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A randomised, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of three dosing schedules of agalsidase alfa enzyme replacement therapy for Fabry disease

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ABSTRACT

Anecdotal reports suggest that the currently approved dosing interval of agalsidase alfa (0.2 mg/kg/2 weeks) for Fabry disease treatment is too long. This randomised, double-blind, placebo-controlled, crossover study investigated three altered dosing intervals. 18 Fabry patients received three agalsidase alfa dosing schedules, each for four weeks (A: 0.2 mg/kg * 2 weeks, B: 0.1 mg/kg/week, C: 0.2 mg/kg/week). Health state, pain levels, sweat volume and latency and plasma and urinary globotriaosylceramide levels were recorded throughout the study. No significant differences were found among the schedules for the primary efficacy outcome of self-assessed health state, or for pain scores. A trend toward increased sweat volume on QSART testing, and reduced urine globotriaosylceramide concentration were seen with treatment schedule C. Agalsidase alfa was safe and well tolerated with all schedules. In conclusion, the primary analyses did not find weekly infusions of agalsidase alfa to be statistically better than the approved dosing schedule however the data indicates that further studies with more patients over a longer period are required to more accurately determine the optimum dose and schedule.

1. Introduction

Fabry disease is an X-linked glycosphingolipid storage disorder caused by deficient activity of the lysosomal enzyme α-galactosidase A [1]. Globotriaosylceramide (GB3), the glycosphingolipid substrate for this enzyme, progressively accumulates within cells and tissues of affected patients [1–4]. The estimated prevalence of Fabry disease is approximately 1 in every 40,000 to 60,000 males [1,5]; however a recent newborn screening study suggests that it may be more common [6]. Symptoms during childhood or adolescence include chronic severe pain in the extremities, cutaneous lesions known as angiokeratomas, asymptomatic corneal dystrophy, fatigue, heat and cold intolerance, decreased sweating, fever, and gastrointestinal difficulties. Vital organs are affected with increasing age, and death in untreated males usually occurs during the fourth or fifth decade of life from complications of renal failure, cardiac or cerebrovascular involvement. Two preparations of enzyme replacement therapy (ERT) have EU marketing approval. Agalsidase alfa (Replagal®, Shire HGT, Basingstoke, UK), is manufactured using a gene activation technology within a human cell line and the licenced dose is 0.2 mg/kg * 2 weeks. Agalsidase beta (Fabrazyme®, Genzyme Corporation, Cambridge, MA, USA), is manufactured using a recombinant technology within Chinese hamster ovary cells and the licenced dose is 1.0 mg/kg * 2 weeks. Although agalsidase alfa and beta are generally considered to have similar clinical efficacy [7], the only comparative study so far reported suggested that rates of decline of GL3 with ERT were higher with agalsidase beta [8] and that this difference was principally due to the larger dose. A comparative study has also been initiated in Canada and the data presented thus far suggest that up to 3 years of therapy there is little difference between the clinical outcomes for the preparations [9]. However recently agalsidase beta has had limited availability due to production difficulties and many patients are currently being treated with lower doses of agalsidase beta or have transitioned to agalsidase alfa [10].

Beneficial effects of agalsidase alfa are well documented and include reduction in pain, stabilisation of cardiomyopathy, and stabilisation in renal function [11–16].

Personal experience suggest that some patients describe recurrence of pain and a reduced sense of well-being a few (1–3) days before the next infusion, which raise the question as to whether the dosing interval is too long or the dose is too small (or both). This study aimed to evaluate if a reduced interval, one week instead of two weeks, but with maintained dose exposure was beneficial. It also tested whether the currently approved dose, 0.2 mg/kg given weekly instead of every

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other week, was perceived as better or associated with better treatment outcomes.

2. Patients and methods

The study was approved by the Royal Free Hospital and Addenbrookes Hospital local research ethics committees before any patients were enrolled at the centres, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent before entering the study.

2.1. Study population

Eligible study patients with Fabry disease (confirmed α-galactosidase A deficiency and mutation of the α-galactosidase A gene), were at least 18 years of age, and had been treated with agalsidase alfa (0.2 mg/kg IV every second week) for a minimum of three months to minimise the possibility that differences seen between the schedules were related to ongoing positive trajectory of response at the beginning of therapy.

2.2. Study design

This was a randomised, double-blind, placebo-controlled, three-period, crossover study at two hospitals (Royal Free Hospital, London and Addenbrookes Hospital, Cambridge).

Patients received each of the following dosing schedules of agalsidase alfa for four weeks, one after the other, without a washout period (however in the primary analyses week 1 data was omitted to reduce any carry over effects):

- Schedule A (the currently approved treatment): 0.2 mg/kg agalsidase alfa administered every other week as a 40 minute IV infusion. To maintain consistency of weekly infusions in each schedule and therefore the blind, placebo was administered in the alternate week to agalsidase alfa in schedule A.
- Schedule B: 0.1 mg/kg agalsidase alfa administered once a week as a 40 minute IV infusion.
- Schedule C: 0.2 mg/kg agalsidase alfa administered once a week as a 40 minute IV infusion.

The order of treatment was randomised and as there were three dosing schedules there were six possible treatment sequences.

The study comprised 14 weekly visits: a patient enrolment visit to obtain informed consent, four evaluation and infusion visits for each of the three dosing schedules, and a final evaluation. Visits 1, 5, 9, and 13 were in hospital; visits 2–4, 6–8, and 10–12 could be in hospital or in the patients' home. At each visit, pieces of information on health state, pain, and analgesic use were collected and samples for plasma and urine GB3 were taken; patients completed a daily diary sheet, recording state of health, pain, and analgesic use.

The study was double-blind and the method for preparing and administering the infusion was the same for all infusions. The solution or normal saline placebo (made up to 100 mL in 0.9% sodium chloride solution) was infused intravenously over 40 min. Blinding at home was facilitated using GCP trained home care nurses of a home care provider with clinical trials pharmacy for reconstitution and distribution of the scheduled drugs.

2.3. Outcome measures

The primary outcome variable was self-assessed health state, measured by the visual analogue scale ('thermometer') item of the European quality of life questionnaire (the EQ-5D: Euroqol Group 1990).

Secondary outcome variables were: pain, assessed as the average composite pain severity dimension of the brief pain inventory (BPI) short form, a standard pain assessment tool [17]; each individual item of the BPI short form; health state, calculated from items 1–5 of the EQ-5D questionnaire (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); each individual item of the EQ-5D questionnaire [18]; results of quantitative sudomotor axon reflex test (QSART) testing [19] which tests for abnormalities of resting and evoked sweat production; the Mainz severity score index (MSSI), a scoring system to measure the severity of Fabry disease [20]; plasma and urine GB3 determined by methods previously described [21]; and analgesic use. All questionnaire-based data were completed by the patient on a daily diary sheet (health state, pain and analgesic use) and using weekly investigator administered questionnaires (BPI and EQ-5D).

Safety assessments included physical examination, 12-lead electrocardiogram (ECG), clinical laboratory testing, and vital sign measurements. Adverse events (AEs) and concomitant medications were recorded throughout the study. Anti-agalsidase alfa antibodies were assayed at baseline using an Enzyme-linked Immunosorbent Assay (ELISA) as previously described [22].

2.4. Statistical methods

Statistical analysis was performed by independent statistician (AJ) Dianthus Medical. No formal sample size calculation was performed. The planned number of patients (18) was based on practical considerations, taking into account the potential study population.

The intent to treat (ITT) population (all randomised patients with at least one post baseline efficacy or quality of life assessment) was used for the primary analyses. The primary analysis (self-assessed health state) was taken as an average of all measurements recorded in weeks 2–4 of each treatment period, i.e., ignoring week 1 data to reduce carryover effects. Potential differences among the three dosing schedules were assessed with an analysis of variance (ANOVA) with subject as a random effect. Statistical significance was accepted at the 5% level. Confirmatory analyses of the primary outcome variable were done in the same way as above but not ignoring week 1. A further analysis was done using each individual daily measure. All the above analyses were repeated on the per protocol (PP) population (all patients who completed all three treatment periods without any major protocol violations). Similar analyses were done for pain, QSART results, and plasma and urine GB3.

All other variables were presented descriptively. All data from all study patients were included in the safety population.

3. Results

3.1. Patients studied

20 patients entered the study, 19 received at least one dose of study medication and therefore constitute the safety population. One patient was screened but did not proceed to study medication due to travel difficulties. 18 completed all three dosing schedules and constitute the ITT population. The ITT population consisted of 12 adult men (age 44.25 +/− 11 years) and 6, women (age 52.3 +/− 10.5 years); 9 and 10 males and 5 and 4 females had cardiac (left ventricular hypertrophy or conduction disorder) or renal disease (proteinuria or reduced GFR) at baseline. The mean severity score (Mainz severity score index) of the males was 36 +/− 9 and the females 28.5 +/− 8.5. All patients had received agalsidase alfa up to enrolment in the study. No patient had received agalsidase beta. Four patients had documented antibodies to agalsidase alfa at enrolment.

The disposition of patients throughout the study is shown in Fig. 1. There were two patients with major protocol violations: they received self-administered non-protocol agalsidase alfa immediately prior to visit 13. Most patients had a family history of Fabry disease