



ORIGINAL ARTICLE

Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat

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Article

Figures/Media

Metrics

38 References

124 Citing Articles

Abstract

BACKGROUND

Fabry's disease, an X-linked disorder of lysosomal α -galactosidase deficiency, leads to substrate accumulation in multiple organs. Migalastat, an oral pharmacologic chaperone, stabilizes specific mutant forms of α -galactosidase, increasing enzyme trafficking to lysosomes.

METHODS

The initial assay of mutant α -galactosidase forms that we used to categorize 67 patients with Fabry's disease for randomization to 6 months of double-blind migalastat or placebo (stage 1), followed by open-label migalastat from 6 to 12 months (stage 2) plus an additional year, had certain limitations. Before unblinding, a new, validated assay showed that 50 of the 67 participants had mutant α -galactosidase forms suitable for targeting by migalastat. The primary end point was the percentage of patients who had a response ($\geq 50\%$ reduction in the number of globotriaosylceramide inclusions per kidney interstitial capillary) at 6 months. We assessed safety along with disease substrates and renal, cardiovascular, and patient-reported outcomes.

RESULTS

The primary end-point analysis, involving patients with mutant α -galactosidase forms that were suitable or not suitable for migalastat therapy, did not show a significant treatment effect: 13 of 32 patients (41%) who received migalastat and 9 of 32 patients (28%) who received placebo had a response at 6 months ($P=0.30$). Among patients with suitable mutant α -galactosidase who received migalastat for up to 24 months, the annualized changes from baseline in the estimated glomerular filtration rate (GFR) and measured GFR were -0.30 ± 0.66 and -1.51 ± 1.33 ml per minute per 1.73 m^2 of body-surface area, respectively. The left-ventricular-mass index decreased significantly from baseline (-7.7 g per square meter; 95% confidence interval [CI], -15.4 to -0.01), particularly when left ventricular hypertrophy was present (-18.6 g per square meter; 95% CI, -38.2 to 1.0). The severity of diarrhea, reflux, and indigestion decreased.

CONCLUSIONS

Among all randomly assigned patients (with mutant α -galactosidase forms that were suitable or not suitable for migalastat therapy), the percentage of patients who had a response at 6 months did not differ significantly between the migalastat group and the placebo group. (Funded by Amicus Therapeutics; ClinicalTrials.gov numbers, [NCT00925301](#) [study AT1001-011] and [NCT01458119](#) [study AT1001-041].)

Introduction



FABRY'S DISEASE IS A RARE, PROGRESSIVE, AND DEVASTATING X-LINKED disorder caused by the functional deficiency of lysosomal α -galactosidase.¹ The resultant accumulation of glycosphingolipids, predominantly globotriaosylceramide (GL-3), can lead to multisystem disease and early death.²