Experience With Bisphosphonates in Osteogenesis Imperfecta

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ABSTRACT

Until recently, medical management of osteogenesis imperfecta, a genetic disorder of reduced bone mass and frequent fractures, was elusive, and treatment was focused on maximizing mobility and function. The introduction of bisphosphonates for the treatment of osteogenesis imperfecta 14 years ago changed this paradigm. Cyclic intravenous pamidronate therapy leads to an increase in bone density and a decrease in fracture rate in patients with osteogenesis imperfecta. Pamidronate therapy has a positive impact on functional parameters including improved energy, decreased bone pain, and increased ambulation. Histomorphometric studies have shown that the reduced osteoclast activity results in gains in cortical thickness and trabecular bone volume. Potential negative effects may include prolonged time to heal after osteotomies and a decrease in the rate of bone remodeling. Overall, it seems clear that the benefits of pamidronate therapy outweigh its potential risks in moderate-to-severe osteogenesis imperfecta, and pamidronate therapy has become the standard of care for patients with this condition. Questions remain regarding when treatment should be stopped and the need for pamidronate therapy in patients with mild osteogenesis imperfecta.
OSTEOGENESIS IMPERFECTA (OI) is a heritable disorder that is characterized by bone fragility and reduced bone mass. Severity varies widely, ranging from a lethal form with intrauterine fractures to a very mild form with no or few fractures and normal growth. Extraskeletal manifestations include blue sclera, dentinogenesis imperfecta, skin and ligament hyperlaxity, and presence of wormian bones within cranial sutures. Most patients with a clinical diagnosis of OI harbor a mutation in 1 of the 2 genes encoding the α chains of type I collagen.1 There is growing interest in the search for other genes that may cause the bone abnormalities in patients with OI in whom no mutation in either COL1A1 or COL1A2 can be found.

Until about 10 years ago, medical management of OI consisted mainly of rehabilitation, physiotherapy, and corrective surgery. The overall aim was for each patient to reach his or her potential in terms of mobility and functional capabilities. Various forms of medical therapy to enhance bone formation have been attempted (vitamin D, fluoride, calcitonin, etc) with no tangible results. More promising data have been obtained by using bisphosphonates, which are potent antiresorptive agents. The rationale for using such drugs was found in our histomorphometric studies, which showed a high bone turnover rate in patients with OI2 and the frequent occurrence of superimposed disuse bone loss caused by impaired ambulation attributed to frequent fractures, deformities, and chronic pain.

At the Shriners Hospital for Children in Montreal, the bisphosphonate program was started in October 1992 and uses mainly cyclic intravenous pamidronate. Up to now, 233 patients with moderate-to-severe OI have been treated for periods up to 7 years. The drug has been given in 3-day cycles, every 2 to 4 months depending on the age of the patients (the younger the patient, the shorter the interval between cycles). In all instances, the annual dose of pamidronate was 9 mg/kg per year.3 Within 1 to 2 weeks after the first infusion cycle, bone pain decreased considerably and often disappeared completely. The patients also felt more energetic, as evidenced by a significant increase in grip force.4 Bone mineral density steadily increased over time in the lumbar spine. When the data were transformed to take into account the increase in the third dimension resulting from growth (volumetric bone mineral density), the gain was still evident (>75% over 4 years).5 It was accompanied by a change in shape and size of vertebral bodies (L1–L4). On lateral views, compressed vertebrae became larger and more rectangular, an effect of the drug amplified by the growth process.6 Fracture incidence decreased from 2.3 to 0.6 events per year in our first report.3 In infants under 2 years of age with severe OI, fracture incidence was 2.6 events per year compared with 6.3 events per year in untreated controls.7 This positive effect of therapy has been confirmed by several other studies.8–10 One should keep in mind, however, that such results are directly influenced by age, severity of OI, degree of ambulation, and social environment. In other words, treatment success may translate into higher risk of fractures. In a recent trial, using a daily dosage of oral alendronate, such a beneficial effect on fracture incidence could not be demonstrated.11 Pamidronate therapy, when started early in life, also has a positive effect on the degree of ambulation. When assessed with both Pediatric Evaluation of Disability Inventory scores and a modified Bleck mobility scale, the effect was significantly evident.12

Because osteoclasts play an important role in the process of endochondral bone formation, it was feared that long-term administration of bisphosphonates in growing individuals could have a negative impact on longitudinal growth. This turned out not to be the case. In 41 subjects treated for at least 4 years, we observed, in fact, a significant height gain.13 Another major benefit, the gain in bone mass, was demonstrated in bone histomorphometric studies. After 2.4 years of treatment in 45 patients, there was an 88% gain in cortical thickness and a 46% gain in trabecular bone volume,14 which can be explained by the drug reducing osteoclast activity and, thus, the rate of endocortical resorption. Because periosteal new bone apposition continues during the modeling process, the net effect is a gain in cortical bone mass. In the metaphyseal areas, the gain in bone volume was a result of survival of a larger number of calcified cartilage spicules, which serve as scaffolds for new bone deposition. The thickness of individual trabeculae was not changed. An observation frequently made in patients receiving cyclic pamidronate is the occurrence of dense metaphyseal lines parallel to the growth plate. Each line is the signature of a treatment cycle. It is made in part of unresorbed calcified cartilage (~25% in the line nearest to the plate) and calcified bone.15 These transverse trabeculae may improve bone mechanical resistance. As they move away from the plate, they are progressively remodeled. The distance between lines reflects the amount of bone formed during the intervals between treatment cycles and, thus, are a measure of the elongation process under individual growth plates. The major, potentially negative, adverse effect of long-term bisphosphonate administration is a rapid and important reduction in bone turnover rate.14 Its consequences have yet to be fully evaluated, but they may include prolonged healing time after osteotomies but not fractures16 and delayed removal of damaged bone matrix. In adults, this slowdown of remodeling activity with long-term use of bisphosphonates has been considered as an advantage because it allows for more complete mineralization of the bone matrix to improve its mechanical resistance.17 This advantage cannot be extrapolated to bone in patients with OI. Indeed, we demonstrated that, before any treatment, bone in patients with OI showed higher av-
verage mineralization density than normal bone. This may be the result of failure in matrix assembly such that it has a higher water-volume fraction available for mineral deposition. This is not significantly altered by subsequent pamidronate treatment. Thus, pamidronate increases the amount of bone but not its material density. Assessment of the biomechanical properties of bone material measured by nanoindentation confirm that bone in patients with OI is harder than normal bone at the material level but is not altered by pamidronate.

In conclusion, treatment with cyclical intravenous pamidronate has changed the face of moderate-to-severe OI. Over up to 7 years of treatment, the following positive effects have been documented:

- good short-term safety (particularly with regard to renal function);
- suppression or significant reduction in chronic bone pain;
- gain in muscle force;
- increase in density and size of vertebral bodies;
- thickening of bone cortex; and
- gain in growth rate.

Some negative effects have also been observed:

- decrease in bone remodeling rate;
- reduction in growth plate cartilage resorption; and
- delay in the healing of osteotomy sites.

Bisphosphonates stay in bone for a very long time. They can be released during remodeling. Whether this would cause problems, for instance, during pregnancy remain unclear. Thus, at this stage, it is prudent to restrict this therapeutic approach to moderate-to-severe cases of OI in which the potential benefits clearly outweigh the risks. No established benefits have been documented in the mild cases. How long a patient should be treated, what the criteria for stopping treatment are, and what the criteria are for reactivating it at a later stage remain open questions.

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