Bisphosphonates in Children with Bone Diseases

TO THE EDITOR: In her Perspective article on bisphosphonates in children with bone diseases (July 31 issue), Dr. Marini comments that “treatment with bisphosphonates from infancy does not relieve the short stature of children with osteogenesis imperfecta.” It is important to note that the use of bisphosphonates for the treatment of infants with osteogenesis imperfecta has only recently been attempted, and the patients who have been treated have not yet reached their final height. Thus, it is not feasible to predict the final effects of the treatment. In the meantime, bisphosphonate-treated children with osteogenesis imperfecta appear to be growing faster than untreated children who are affected by the condition to a similar degree.

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TO THE EDITOR: Although there was no clear indication for bisphosphonate treatment, the child who was subsequently referred to and described by Whyte et al. (July 31 issue) received more than seven times the recommended dose of pamidronate. Not surprisingly, a unique and severe complication developed. None of the 42 children we have treated for an average of 4.4 years, in whom therapy had been stopped for at least 1 year, had evidence of metaphyseal osteosclerosis.

We agree with Marini that bisphosphonates should be used cautiously in children and that their effects should be monitored with the proper techniques. However, the effects of pamidronate in osteogenesis imperfecta should be presented in a more balanced fashion. There have been reports of beneficial effects in osteogenesis imperfecta (decreased rates of fracture, pain control, and increased mobility). Recent studies in animals also show that bisphosphonates may increase the mechanical strength of long bones. We therefore submit that until more information than that provided by a unique single case becomes available, statements that imply that current treatment approaches will render bones brittle rather than strong and will lead to osteopetrosis are unwarranted.

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TO THE EDITOR: The report of a boy given a diagnosis of osteopetrosis after three years of intermittent pamidronate therapy emphasizes our limited knowledge regarding the importance of the dose, as compared with the frequency, during treatment with bisphosphonates. It is anticipated that the cumulative dose will prove to be the problem. However, recent studies indicate that the regimen influences the effect and may therefore also affect the toxicity. When 1 mg of ibandronate given intravenously every three months failed to reduce the risk of vertebral fractures, changes in bone turnover were evaluated during therapy with regimens consisting of 1 mg or 2 mg administered quarterly. The levels of markers of bone resorption decreased rapidly by 80 to 90 percent at seven days after the injection of ibandronate, but a progressive increase began on day 14, and the levels approached the baseline values on days 56 through 84. There was, however, a more gradual decrease in the levels of markers of bone formation over two injection periods. The responses in the patients in the two dose-level groups were similar. The huge fluctuation in bone resorption that was observed may be deleterious for bone homeostasis and may therefore be responsible for the lack of protection against vertebral fracture. Accordingly, the once-weekly regimen of ibandronate provides sustained inhibition of bone resorption. Thus, the optimal regimen of intravenous bisphosphonates for children — in addition to the appropriate dose — requires further investigation.

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THE AUTHORS REPLY: Glorieux and colleagues conclude that our patient received seven times the “recommended” dose of pamidronate. The patient’s referral records contained the sequential body weights necessary for the calculation of the dose and permitted the comparison of his cumulative exposure to pamidronate with that provided by other regimens involving this bisphosphonate. As we reported, he was probably given about four times the amount of pamidronate per kilogram of body weight that was typically used by Rauch et al. during a 2.75-year period in children with osteogenesis imperfecta.

The radiograph showing the effects of pamidronate on the growing skeleton of the patient with osteogenesis imperfecta seen by Glorieux et al. (Fig. 1A) shows transverse bands of osteosclerosis (coarsened trabecular bone) in the metaphyseal and metadiaphyseal regions. These densities have persisted essentially unchanged by remodeling for up to 4.3 years, despite skeletal growth. Although these bands surely reflect increased amounts of trabecular bone, they also probably contain unresorbed “rests” of primary spongiosa (calcified cartilage): Rauch et al. noted that, after pamidronate therapy, the frequency of such rests was increased in iliac-crest specimens from their patients with osteogenesis imperfecta.

In addition, the radiograph shows a disturbance of bone modeling (shaping). To highlight this disturbance, we contrast the image in Figure 1A with a radiograph of the knee of a healthy 12-year-old boy (Fig. 1B). The metaphyseal bone surfaces of the patient with osteogenesis imperfecta, especially those in the distal femur, are convex rather than concave during the later stages of pamidronate therapy; this suggests an acquired inhibition of osteoclast-mediated bone contouring. Although they are clearly less pronounced, the modeling changes seen in the patient of Glorieux et al. (Fig. 1A) are reminiscent of those documented in the patient we describe in our article.


Bjarnason makes an interesting point about the frequency of administration as well as the amount of bisphosphonate given to our patient. We agree that dosing schedules should be evaluated in future studies.

Bone modeling, which is increasingly understood to influence skeletal quality and strength, should be assessed in children who are treated with antiresorptive drugs, especially long-acting bisphosphonates. Treatment with bisphosphonates can be anticipated to have additional skeletal effects in children, as compared with adults, because of the active (open) growth plates in children. We remain concerned that some children may be receiving excessive doses of bisphosphonates, which could compromise bone quality despite increases in bone density, thereby diminishing the therapeutic effects of these compounds.

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**Figure 1.** Radiologic Views of the Knee of a 12-Year-Old Boy with Moderate Osteogenesis Imperfecta and Multiple Fractures Who Was Treated with Intermittent Intravenous Pamidronate for 3.3 Years (Panel A) and the Knee of a Healthy 12-Year-Old Boy (Panel B).

The image in Panel A was obtained one year after treatment had been discontinued; the newly formed bone is of normal density, and no severe modeling defect is present. The knee shown in Panel B has properly modeled metaphyses (concave rather than convex surfaces) and no transverse bands of osteosclerosis.

**DR. MARINI REPLIES:*** In my Perspective article, I tried to balance the positive view presented in the medical literature of the off-label use of bisphosphonates in children with the cautionary note provided by emerging data and anecdotal information. The awareness of detrimental side effects of the long-term use of bisphosphonates in children will not undermine the potential benefits of these drugs in lytic conditions or osteogenesis imperfecta.

The bisphosphonate-treated rats mentioned by Glorieux et al. by way of an example of positive studies in animals were 18 months old — equivalent to late middle age in humans — and are not a suitable model of the growing skeleton. Our data on alendronate treatment for osteogenesis imperfecta in the Brtl mouse model from 2 to 14 weeks of age show increased stiffness of treated femurs and an exacerbation of femur brittleness.

The study comparing growth rates to which Dr. Plotkin refers used historical controls for treated children with osteogenesis imperfecta. We have not seen increased growth rates, in comparison with pretreatment growth rates, in our treated children older than four years of age. The growth curves characteristic of osteogenesis imperfecta have not been altered in school-age children. A substantial portion of the growth deficiency of osteogenesis imperfecta is incurred during the plateau phase of growth, between one year of age and three or four years of age. We have seen no evidence, among the younger children with osteogenesis imperfecta who have been treated at other centers, that bisphosphonate therapy has overcome this plateau. For example, a three-year-old girl with type IV osteogenesis imperfecta who has been treated since one month of age is the same height as her mother (who also has osteogenesis imperfecta) was at the same age. Any small increase in growth in treated children with this condition is most likely attributable to increased trunk size resulting from increased vertebral resistance to compression.

The treatment of pediatric bone disorders with bisphosphonates remains experimental. Controlled trials in children and animal models will better define the positive and negative aspects of treatment. Limited courses of treatment (two to three years) may preserve skeletal benefits while limiting detrimental effects.

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**G-CSF Priming in Acute Myelogenous Leukemia**

**TO THE EDITOR:** The study by Löwenberg et al. (Aug. 21 issue) suggests that the possible priming effect of the administration of granulocyte colony-stimulating factor (G-CSF) concurrently with remission-induction therapy may improve the outcome of some cases of newly diagnosed leukemia. However, the priming effect of G-CSF was not demonstrated in an intention-to-treat analysis, only in a subgroup analysis. In addition to the small benefit of this treatment, if it has any at all, its safety remains questionable. During an early postinduction phase, the G-CSF group had a significantly higher mortality rate (55 of 321 patients died) than the group that did not receive G-CSF (34 of 319 patients; P=0.02). Early deaths of high-risk patients might have led to the apparent improvement in survival among patients who had a complete remission. The increase in mortality might be explained by the possibility that G-CSF aggravates leukemia by stimulating blasts or the possibility that G-CSF is associated with unrecognized fatal toxicity. It would be informative if the authors could present the causes of early deaths.

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