search strategies and the inclusion criteria were different. Besides that, this is the first paper to present its results in form of a meta-analysis.

Unfortunately, the available RCTs exhibited substantial heterogeneity in endpoints, with the latter ranging from

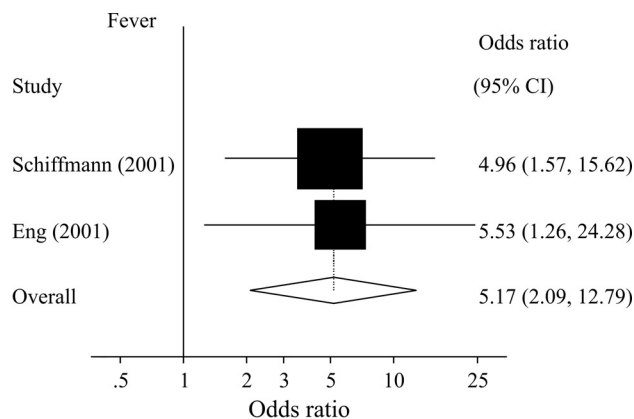


Figure 2 - Meta-analysis: increased odds of fever as an adverse event of enzyme replacement therapy (ERT) as compared to placebo.

surrogate endpoints such as tissue deposition of GL-3, to major clinical events such as stroke and death. This heterogeneity posed a major challenge to the comparisons and prevented the collection of sufficient data for a meta-analysis of all relevant variables. Furthermore, patients were enrolled at different phases of the disease, which may have influenced their response to ERT. Another limitation was the very restricted recruitment of female patients and no enrollment of asymptomatic patients or patients under the age of 16, thus making it difficult to extend to these populations any conclusions as to the efficacy and safety of ERT.

Because FD is a rare disease, the number of patients available for clinical trials is rather limited, and this restricts the statistical power of any assessment of relevant endpoints. The guiding principle behind treatment of diseases of exceedingly low incidence often referred to as “orphan diseases,” runs into bioethical issues involving questions such as equity, scarcity of resources, and the legal concept of the “proviso of possibility” (*Vorbehalt des Möglichen*). This broad set of challenges means that orphan diseases and the agents meant to treat them - known as orphan drugs - would require specific ways of assessing efficacy and safety. In the case of FD, the methodological limitation of available RCTs creates difficulties in the decision making process not only for drug approval but also for reimbursement. In the author’s opinion, the decision about reimbursement for agalsidase should also take into account the fact that there is no other specific treatment for these diseases, as well as the public opinion on this issue.

As of the time of writing, only one published study had assessed clinical endpoints. In this single trial, ERT was not found to reduce mortality or slow progression of kidney, cerebrovascular or heart disease in patients with mild-to-moderate renal impairment, and was not able to reduce the individual or combined incidence of renal, cerebrovascular or cardiovascular events as compared to placebo (Banikazemi *et al.*, 2007). Subgroup analyses showed a greater effect size for treatment in patients with mild kidney disease, which suggests that ERT may be most beneficial in patients with early-stage deterioration of renal function (Banikazemi *et al.*, 2007).

FD is believed to induce neuropathy secondary to GL-3 storage. These changes are considered the main cause of chronic pain in FD patients and are also associated with limb paresthesias, reduced sensitivity to temperature and significant reductions in intraepidermal nerve fiber density. One study tested the hypothesis that intraepidermal nerve fiber density and thermal threshold could be useful markers of central nervous system response to ERT. However, the study showed no significant differences between ERT and placebo for the studied parameters, and there is no evidence that ERT enables nerve regeneration in the epidermis (Schiffmann *et al.*, 2006). Neuropathic pain is usually described as one of the most frequent and debilitating symp-

oms of FD, and is rarely amenable to pharmacological treatment. One RCT found improvement in neuropathic pain as measured by the Brief Pain Inventory (Schiffmann *et al.*, 2001). But there are some confounding factors in this study, as methods are unclear as to how neuropathic pain medication was withdrawn prior to pain measurement, and that patients allocated to the placebo group had higher pain scores at baseline. Another study used the McGill Pain Questionnaire and found substantial improvement in ERT and placebo groups alike (Eng *et al.*, 2001). Therefore, further studies of pain intensity, measured with the same instruments, are required before more robust conclusions can be drawn.

ERT was not associated with improved renal function (Schiffmann *et al.*, 2001; Banikazemi *et al.*, 2007) or proteinuria (Banikazemi *et al.*, 2007), changes in the cytoarchitecture of the kidney (Schiffmann *et al.*, 2001), cardiopulmonary stress test performance (Bierer *et al.*, 2006), or diastolic blood pressure (Bierer *et al.*, 2006). A reduction in left ventricular mass was found, but was only detectable on MRI, not on echocardiography (Hughes *et al.*, 2008). All other cardiac-related parameters remained unchanged (Eng *et al.*, 2001; Schiffmann *et al.*, 2001; Hughes *et al.*, 2008). Two studies carried out in the same patient cohort (Moore *et al.*, 2001, 2002) assessed changes in cerebral blood flow at rest and after visual stimuli or acetazolamide challenge and found this parameter to be significantly improved in patients receiving ERT.

Most studies reported reductions in GL-3 buildup in heart, kidney and skin tissue at higher doses and in plasma at both doses (Eng *et al.*, 2001; Schiffmann *et al.*, 2001; Hughes *et al.*, 2008). However, studies that assessed different doses used different methods for measuring GL-3, which makes it difficult to draw any conclusions as to the existence of a dose-dependent effect of agalsidase. Furthermore, although GL-3 represents the biochemical manifestation of FD in body tissues, the reduction in GL-3 buildup is of uncertain clinical significance.

Only one RCT evaluated quality of life (as measured by the SF-36 instrument). However, results were described qualitatively and reported as “improvement” in both groups, and no description of questionnaire administration methods was provided (Eng *et al.*, 2001).

Overall, ERT was well tolerated. Mild and severe adverse effects were rare, and any that did occur were easily controlled with premedication and slower infusion rates (Eng *et al.*, 2001; Schiffmann *et al.*, 2001; Banikazemi *et al.*, 2007). Although not all studies approached the issue of adverse events or development of IgG antibodies, adverse events appear to be more common in patients receiving higher doses of agalsidase. On the other hand, the lower-dose study may simply have been underpowered to assess these effects (Eng *et al.*, 2001), as the higher-dose study enrolled a larger patient sample and featured longer follow-up (Schiffmann *et al.*, 2001; Banikazemi *et al.*, 2007).

Very few variables could be included in the meta-analysis, due to little overlap of endpoints and results in the available studies. According to our data, ERT was not significantly associated with changes in QRS duration or development of hypertension as a treatment-emergent adverse effect. Not surprisingly, the meta-analysis showed that patients given ERT are at a higher risk of fever, rigors and development of IgG antibodies to agalsidase during infusion when compared to the placebo group.

In conclusion, although the RCTs carried out thus far have failed to elucidate all questions concerning the efficacy of ERT, this therapy appears to provide some benefit in FD. The current evidence suggests that ERT with agalsidase reduces the severity of neuropathic pain, improves pain-related quality of life, brings about minor changes in left ventricular mass, and reduces plasma, urine and tissue levels of GL-3. The available evidence also suggests that ERT is able to slow down the progression of FD. However, further studies with greater methodological quality, larger sample sizes and better assessment of clinical endpoints are required before firm conclusions can be drawn.

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