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EDITORIAL

Bisphosphonate Treatment of Children and Adults with Osteogenesis Imperfecta: Unanswered Questions

Evelise Brizola[1,2] · **Jay Robert Shapiro**[1]

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Abstract Bisphosphonates are extensively used for treatment of children and adults with osteogenesis imperfecta. Over years, studies have reported the response of BP treatment in individuals with OI but some questions remain still unanswered.

Keywords Osteogenesis imperfecta · Bisphosphonate · Treatment

In 1987, Devogelaer et al. [1] first reported the treatment of a 12-year-old girl with osteogenesis imperfecta (OI) for 1 year with a newly available bisphosphonate (BP), 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD); treatment with APD orally was well-tolerated, and the radiological and clinical improvement was striking. Glorieux et al. [2] reported positive responses to the intravenous administration of pamidronate in 30 children aged 3–16 years old with severe OI who had received between 4 and 12 cycles of treatment. The mean incidence of radiologically confirmed fractures decreased by 1.7 per year ($p < 0.001$), and treatment with pamidronate did not alter rate of fracture healing, growth rate, or appearance of the growth plates. In 2003, Shapiro et al. [3] reported on the histologic response of bone to treatment with IV pamidronate (30 mg every 3 months) in 5 adults with OI type I. Treatment led to a significant increase in bone trabecular volume ($p = 0.01$), cortical thickness ($p = 0.01$), and bone formation rate ($p = 0.01$).

There followed many reports from different countries documenting the results of treatment with different BPs, administered orally or intravenously, in children and adults. Reported effects on fracture rate in children were variable but not initially defined for adults. While cautioning that BP treatment be reserved for more severe OI types, it was clear that BP treatment had become the "standard of care" for both children and adults including the very young [4]. Indeed, BP treatment has been associated with multiple positive effects such as an increase in bone mineral density and in vertebral height, relief of musculoskeletal pain and fatigue, improvement in muscle strength and mobility, and a positive impact on activities of daily living [5].

However, in 2009, Marini [6] urged "caution" as regards BP use in children, specifically with regard to (a) a decline in bone quality with high cumulative doses of BP and, (b) the insufficient data at that time supporting decreases in fracture rates. It is clear that BPs lessen fracture rates in many children, but whether BP is uniformly effective and how long treatment should be continued are subjects for discussion.

Recently, there have been two Cochrane reports [7, 8], and well as two recent meta-analyses by Hald et al. [9] and Shi et al. [10] reporting the effects of BP on the fracture incidence in both children and adults with OI. The 2014 Cochrane report [8] surveyed 14 trials (819 patients) focusing on randomized and quasi-randomized controlled trials comparing BP to placebo, no treatment, or

✉ Jay Robert Shapiro
Shapiroj@kennedykrieger.org

Evelise Brizola
Brizola@kennedykrieger.org

[1] Bone Disorders Program, Kennedy Krieger Institute, Johns Hopkins University School of Medicine, 707 N. Broadway, Baltimore, MD 21205, USA

[2] Postgraduate Program in Child and Adolescent Health, Faculty of Medicine, Federal University of Rio Grande do Sul, Rua Ramiro Barcelos, 2400, Porto Alegre, RS 90035-003, Brazil

comparative interventions in all types of OI. The authors concluded that it was unclear whether oral or intravenous BP treatment consistently decreases fractures, though multiple studies had reported that independently. The review by Hald et al. [9] was restricted to placebo-controlled randomized clinical trials ($n = 6$). As with the Cochrane study, the conclusions were that the available data did not indicate that BP treatment decreased the incidence of fracture in individuals with OI [8, 9]. By contrast, a meta-analysis by Shi et al. [10] concluded BP treatment did decrease fracture rate in children but not in adults. In addition, Dwan et al. [8] did not confirm that treatment decreased musculoskeletal pain or improved mobility.

Both this author's experience and that of Marini indicate that, although an increase in bone mineral density has been widely reported in several studies with BP treatment, it is neither a measure of bone strength nor a predictor of fracture risk: in this context, *bone quality* is the important unmeasured variable with regard to fracture risk [6]. In the adult OI risedronate study [11], there were modest but significant increases in BMD at LS, and decreased bone turnover but there was no significant difference to fracture incidence. What data may explain these inconsistencies with regard to BP effect on bone quality and fracture risk?

Rauch et al. [12] analyzed bone histomorphometry in 45 children and adolescents with OI treated with pamidronate for 2.4 ± 0.6 years (range 1–4 years). During pamidronate treatment, more samples contained calcified cartilage or abnormally large osteoclasts when compared to non-treatment control. An unexpected finding was that antiresorptive treatment with pamidronate led to a larger relative decrease in bone formation parameters than in bone resorption measures. However, areal and volumetric bone density by dual energy X-ray absorptiometry (DEXA) increased. Weber et al. [13] conducted background electron imaging and nano indentation on iliac crest bone samples from OI patients who had received 2.5 ± 0.5 years of pamidronate treatment and in controls. It is recognized that in the basal state, bone matrix in OI is hypermineralized. The matrix may be abnormally dense and the bone is stiff at the material level. It appeared that basic bone material properties of the samples were not additionally affected by pamidronate treatment. A conclusion was that long-term treatment might not be associated with an increase in fracture rate. However, this misses potential negative long-term effects of BP in the setting of hypermineralization and increased bone stiffness on the resistance of bone to fracture.

A second question addresses fracture rates in children and adults treated with BP and how long treatment should be continued to maximize fracture protection. A recommendation stated at various scientific meetings and published by Bachrach and Ward [14] is that BP treatment should be continued, perhaps a low dose, until growth is completed, in order to avoid fractures in areas unprotected by BP as might occur in the distal femur with growth. However, as Rauch et al. [15] observed in bone biopsies, the gains that can be achieved with pamidronate appear to be largely realized in the first 2–4 years of treatment. Can continued treatment adversely affect fracture risk?

BP localizes to the growth plate and affects chondrocyte maturation and trabecular bone development. In growing wild-type mice, treatment with alendronate, pamidronate, and zoledronate led to a decrease in the number of chondrocytes in the hypertrophic chondrocyte layer. This was not associated with altered chondrocyte apoptosis or altered vascular invasion at the growth plate [16]. However, this may differ in OI. Evans et al. [17] observed in the *oim* mouse models that pamidronate increased growth plate area secondary to reduced chondrocyte turnover. Furthermore, unlike in the wild-type mice, osteoclast numbers were decreased impairing vascular invasion at the growth plate and permitting the accumulation of calcified cartilage in primary trabeculae. Rauch et al. [15] had observed in patients, an increase in trabecular number but no increase in trabecular mineralization following pamidronate. How does this relate to fracture susceptibility and the question of proposed duration of treatment?

BP treatment is associated with the appearance of metaphyseal "zebra lines" above the growth plate. These sclerotic bands reflect a delay in chondrosseous maturation and decreased osteoclastic activity occurring in response to drug. When growth plate activity is temporarily interrupted by BP, osteoblasts deposit bone matrix on the metaphyseal site of the growth plate. Harcke et al. [18] have proposed that these thin bands of mineralized tissue at the interface between growth plate and metaphysis create a transition area of high and low density, which can produce a stress riser effect and facilitate fracture. Sixty-three per cent of the fractures observed in the children with cerebral palsy (CP) treated with BP were metaphyseal fractures either above, through or below the "zebra lines" [18]. Currently, there are no data indicating that continuing BP until growth ceases will limit fracture at this site. However, there are recent reports of mid-femoral fractures in both young and old individuals with OI, previously treated with BP for 3–5 or more years. Hegazy et al. [19] identified five patients in a group of 72 OI patients who had subtrochanteric fracture and one had mid-diaphyseal femur stress fractures with minimal or no trauma. None were located at stress riser areas (such as tip of the implant) or at metaphysis (site of typical OI-related fractures), or at growth lines related to pamidronate at the metaphysis.

The response to BP treatment is frequently reported as 1 or 2 years post-treatment. Fracture rate over several years

during and after treatment is not reported. Thus, the question of defining the optimal duration of BP treatment has not been addressed. Nevertheless, in the face of these uncertainties, parents of OI children and many OI adults and their physicians seek prolonged BP treatment. Room exists for expanded and focused clinical research on these topics.

To summarize, the central feature of treatment in OI is fracture prevention. BPs are widely prescribed and administered for years to children with OI and treatment is offered to adults. Yet there is an obvious lack of enough properly controlled data to warrant the recommendation that treatment should be continued in the absence of a sustained decrease in fracture rate in children or adults, and the absence of data to counter the concern that continued long duration treatment may incur adverse effect on bone.

Conflict of interest Evelise Brizola and Jay Robert Shapiro have no conflict of interest.

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