RESPONSE LETTER TO THE EDITOR

Response to "Oral Chaperone Therapy Migalastat for the Treatment of Fabry Disease: Potentials and Pitfalls of Real-World Data"

Jonas Müntze[1,2] and Peter Nordbeck[1,2]

To the Editor:

We thank Dr Körver and colleagues for their interest in our work.[1] We absolutely agree that validity of current amenability criteria arguably might still be subject to discussion. From the clinical viewpoint, the cutoff values of 1.2-fold relative and 3% absolute increase in alpha galactosidase activity chosen in the recent multicenter trials might be questionable particularly in patients with polymorphism-like genotypes, such as the benign variant D313Y, presenting with near-normal wild-type enzyme activity but currently still categorized as amenable.[2,3] Limitations in knowledge on the genotype-dependent absolute and relative changes in enzyme activity in the clinical setting, and the question which cutoff value might be most suitable to forecast therapy success, represent a clinical dilemma for the treating physicians. This was one of the main drivers for execution of the current investigations. Given the exceptional bandwidth of genotypes and phenotypes in Fabry disease, it is not surprising that not only chaperone therapy but also alternative specific treatment options—namely enzyme replacement but also substrate reduction therapy—have shown marked variance in individual patients' treatment response.[4,5]

However, we disagree with the claim that lyso-Gb3 represents the ideal biomarker to determine amenability or therapy success, and neither can support the hypothesis that an increase in lyso-Gb3 in one patient switched from enzyme replacement therapy to migalastat verifies non-amenability in this particular mutation or even patient. Obviously, as also pointed out by Dr Körver *et al.*, laboratory as well as imaging biomarkers, such as left ventricular mass derived by echocardiography, can show substantial variability over time. Importantly, such variance does not necessarily reflect methodological limitations or measurement errors, but at least in part can be explained by varying biological parameters, which often strongly affect numerical data even when extreme care is taken to avoid any technical bias. With regard

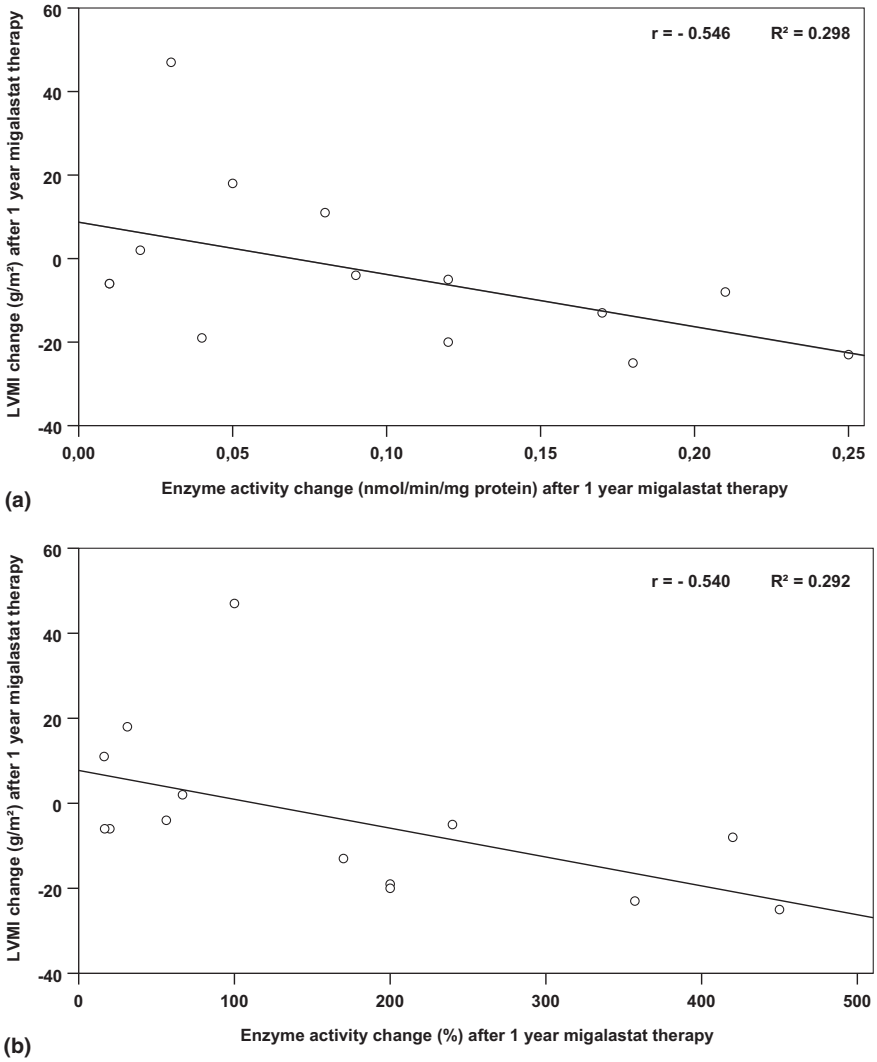

Figure 1 Individual measures for absolute (**a**) and relative (**b**) enzyme activity change and change in left ventricular mass index (LVMI) after 1 year of migalastat therapy.

to echocardiography data in our study, it is important to stress the fact that blinded analysis revealed no relevant changes in left ventricular mass in the previously non-hypertrophic hearts but a strong effect in the cases with prevalent hypertrophy. Individual absolute and relative enzyme activity changes over time correlated with respective changes in left ventricular mass index are shown in **Figure 1**.

Given the fact that—despite limited patient numbers—our study reveals a robust correlation between the increase in alpha galactosidase enzyme activity and reduction of left ventricular mass index in response to therapy, we see strong evidence and, therefore, confirm our claim that migalastat does improve cardiac integrity in amenable patients with Fabry disease. Answering the question which specific patients might benefit most also in the long run and how migalastat therapy compares with other specific therapeutic options with regard not only to organ involvement and symptoms but also genotype and additional individual disease-modifying factors will certainly require additional investigations from larger trials.

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CONFLICT OF INTEREST

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[1]Department of Internal Medicine I, University Hospital Würzburg, Würzburg, Germany; [2]Comprehensive Heart Failure Center, University of Würzburg, Würzburg, Germany. *Correspondence: Peter Nordbeck (nordbeck_p@ukw.de)

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