To the editor:

Low-dose versus high-dose therapy for Gaucher disease: goals and markers

Zimran et al state in their commentary1 that the title of our study2 is misleading because the superior effect of a high dose of imiglucerase compared with a low dose is “limited to the response of 2 surrogate markers, serum chitotriosidase and MRI scanning of the marrow.”3 To our surprise, we agree that no superiority of the higher dose was established with respect to the most widely used parameters of disease (ie, cytopenia and organ volumes), although subtle differences may not have become apparent due to the limited number of matched pairs for each parameter. In fact, we have shown in the past that one ninth of the originally established dose leads to sustainable improvements in a subset of adults.3 The question arises: how do we best evaluate the efficacy of enzyme replacement therapy in Gaucher disease by optimally exploiting available biomarkers? By definition, biomarkers are either clinical markers or mechanism-based biochemical markers that correlate with observed outcomes. The biomarkers could be used in clinical studies as proof of concepts or clinical end points.4 For example, in diabetes, glycosylated hemoglobin can serve as a biochemical marker and measures of nephropathy as a clinical marker, which should be evaluated against clinical end points, such as life or death, cure or failure, or time to an event. Of interest, for Gaucher disease, these clinical end points are not at all clearly defined: the overall goals of treatment are still the subject of debate.5 Obvious goals are to achieve normal growth and development in children, normal blood counts, absence of symptomatic organomegaly, and absence of new skeletal events. Ultimately, complications such as fibrosis of the liver and the occurrence of malignancies should be prevented. How do these goals relate to the existing biomarkers? Earlier meta-analyses have focused on liver size as a clinical marker,6 however, its relation with these outcome measures was never thoroughly validated. The absence of a “gold standard” for disease severity in Gaucher patients hampers the validation of any marker, whether liver size or chitotriosidase. At least for chitotriosidase, there is the observation that in spleen tissue the relation between chitotriosidase levels and stored glucosylceramide is almost linear, and there is immunohistochemical evidence that chitotriosidase is secreted by Gaucher cells.7 Clinically, the enormous elevation in plasma, the prompt decrease upon successful treatment,2 and the increase of chitotriosidase upon treatment interruption8 indicate that it might even be the best of all biomarkers. As to the validity of decreased bone marrow fat fraction (the triglyceride content of the marrow and not the “Gaucher fat”) in relation to clinical bone disease, a decrease in the fat fraction of 10% is associated with an increased risk for occurrence of bone complications of 85%.9 No other marker for skeletal disease has proved superior.

In summary, there is novel evidence for dose dependence for the enzymatic effects of imiglucerase on 2 well-established markers. Apparently, this finding has aroused a discussion that hopefully will stimulate a critical evaluation of clinical and biochemical markers against predefined goals of therapy.

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References


Response:

Correlation between Gaucher disease clinical severity and surrogate markers is weak

We are in agreement that the role of surrogate markers in the treatment of Gaucher disease requires further critical examination. We also agree with Hollak et al that there are several aspects of serum chitotriosidase levels that make this parameter a promising surrogate for disease severity. The high levels found in Gaucher disease and the fact that Gaucher cells secrete the enzyme make

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chitotriosidase an excellent candidate for a useful biomarker. However, the “it stands to reason” approach often does not work out in medicine, and it is necessary for us to depend upon hard evidence to decide how useful a given biomarker is as a surrogate for disease severity. As we pointed out in our commentary, the published data are far from encouraging in this regard. Neither our own experience nor the published work of Deegan et al. suggest that, in reality, chitotriosidase levels strongly reflect clinical disease severity. The data available from our patients at the Shaare Zedek Gaucher Clinic are limited by the fact that chitotriosidase genotypes were not available on all patients and because we could include only those who had not received enzyme therapy before the levels of the enzyme were measured.

But the relationship between severity and enzyme level is very weak in those who could be included (Figure 1), and the average enzyme activity of the 2 patients with bone lesions averaged 6740, compared with an average of 8701 nM/mL per hour for the patients without bone lesions. Hollak et al. found that the fat fraction is a good surrogate for severity of bone disease. We reproduced Figure 3 from this paper in our commentary to show how weak the correlation was. Their study shows that 7 of 9 patients with mild or severe bone complications had fat fractions of less than 0.23, an arbitrary cutoff based on the data. But it also shows that 11 of 21 patients without bone complications had fat fractions below this arbitrary cutoff.

Finally, while we agree that more work needs to be done to establish a role of surrogates in the treatment of Gaucher disease, the results with the parameters that gave “superior results” with high-dose therapy are not promising. These are slender reeds, indeed, upon which to make a $300 000-a-year treatment decision.

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References

To the editor:

Platelet transfusion in neonatal alloimmune thrombocytopenia

We read with interest the article “Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia (NAIT)” by Kiefel et al. The authors describe the outcome of 27 neonates with anti–HPA-1a–mediated NAIT treated with random donor platelet transfusions. They found that 24 of these neonates achieved platelet counts higher than 40 × 10^9/L and concluded that random donor platelet transfusion is an acceptable strategy for the management of severe index cases of NAIT.

The National Blood Service in England provides HPA-1a/5b–negative platelets for immediate treatment of neonates with a presumptive diagnosis of NAIT. We have compared the transfused platelet counts and clinical outcome in neonates with anti–HPA-1a– and anti–HPA-5b–mediated NAIT transfused with HPA-1a/5b–negative platelets (ie, antigen-compatible transfusion [AC-Tx]) versus random donor platelet transfusion (R-Tx). In many cases of NAIT, a spontaneous recovery in platelet count is seen, and some are apparent in the study of Kiefel et al (eg, cases 1, 4, and 9). In such cases, it is difficult to be sure of the contribution of the transfused platelets to the increase in platelet count; we have therefore excluded such cases from our calculations (Figure 1; Table 1).

Figure 1. Mean platelet increments in neonates with NAIT following HPA-1a/5b–negative platelet transfusions or random donor platelet transfusions. The mean platelet increments in neonates with anti–HPA-1a– and/or anti–HPA-5b–mediated NAIT following HPA-1a/5b–negative platelet transfusions (n = 29) (open circles) or random donor platelet transfusions (n = 9) (closed squares) are shown. The error bars represent the standard deviation of the measurements. The dotted curves represent the fitted exponential decay curves to the data. The individual patient data are given in Figure 2.
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