Protocol RC 92-0301: An Evaluation of Effectiveness of Different Dosing Schedules of Recombinant, Human, Macrophage-Targeted β-Glucocerebrosidase.

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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Investigators and Study Center(s)

This was a single-center study conducted in Israel.

Studied Period

First Patient Enrolled May 1992
Last Patient Completed May 1994

Phase of Development

Phase 3

Objectives

To compare the safety and effectiveness of two different dosing schedules of Cerezyme® in the treatment of patients with Gaucher disease.

Methodology

Randomized, matched pair, parallel-group design, comparing two different dosing schedules of Cerezyme® over a period of 24 months. Ten eligible patients were matched and paired based on age and disease severity by two independent reviewers. One patient in each pair was assigned to receive Dosing Schedule A (15 U/kg every other week), and the second patient in each pair received Dosing Schedule B (2.5 U/kg, 3x per week). All patients received a total dose of 30 U/kg/4 weeks.

Number of Patients (Planned and Analyzed)

10 patients (8 females, 2 males) with a confirmed diagnosis of Type I Gaucher disease.
10 patients planned, enrolled and treated

Diagnosis and Main Criteria for Inclusion

Male and female patients with a confirmed diagnosis of Type I Gaucher disease, who were between 2 and 75 years of age, and had a hemoglobin value of at least 1.0 gm/dL less than normal lower limit for their age and sex: male adults. 14 g/dL; female adults, 12 g/dL; children $\leq$12 years, 12 g/dL; and children 13-18 years, 12.5 g/dL.

Test Product, Dose, and Mode of Administration

Cerezyme®, Dosing Schedule A: 30 U/kg/4 weeks, administered as 15 U/kg every other week. Dosing Schedule B: 30 U/kg/4 weeks, administered as 2.5U/kg three times per week. Mode: I.V. infusion.

Duration of Treatment

18 months (2 patients in each group) to 24 months (3 patients in each group). Treatment and observation period ended upon approval of Cerezyme® by FDA.

Reference Therapy, Dose and Mode of Administration

Not applicable.

Criteria for Evaluation
Efficacy

Primary efficacy variables were: an increase in hemoglobin concentration ≥1.0 g/dL; an increase in platelet count ≥30%; and a ≥10% decrease in the volume of the spleen or liver. Secondary efficacy variables were: an increase in hemoglobin concentration ≥1.5 g/dL; an improvement in liver function, as evidenced by a decrease in serum transaminases (serum glutamic pyruvic transaminase[SGPT], serum glutamic oxaloacetic transaminase [SGOT]); a decrease in acid phosphatase or in angiotensin converting enzyme (ACE); and changes in bone density (i.e., trabecular and cortical density), as evaluated by bone densitometry (dual energy X-ray absorptiometry [DEXA]) or magnetic resonance imaging (MRI).

Safety

Safety measures consisted of the evaluation of clinically significant changes from Baseline in specific laboratory parameters, the formation of antibodies to Cerezyme®, and the occurrence of adverse events (AEs).

Statistical Methods

The following endpoints were considered and assessed at 6 month intervals and at the end of the study. AEs were monitored continuously. Patients were analyzed both by treatment regimen and as matched pairs.

Efficacy

An increase in blood hemoglobin concentration of 1.0 g/dL or greater from baseline was considered a primary endpoint. Increases of 1.5, 2.0, and 3.0 g/dL hemogloblin were secondary endpoints. An increase of 30% or more in the platelet count was considered a primary endpoint; an increase in the platelet count of 50% or more was a secondary endpoint. Fisher's Exact Test was used to analyze endpoints and compare the groups.

Absolute and percent changes in blood hemoglobin, platelet levels, and hepatic and splenic volumes were compared between groups with the Wilcoxon Rank Sum test. Baseline values were compared to each subsequent time point. Time to response in the two groups was compared using Kaplan-Meier methodology. Response was defined prospectively as at least a 1.5 g/dL increase in blood hemoglobin, a 30% increase in platelets, or a 10% decrease in liver or spleen volume.

Baseline blood hemoglobin levels and platelet counts, and spleen and liver volumes were compared between treatment groups using the t-test and Wilcoxon Rank sum test. Descriptive summary statistics for secondary hematology endpoints were computed without inferential testing at each time point.

Safety

The formation of antibodies to Cerezyme®, the incidence of AEs, and the occurrence of abnormal laboratory test results were safety endpoints. Endpoints were evaluated for each treatment group.

Summary – Conclusions

Eight (8) females and two (2) males were enrolled into the study. There were two males and three females in Dosing Schedule A; all patients in Dosing Schedule B were female. Baseline characteristics of patients in the two Dosing Schedules were similar.

Efficacy

At study completion, seven of 10 patients (70%) achieved a ≥1.0 g/dL or greater change in hemoglobin concentration from Baseline. There were no differences between Dosing Schedule A and B in the percentage of patients achieving an increase in hemoglobin concentration of ≥1.0 g/dL. A secondary measure of efficacy, a mean change of ≥1.5 g/dL in hemoglobin concentration, was achieved by 4 patients at the end of the study. A ≥2.0 g/dL increase in hemoglobin concentration was achieved by 3 patients at study completion. None of the differences between dose groups were statistically significant.

For this study, a ≥30 % increase in platelet count was considered to be a meaningful response. Four patients in this trial achieved ≥30% increase in platelet count at study completion. A majority of patients presented at Baseline with normal levels of SGPT and SGOT. Following further evaluation, it was determined that transaminase levels were not considered to be a significant response parameter in this population of Gaucher patients. All 10 patients had elevated ACE at Baseline. One of 9 patients with acid phosphatase data had normal levels at Baseline. No significant changes occurred during the study in either of these biochemical markers.

The most complete set of DEXA data were obtained from the lumbar spine. Results indicate that at the 3 and 6 month time points, bone mineral density (BMD) values decreased in all patients by an average of 2.5%. The initial decrease was followed in some patients by an increase at the 9 and 18 month time points in BMD. In general, the average BMD for the entire group remained slightly below Baseline. This was not unexpected, since the ability to augment bone mass in the mature skeleton is limited. It was concluded that some modest bone gain probably occurred with Cerezyme® therapy.

All patients in this clinical trial presented with hepatosplenomegaly. Treatment with Cerezyme® reduced organ volume significantly on both Dosing Schedules A and B. The overall mean multiple of normal for liver volume at Baseline was 1.79 x normal [range: 1.05 to 2.62, SD: 0.53], and the overall mean multiple of normal at Baseline for splenic volume was 18.5 x normal [range: 7.85 to 35.46, SD: 9.52]. The overall mean decrease in liver volume at the end of the study for all patients was 20.5%; the mean splenic volume decrease was 47.8% at the end of the study.

Seven of 10 patients achieved a ≥10% decrease in liver volume at the end of the study (2 of 5 in Dosing Schedule A; 5 of 5 in Dosing Schedule B), thereby showing a response to treatment. The overall mean percentage decrease from Baseline in hepatic volume at the end of the study was 19.4% (N=10). Patients in Dosing Schedule A had a mean percentage decrease of 14.3%, and patients in Dosing Schedule B had a mean percentage decrease of 24.4%. When comparing liver volume between the two treatment groups, no significant statistical differences were found at either Baseline or study completion.

Nine of 10 patients demonstrated a ≥10% decrease in splenic volume at the end of the study and met the criterion for response (4 of 5 in Dosing Schedule A; 5 of 5 in Dosing Schedule B). The overall mean percentage decrease from Baseline in splenic volume in the 10 patients at study completion was 42.8%. There were no significant statistical differences in the 2 treatment groups at either Baseline or at study completion.

Safety Results

In the course of this clinical study, there were no reports of serious AEs or deaths. A total of 35 non-serious AEs were reported in 8 of 10 patients. The majority of AEs were classified as mild (87%) and none were reported as severe. In Dosing Schedule A, a total of 12 AEs were reported in 4 of the 5 patients and in Dosing Schedule B a total of 23 AEs were reported in 4 of 5 patients. Twenty-eight (28) of the 35 AEs (80%) were considered unrelated to study drug (11 in Dosing Schedule A; 17 in Dosing Schedule B), 6 AEs (17%) were considered possibly or probably related to study drug (1 in Dosing Schedule A; 5 in Dosing Schedule B) and for 1 AE the relationship was unknown. No AEs were reported to be definitely related to the study drug. The most frequently reported AEs were pain (5 patients), diarrhea (3 patients) and unspecified infection (2 patients). None of these AEs were considered related and no other AEs were reported for more than 1 patient. The AEs reported in 1 patient only were chills, abdominal pain, hyperesthesia, chest pain, injection site reaction, injection site hematoma, arthralgia, vasodilation, nausea, nervousness, fever, sinusitis, vaginal hemorrhage, metrorrhagia, ecchymosis, palpitations, flatulence and pharyngitis. One of the 10 patients (10%) developed antibodies to Cerezyme® as detected by enzyme-linked immunosorbant assay (ELISA) and confirmed by radio-immunoprecipitation (RIP) at Month 6. This patient remained antibody positive through 24 months of follow-up with no evidence of diminished response (continued improvements in the four primary efficacy variables) and experienced no AEs considered related to the study drug. Therefore, no correlation between antibody development and an impact on response to treatment or adverse event profile was noted in this small study population. Overall, there was no apparent difference between the 2 Dosing Schedules (A and B) in any of the safety parameters observed and evaluated. The overall AE profile indicates that Cerezyme® is a safe therapeutic for patients with Gaucher disease when administered at a dose of 30 U/kg/4 weeks, on either a 3 times weekly or once every other week dosing regimen.

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