

Commentary

Measuring the response of organomegaly of severely affected patients with Gaucher disease to alglucerase (1) we found no demonstrable advantage high doses of alglucerase over low doses. However, some have continued to insist that there must be some advantage to the much more costly high dose therapy that is considered to be the standard by Genzyme Corp., the manufacturer of Ceredase. One-by-one objections to the concept that the dosage response curve is flat have been disproved by additional data; the equivalence of high and low doses in the treatment of visceral disease has been confirmed in all published studies (2-10). Most recently it has been suggested that high dose therapy may be required for the treatment of bone disease (11). The logic behind this contention was strange. Data had been published indicating that after prolonged therapy patients receiving high dose therapy showed some improvement in skeletal lesions (11) but no data had been published on the

effectiveness of low dose therapy. The conclusion that high dose therapy might be better is difficult to understand because no comparison between the results of high dose and low dose therapy had been made. However, anecdotal evidence seemed to show that the response of skeletal disease to low dose therapy was equivalent to that to high dose therapy (8). Nonetheless, the contention that high doses are needed has caused some clinicians (12) to greatly increase the dose of alglucerase given to patients with skeletal involvement.

It is in the context of the relative void of information about the effect of low dose therapy on bone lesions that the study of Elstein, et al. is so important. They have measured a critically important parameter of skeletal Gaucher disease, viz., cortical bone thickness. Control patients were also studied and the measurements were done by a "blinded" radiologist. The results are clear. Low doses of Ceredase do produce a skeletal response. Indeed, the response appears to be quite equivalent to that obtained with more expensive high doses (fig 1).

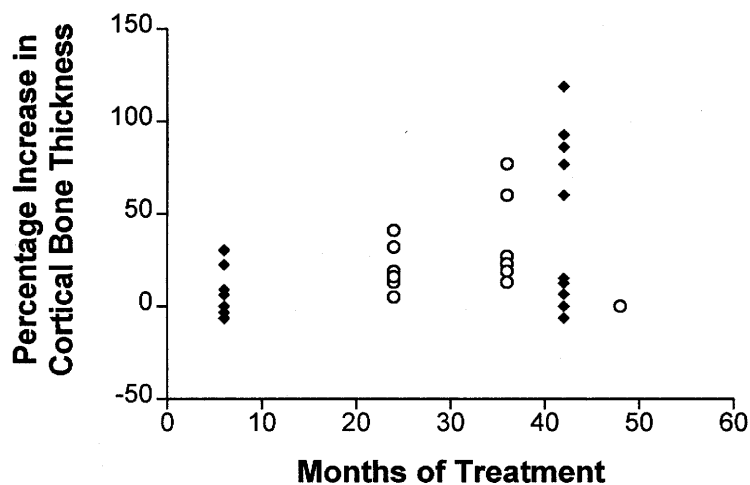


Figure 1: The increase in cortical bone thickness as reported in 12 patients at 6 months and 11 of these patients at 42 months by Rosenthal et al (11) (solid symbols) compare with the data obtained by Elstein et al in 14 patients (open symbols)

The results they have documented are all the more impressive because the patients they studied are considerably older than those investigated by Rosenthal et al (11). Indeed the 4 adult patients reported by Rosenthal et al (11) failed to show any increase in cortical bone thickness. As Grabowski has pointed out in his commentary, "...there is no a priori to expect lower efficacy with more enzyme." One could speculate that the higher dose frequency is important, but patients #6 and #9, who received imiglucerase only every two weeks enjoyed a response comparable to those of other patients.

As Elstein, et al. point out, it is unlikely that larger controlled studies will ever be done. It is true, of course, that there may be other parameters that would be useful, but today's physicians must deal with today's evidence. Let us hope that this excellent study put to rest the myth that high dose Ceredase is required for skeletal responses. The presence of skeletal disease is certainly is not a valid indication for giving large doses of Ceredase to patients with Gaucher disease. The drug used to treat a 50 Kg patient for 42 months with the dose used by Rosenthal et al (11) cost approximately \$1,090,000. The cost of drug for the treatment using the protocol employed by Elstein et al costs "only" \$250,000. Can anyone maintain that the additional cost and additional risk of high dose therapy is worth it?

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