

## **Commentary: Low-dose High-frequency Enzyme Replacement Therapy Prevents Fractures Without Complete Suppression of Painful Bone Crises in Patients with Severe Juvenile Onset Type I Gaucher Disease**

Since the advent of enzyme replacement therapy for Gaucher disease, the controversy surrounding minimal effective dosage has not been resolved (1) and there is still no universally accepted starting regimen. It is clear, however, that comparable rates of normalization of hematological parameters and similar dramatic reductions in organomegaly can be achieved with the "low-dose" (30 units/kg/month) protocol (2,3) as with the original "high-dose" (120 units/kg/4 weeks) regimen (4). With reference to skeletal involvement, often the most debilitating feature of type I Gaucher disease, the issue of dosage is further complicated by other issues, including lack of standardized objective measures, heterogeneity of bone-related signs, splenic status, and age at onset of bone disease. For example, although enzyme treatment engenders increased cortical bone thickness in patients on various dosage regimens (5,6), this measure is not necessarily correlated with clinical improvement or with cessation and/or reversal of skeletal complications. In fact, other than one early case report (7) with improved bone histology after 3.5 years on the high-dose protocol, normalization of the bone matrix has not been shown. Moreover, bones with severe damage appear to be unimproved by long-term therapy at all dosage levels, and infrequently patients suffered from the emergence of new bone pathology (6,8-10).

Cohen et al (11) present a cohort of 10 patients with early onset of symptoms, who were started on the low-dose high-frequency regimen of alglucerase (half of whom were between the

ages of 6-14 years and half between the ages of 17-23 years). It is unclear how these 10 patients were chosen from the original group of 18 children and young adults treated by the authors as published in 1995 (12). This is a cogent question since 8 of the 10 patients had radiological evidence of serious bone involvement (e.g. avascular necrosis of the hip and pathological fractures), before starting treatment. The good news reported herein is that none of these young patients developed new pathological fractures or osteonecrosis on this protocol. However, the authors conclusion vis-a-vis dosage incrementation, suffers from misinterpretation of the natural history of the disease and the benefits that can be derived in bones from enzyme therapy. The authors employ the incidence of bone crises as a marker for response to treatment. Yet, it is well known, that the prevalence and intensity of bone crises decrease with puberty and early adulthood, even among untreated patients (13, 14). Similarly, the consensus of investigators is that the skeletal response lags behind that of other parameters requiring 2-4 years for radiological changes, regardless of dosage regimen (1,5,6,8). Thus, the experience of Cohen et al. as well as the anecdotal case reports from the literature described in the paper (11) cannot be used as evidence for the success of any regimen in preference to another. Therefore, the younger patients, in retrospect, did not suffer from "inadequate therapy" (12), but rather were victims of the unforgiving criteria of the original Joint Gaucher Committee in Israel, that required pathological fractures and splenectomy for treatment approval.

It should be pointed out, that we do not criticize Cohen et al. for prescribing more enzyme while facing children in pain; we only doubt the theoretical underpinnings of their conclusions. In fact, our group currently advocates the 60 units/kg/month as a starting regimen in young children with severe symptomatic disease at presentation, but this is primarily to ensure adequate linear growth (13).

In our clinic, we have followed 13 patients, who are comparable by virtue of ethnicity and genotype to those reported by Cohen et al. Our patients were mostly compound heterozygotes for the 1226G (N370S) mutation and a null or severe mutation on the other allele (12 of 13), and presented with symptomatic disease (mean hemoglobin = 9.0 gr%; mean splenic excess = 27.1 fold) before the age of 6 years. These children presented earlier than those discussed herein (7/13 under 2 years of age) but we would be loath to coin a new category of "severe juvenile-onset type I" as suggested by Cohen et al, since type I disease appears to evince a continuum of clinical manifestations. Our group began therapy on the low-dose regimen before the age of 10 years (primarily from private funds or compassionate care provided by the smaller health care schemes). More importantly, they all started therapy *before* the development of skeletal complications. We have not seen any incidence of bone pain/crises, pathologic fractures or avascular necrosis in nearly 8 years of follow-up. The fact that none of our patients were splenectomized (15) may have also contributed to our excellent results, similar to case #6 in Cohen et al, who was the only patient with intact spleen among the ten reported, and the only one who was considered by them "a treatment success" on the low-dose regimen.

In addition, we would like to take exception to the authors claim that the issue of pain is "now overcome by the introduction of oral ambulatory high-dose prednisone therapy" (11). It is not at all clear that this treatment modality is unequivocally recommended, particularly in children and young adults who are at risk for avascular necrosis and osteoporosis. Therefore, we still prefer non-steroidal anti-inflammatory drugs for pain management, and if necessary, narcotics that can be patient-controlled even by adolescent (16); failure of narcotic therapy typically implies insufficient and inappropriate administration.

Finally, this paper confirms the ability of low-dose high-frequency alglucerase to prevent fractures and avascular necrosis in symptomatic

pediatric and young adult patients with type I Gaucher disease. It behooves us, however, to mention that this protocol has been superseded in Israel by all (but one) patients in preference to the recombinant form, imiglucerase, which is administered at a low-dose low-frequency regimen. The results of our experience of up to four years with imiglucerase have shown equal efficacy with improved quality of life (17).

In conclusion, it is to be reiterated that we recommend early enzyme replacement therapy in young symptomatic children, and even as prophylaxis in those at risk ("bad" genotype and/or siblings with bone involvement). In children with an intact spleen and receiving low-dose treatment, irreversible skeletal complications may thereby be prevented. It is to be hoped that biochemical and/or molecular markers can be developed as predictive measures of bone involvement, and by extension as means of assessment of therapeutic response. Equally it is to be hoped that in the future, newer means of enzyme targeting, as well as new adjuvant treatment modalities, will ensure more efficient management of Gaucher-related skeletal pathology.

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