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LETTER

Evaluation of the efficacy and safety of three dosing regimens of agalsidase alfa enzyme replacement therapy was underpowered

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Dear editor

We read with interest the report by Goláň et al on the "Evaluation of the efficacy and safety of three dosing regimens of agalsidase alfa enzyme replacement therapy in adults with Fabry disease".[1] Based on the reported results, the authors conclude that no efficacy or safety differences were found when the approved every-other-week (EOW) dosage of agalsidase alfa was increased to weekly administration. However, the key question is whether the study, as designed and performed, could have had a different outcome. Estimation of the sample size was based on the 1999 report by Palmieri et al.[2] Table 3 in this publication indicates that the sample size per group needed to detect a change in left ventricular mass (LVM) of 5 g/m$^{2.7}$ assuming a 5% type I error rate and an 80% power is 19.[2] This would yield a total sample size of 38. The authors state that the sample size calculations assumed a 10% dropout rate, but this assumption did not appear to result in a 10% increase in sample size to 42. In addition to this failure to increase the sample size in order to account for a 10% dropout, the real dropout was even higher than 10%. Thus, the dropout rate in the 0.2 mg/kg/2 weeks group was 25% (5/20) when including real dropouts and patients with missing end-of-study assessment of the primary end point (left ventricular mass index [LVMI]). Thus, according to the authors' estimates, the study was underpowered to detect differences. The ability to detect differences may have been further compromised by the heterogeneity of the patient population. Thus, for the main analysis, males and females were grouped together. However, the response to therapy appears to be divergent between males and females. The least squares mean (LSM) difference (0.2 mg/kg weekly minus EOW) was −7.6 g/m^2 for males and +7.85 g/m^2 for females. Indeed, the −7.76 value observed in males was outside the 95% confidence interval for the LSM difference in females (−2.55 to 18.25). In this regard, the study was theoretically powered to detect a 5 g/m$^{2.7}$ treatment difference in the primary efficacy end point for the whole group. Both sex subgroups exceeded this difference but in opposite directions, thus further limiting the power of the study when results from both sexes were added. Some important information that may help better interpret the study is missing. Thus, the standard deviation for the baseline and 53-week LVMI data is not reported. There is also no information on the baseline LVMI values of the patients for whom 53-week data are available. We suggest that the conclusion be modified to state that no efficacy or safety differences were found when the approved EOW dosage of agalsidase alfa was increased to weekly administration, but the study was underpowered to detect such differences.

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Disclosure

AO has received honoraria and travel support from Genzyme and Shire. The authors report no other conflicts of interest in this communication.

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Authors' reply

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Dear editor

We appreciate the interest in the publication of "Evaluation of the efficacy and safety of three dosing regimens of agalsidase alfa enzyme replacement therapy in adults with Fabry disease", and we would like to clarify the calculation of the study power.

The study was powered to detect a difference in the change of left ventricular mass (LVM) indexed to height from baseline to week 53 between the groups administered 0.2 mg/kg every other week (EOW) and 0.2 mg/kg every week (EW). Per the study protocol, the sample size was based on the effect size of 1 (ie, standardized treatment difference = treatment difference/standard deviation [SD] of the change). It was assumed that the SD of the change was 5 g/m$^{2.7}$. Statistical analyses were performed using SAS® statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA).

The formula used to calculate the sample size for the study was $[(Z\alpha/2 + Z\beta)^2 \times 2\sigma^2]/\Delta^2$, where α is the type I error rate, β is the type II error rate, σ is the common SD, and Δ is the desired treatment difference.[1] It is based on standard normal distribution and gives a sample size per 0.2 mg/kg group of 17, ie, a total of 34; the number of patients from the two 0.2 mg/kg groups who completed the study was 35.

The discontinuation rate was 3 out of 20 in the 0.2 mg/kg EOW group and 1 out of 19 in the 0.2 mg/kg EW group.

The study was not powered to detect differences between male and female patients.

The SD of the change in left ventricular mass index (LVMI) was 12.5 g/m$^{2.7}$ in the 0.2 mg/kg EOW group and 15.8 g/m$^{2.7}$ in the 0.2 mg/kg EW group, implying that the common SD is ~14 g/m$^{2.7}$.

It is apparent that the SD used in the calculation assumption was relatively smaller than the "observed" SD. No interim analysis for the primary efficacy endpoint was performed; hence, no sample size adjustment (or increase) was planned for the study.

Baseline LVMI data are shown in Table 2 of the original publication.

The fact that Fabry disease is a rare disease makes the undertaking of clinical trials challenging. The length of the study also plays an important role. We continue to follow our patients, and the findings from these longer term studies will be published.

Disclosure

LG was the principal investigator for the current study with Shire and has received travel funding from Genzyme and Shire. PC is an employee of, and holds stock options in, Shire.

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