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Investigators and Study Center(s)

This was a single-center study conducted in the United States (US).

Studied Period

First Patient Enrolled: 21 April 1998
Last Patient Completed: 16 October 1998

Phase of Development

Phase 1/2

Objectives

- determine the pharmacokinetics of recombinant human α-galactosidase (r-hα GAL) following intravenous infusion of a single dose of r-hα GAL at 0.3, 1.0, and 3.0 mg/kg in male patients with Fabry disease,
- determine the pharmacokinetics of r-hα GAL following intravenous infusion of a single dose of r-hα GAL after 4 previous doses of r-hα GAL with doses administered at intervals of either 14 days (0.3, 1.0, and 3.0 mg/kg) or 48 hours (1.0 and 3.0 mg/kg),
- measure α-galactosidase (α GAL) and globotriaosylceramide (GL-3) concentration in plasma, urine sediment (GL-3 only), liver, and skin in male patients with Fabry disease after 5 intravenous doses of r-hα GAL with doses administered at intervals of either 14 days (0.3, 1.0, and 3.0 mg/kg) or 48 hours (1.0 and 3.0 mg/kg), and evaluate the safety of 5 intravenous doses of r-hα GAL, with doses administered at intervals of either 14 days (0.3, 1.0, and 3.0 mg/kg) or 48 hours (1.0 and 3.0 mg/kg) in male patients with Fabry disease.

Methodology

This was a single-center, multi-dose, non-randomized, open-label study.

Number of Patients (Planned and Analyzed)

The number of patients enrolled, treated, and analyzed was 15.

Diagnosis and Main Criteria for Inclusion

Patients were included in this study if they were male, aged 16 years or more with a current diagnosis of Fabry disease as evidenced by a plasma α GAL activity of < 1.5 nmol/hr/mL and a plasma GL-3 level ≥ 5.0 ng/µl.

Test Product, Dose, and Mode of Administration

Five intravenous doses of r-hα GAL with doses administered at intervals of either 14 days (0.3, 1.0, and 3.0 mg/kg) or 48 hours (1.0 and 3.0 mg/kg).

Duration of Treatment
5 intravenous doses

**Reference Therapy, Dose and Mode of Administration**

None

**Criteria for Evaluation**

**Efficacy**

Pain was assessed according to the McGill Pain Questionnaire and a daily pain diary. Quality of life (QOL) assessments included the Profile of Mood States; the Beck Depression Scale; the Impact of Events Scale; the Short Form (SF-36) QOL Health Survey; and a list of additional QOL questions specific to Fabry disease.

Clinical evaluations for all patients included: echocardiography (ECHOs) (2D with contrast marker); magnetic resonance imaging (MRI) of heart and abdomen; thermal discrimination test; signal-averaged electrocardiogram (ECG); ophthalmologic examination and sympathetic skin response (SSR, patients in the every 48-hour treatment groups only).

Pharmacokinetic (PK) parameters were determined from serial blood draws obtained during the first and last infusions. Plasma r-hα GAL concentrations in these samples were measured using an enzyme activity assay.

Pharmacodynamic (PD) evaluation included monitoring the concentration of GL-3 in plasma and urinary sediment, as well as histologic scoring of GL-3 content in biopsied tissue. In addition, all tissue samples were assayed for GL-3 concentration. Plasma GL-3 was measured periodically throughout the study and at study completion (21 to 28 days following the final study drug infusion). Temp sample collections included 24-hour urine collection and pre- and post-treatment biopsy samples of liver, skin, endomyocardial (optional), kidney (optional), and duodenum/jejunum (optional) cells. All biopsies were split into several aliquots to allow for biochemical analysis of GL-3 content and evaluation of GL-3 distribution by light microscopy (LM) and transmission electron microscopy (TEM).

**Safety**

Safety evaluations consisted of a physical examination including vital signs (heart rate, blood pressure, respiration rate, body temperature, and pre- and post-study body weight); standard 12-lead ECG; monitoring of adverse events (AEs); and laboratory analysis including serum chemistry, hematology, electrolytes, lipids, drugs of abuse, urinalysis, and immunoglobulin G (IgG) antibody to r-hα GAL. Patients were monitored for any incidents suggestive of a hypersensitivity reaction.

**Statistical Methods**

**Efficacy**

Tabular summaries of the data collected during the study were presented in order to provide an overview of the PK, PD, efficacy, and safety findings. Plasma GL-3 concentration over time and skin GL-3 concentrations were used as the primary PD variables for selecting dose and dosage frequency for future studies. Descriptive statistics (range, mean, standard deviation, and coefficient of variation) for the plasma and skin GL-3 concentrations were presented. Graphs were presented of PD parameters that displayed variability across time. PK parameters were computed from the plasma activity of α GAL of each patient. Plasma α GAL activities below the quantifiable assay limits (LOQ) were considered as zero when computing PK parameters.

The SF-36 Health Scoring System was used for analysis of the original SF-36 questionnaire. Figures and summary statistics were presented that showed the mean score of the SF-36 and the change from Baseline by treatment group. Since there was no control group, the only statistical analysis that was performed was a Wilcoxon Signed-Rank test on change from baseline for pain and QOL parameters. Descriptive statistics of the other clinical and QOL Baseline and the post-treatment assessments were also presented.

**Safety**

All clinical safety data were summarized for all patients who received any amount of study drug. Continuous variables were summarized through median, mean, standard deviation, minimum and maximum values. Categorical variables were summarized through by number and percentage of patients in each category.
AEs were coded using the WHO-ART dictionary. The number and proportion of patients reporting AEs, grouped by body system and preferred term, were summarized for the respective dose conditions. Patients experiencing serious adverse events (SAEs) were listed separately.

Summary – Conclusions

Efficacy

Patients were infused with r-hα GAL 0.3 mg/kg every 14 days, 1.0 mg/kg every 14 days, 3.0 mg/kg every 14 days, 1.0 mg/kg every 48 hours, or 3.0 mg/kg every 48 hours for a total of 5 infusions.

r-hα GAL demonstrated dose-dependent (non-linear) pharmacokinetics and the PK parameters were consistent with r-hα GAL being cleared from circulation via both saturable and non-saturable (concentration independent) pathways. AUC values were disproportionate to dose, increasing from approximately 80 to 500 to 4000 µg min/mL as the dose was increased from 0.3 to 1.0 to 3.0 mg/kg. The mean volume of distribution at steady state (Vss) ranged between 80 and 330 mL/kg (1 to 4 times blood volume). Clearance decreased from 4 mL/min/kg to approximately 1 mL/min/kg with increasing dose. The mean PK parameters did not change between the first and fifth infusion when administered every 14 days or every 48 hours despite the development of antibody titers to r-hα GAL, suggesting that seroconversion does not affect the pharmacokinetics of the enzyme.

The small number of patients in each treatment group (3 patients per group) allows observation of general trends following r-hα GAL therapy. Histological analysis revealed a reduction in the vascular endothelial accumulations of GL-3 in all dose regimens tested in organs of clinical importance. Although enzyme was taken up by the liver and resulted in clearance of GL-3 from that organ, clearance was also demonstrated from the endothelial vasculature of the skin, heart, and kidney.

In the liver the 2 principal reservoirs of glycolipid, the endothelial cells of the sinusoids and the Kupffer cells, were almost totally cleared of glycolipid. This was confirmed by whole tissue Enzyme Linked Immunosorbert Assay (ELISA), which demonstrated a greater than 84% mean clearance of GL-3 from this organ.

In the skin, clearance of glycolipid from components other than the superficial vasculature was more variable, as reflected in the lesser degree of overall clearance noted by whole tissue ELISA. Some of this variation was evident in the histologic scoring of other structures. It may also represent greater variability in extraction of GL-3, due to the epidermal layer and the collagen matrix of the dermis.

In comparison to other organs, accumulation in the heart was substantial. Tissue burdens of GL-3 were on an order of magnitude greater than that in the kidney, the second most burdened tissue. From the histologic examination, almost all of this GL-3 content was deposited in the cardiomyocytes. In the heart, GL-3 clearance occurred predominantly in the endothelium and to a much lesser extent in the cardiomyocytes. Histomorphometry of cardiomyocytes revealed that approximately 15% of GL-3 stores (as percent volume of the cell) were cleared after 5 doses of r-hα GAL, suggesting that a longer duration of treatment may be associated with a significant decrease in the cardiomyocyte GL-3 burden.

An important area of accumulation was the vascular endothelium of the kidney. Paired pre- and post- kidney samples were obtained from 5 patients – 2 in the 14 day 3mg/kg group, 2 in the 48 hour 1 mg/kg group, and 1 in the 48 hour 3 mg/kg group. All 3 vascular beds evaluated in the kidney showed the same response to treatment, a prominent reduction in GL-3 content of the vascular endothelium. From the ELISA assay results (82% decrease in total GL-3 for 4 of 5 patients with pre- and post-treatment samples), and the fact that the vascular component was small and the podocyte inclusions were unchanged, it is clear that almost all of the reduction in glycolipid was accounted for by a significant effect on the tubules. Taken together with the reduction in vascular endothelial content and the decrease in urinary GL-3 content, these results point to a considerable potential benefit for the kidney.

As expected, infusion of r-hα GAL rapidly cleared GL-3 from the plasma in a dose-dependent manner. In the every 14-day schedule both the 1.0 and 3.0 mg/kg dosing groups showed GL-3 reduced to minimal levels by the second infusion and maintained for the duration of the study period. At the 0.3 mg/kg dose, circulating GL-3 did not reach minimal levels until the third or fourth infusion. GL-3 elimination in both groups receiving treatment every 48 hours was inconsistent, but minimal levels were generally reached by the fourth infusion.

Abnormal sympathetic skin response in Fabry disease is due to abnormal sympathetic fiber response and deficient sweat gland function. Restoration of sympathetic response in Fabry disease will require a longer duration of therapy. Thermal discrimination and sympathetic skin response did not change consistently or predictably in the same direction in individual patients or among patients. The variability of glomerular filtration rate (GFR) data was high. Some of the errors inherent in timed urine collections, e.g. longer urine collections than reported, appeared as supraphysiologic GFR. In addition,
Creatinine clearance and, by implication, GFR were minimally impaired or within the normal range at Baseline in this patient population because patients with compromised or impaired renal function were excluded from the study. Cardiac function appeared marginally affected by 5 treatments of enzyme replacement therapy. In general, physiologic changes were inconsistent and difficult to interpret in this short-term study.

Clearance of GL-3 was associated with a statistically significant trend towards reduced pain and improved quality of life in these patients. Interpretation of these measures is limited by the absence of a control arm. Nevertheless, the trend is encouraging and suggests a potential effect of r ha GAL therapy on a disease manifestation that accounts for much of the morbidity in young patients with Fabry disease.

**Safety Results**

No deaths occurred during this study. Two patients experienced SAEs; 1 patient (1.0 mg/kg every 14 days) experienced symptoms of abdominal discomfort, nausea, vomiting, diaphoresis, urticaria, edema, pruritus, and decreased heart rate which the investigator attributed to study drug administration. A second patient (3.0 mg/kg every 48 hours), who had anticoagulation therapy discontinued prior to study participation and developed pulmonary emboli; the investigator could not rule out a relationship between study drug and this event. Both events resolved by the completion of the study.

The majority of adverse events were mild or moderate in severity. The most commonly reported adverse event was mild to moderate transient elevation in blood pressure (WHO-ART preferred term: hypertension). Overall, increases in blood pressure were not substantially high or sustained. In addition, patients with a history of high blood pressure entering this trial were able to safely receive infusions of r-ha GAL.

Treatment with r-ha GAL was not precluded by the development of IgG antibodies. Eight of 15 patients developed IgG antibodies specific to r-ha GAL. Four of these 8 patients also developed symptoms suggestive of a possible hypersensitivity-type reaction. Two of these 4 did not complete the final infusion of r-ha GAL. Of the 4 patients who developed symptoms suggestive of a hypersensitivity-type reaction, 3 were assigned to the 3.0 mg/kg every 14 days dose group and 1 was assigned to the 1.0 mg/kg every 14 days dose group.

Throughout the study laboratory parameters did not change significantly from Baseline. Serum chemistries and hematology measurements remained stable. Similarly, ECG did not demonstrate clinically significant changes from Baseline.

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