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ORIGINAL ARTICLE

Cyclic Pamidronate Therapy in Children with Osteogenesis Imperfecta

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The main objective of this study was to determine the efficacy and safety of pamidronate in improving bone mineralization and reducing fracture incidence in osteogenesis imperfecta (OI).

Materials and Methods: Intravenous pamidronate was administered to 64 children, aged 18 months to 10 years old, with severe OI, in a 1 mg/kg single daily dose for 3 sequentional days at 4 month intervals, for over a period of 24-48 months. Clinical status, biochemical characteristics including bone turnover markers, the bone mineral density of the lumbar spine and femoral neck, and radiologic changes were assessed regularly during treatment.

Results: The number of fractures decreased from median of 8 (range 4-11) to 0 fractures/year (range 0-4) (P<0.05). After 16 months of treatment, there was significant improvement in bone mineral density (BMD-DEXA) z-scores of the lumbar spine from median of -5.90 (range -7.01 to -4.76) to -2.70 (range -4.46 to -1.98) (P<0.001). Serum alkaline phosphatase (ALP) (bone formation marker) decreased from a median of 731.0 U/L (range 438-998 U/L) to 183 U/L (range 95-286 U/L) (P<0.001), implying a significant reduction in bone turnover and its resorption and increase in bone mineralization. There was no improvement either in their height growth velocities or in their standard deviation scores. Mobility and ambulation improved in all but 5 children, (all five took the drug for less than 2.5 years).There was a significant relief in chronic pain and fatigue but no adverse effects in any of the children using the drug.

Conclusion: Cyclic pamidronate administration is effective in improving bone mineralization and reducing fracture incidence in childhood osteogenesis imperfecta.

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Introduction

Osteogenesis imperfecta (OI) is disorder with congenital bone fragility, caused by mutations in the genes that codify for type I procollagen (COL1A1 and COL1A2).[1] Four types of OI are described: Type I (mild forms), type II (extremely severe); type III (severe with deformities), type IV (undefined) and type V (newly added). However, precise typing is often difficult. Severity ranges from mild forms to lethal forms in the perinatal period.[2] Recently, two variants of OI (labeled types V and VI), which involve mutations affecting genes other than those encoding type 1 collagen chains, have been described.[3-5]

Severe osteogenesis imperfecta is a disorder characterized by osteopenia, frequent fractures, progressive deformity, loss of mobility, and chronic bone pain. There has been

no effective therapy for the disorder until recently. The results of histomorphometric studies of bone suggest that this disorder is associated with an increase in osteoclastic activity and a reduction in the formation of new bone.[6]

A variety of agents including anabolic steroids, sodium fluoride, magnesium oxide, and calcitonin have been used to decrease the fracture rate and to increase bone stability, but none of them have had any significant effect in improving the disease.[7-10]

Orthopedic surgery is one of the pillars of treatment for patients with OI. Surgical interventions include intramedullary rod placement, surgery to manage basilar impression, and correction of scoliosis. These are not satisfactory enough for the brittle bones of these patients, as the pathologic base of bone fragility still remains, unless a contemporary significant medical treatment be used. [11-13]

The intravenous bisphosphonates, such as pamidronate, are potent inhibitors of bone resorption, and they have been reported to have beneficial effects in children with osteogenesis imperfecta. Cyclic administration of intravenous pamidronate reduces the incidence of fracture and increase bone mineral density, while reducing pain and increasing energy levels. Doses vary from 4.5 to 9 mg/kg/y depending on the protocol used.[14-21] Although some studies imply that alendronate has positively influenced quality of life in pediatric patients with osteogenesis imperfecta,[22, 23] Current evidence does not support the use of oral bisphosphonates in patients with OI.[17,18] Nutritional evaluation and intervention are paramount to ensure appropriate intake of calcium and vitamin D.[24]

We performed a prospective, open, uncontrolled observational study to determine the efficacy and safety of pamidronate in improving bone mineralization and reducing fracture incidence in OI.

Materials and Methods

Between December 2002 and November 2006, we administered pamidronate to 64 children, 1.5-10 years old, referred to Mofid Children's Hospital with severe osteogenesis imperfecta (Table 1).

Table 1. Study population before pamidronate administration and their management program

Patients	No.	Age (year)	HSDS	Fractures /year	Alkaline Phosphatase(U/L)	Duration Pamidronate Rx (months)	Cycles: one 3-day infusion
Boys	35	4±2*	-3.9±2.1	7±3	782±147	36±12	9±2
Girls	29	7.3±2.5	-3.4±1.8	8±3	716±129	32±12	8±3
All	64	6±4	-3.5±2	8±4	731±258	36±12	9±3

* Mean±SD; HSDS: Height standard deviation score; OI: Osteogenesis Imperfecta

All had severe osteoporosis, and short stature (below the third percentile of standard height-for-age curve). In addition, all had severe difficulties in motivation due to bone pain, deformities or current fractures. All, but eleven, of the children had type II or III, both severe forms of the disease. From the legal and ethical points of view, all the parents were informed about the possible hazards of therapy and their written consent was obtained before starting the study.

In very young children who are not able to express their feeling of pain, the "pain" is rather a qualitative value and it cannot be defined and changed to a quantitative one; hence, in pediatrics, if there is a tenderness and lack of mobility in a fractured bone of an irritable child, it is considered and accepted as a sensation of "PAIN", which is a constant finding in all uncured patients of OI. In this study, "the improvement of pain" was quantitatively described as cessation of initial irri-

tability and limb tenderness plus promotion in at least 2 classes of the Bleck scoring system.

At the beginning of therapy all the patients were evaluated for rickets both clinically and paraclinically (using x-rays and serum 25-OH Vitamin D levels). If there was any indication for rickets, it had been treated before starting pamidronate administration. In all the children, the bone ages corresponded to the chronologic age.

Height standard deviation score (HSDS) and weight standard deviation score (WSDS) as parameters for linear growth evaluation, as well as serum calcium, phosphate and alkaline phosphatase and urinary calcium and creatinine were assessed at the beginning of the study, and thereafter every 4 months. Bone densitometry using Dual X-ray Absorptiometry (DEXA) was performed every year for patients over than 2 years old; two girls were less than 2 years old, for which reason, the BMD assessment was performed 6 months later.

Pamidronate bisodium (1 mg/kg body weight), diluted in 500 ml of normal saline, was administered by intravenous infusion over a four-hour period, daily on three successive days (3 mg/kg/cycle). If there was a slow initial response to therapy in the first 3 cycles, the dose would be increased to 2 mg per kg/day (6 mg/kg/cycle). All the patients, except for 5, received a 9 mg per kilogram dose per year and 6 to 12 cycles of treatment. The other five children received a 3-6 mg/kg/cycle, due to their refractory fractures, severe bone pain, not responsive bone density parameters, refractory serum alkaline phosphatase or urinary calcium levels. The mean duration of treatment was 36 months (range 24-48 months) and the interval between cycles was 4 months. Each patient's calcium intake was regulated through diet by an expert nutritionist and 500 mg calcium and 200 IU Vitamin D as daily oral supplements were administered to all of the cases.

At the beginning and every 4 months thereafter, serum calcium, phosphate and alkaline phosphatase and urinary calcium and creatinine were measured regularly. In 4 patients, the pamidronate administered per cycle was increased due to refractory high serum alkaline phosphatase or urinary calcium/creatinine levels.

Height standard deviation score as a parameter for linear growth evaluation was assessed at the beginning of the study and thereafter every 4 months. Bone densitometry using Dual X-ray Absorptiometry (DEXA) was performed every year for the patients, aged over 2 years. Each patient's bone age was determined according to the Greulich and Pyle atlas. Skeletal X-rays taken before pamidronate administration and those obtained during therapy were compared for any evidence of a new fracture.

Bleck's five-point scale was used to evaluate the disability of patients to ambulate 0=bed- or wheelchair-bound, 1= able to walk with aids, but not functionally mobile, 2= able to walk in the house, with or without aids, 3= able to walk short distances, with or without aids, and 4= able to walk independently.[23]

Data were transferred to SPSS software, where the results were analyzed by paired t test, ANOVA, Tukey, Wilkakson – Krueskwalis, and Mann–Whitney rank-sum tests. Paired *t* tests were used to analyze changes during treatment. All tests were two-tailed, and a 5% significance level was maintained.

Results

Bone pain improved significantly in all 64 children, within 1 week to 1 month after the initiation of pamidronate. Only in 5 cases with BMD- z score less than -6.5 (before treatment), a recurrence of pain was observed in the weeks preceding a treatment cycle.

Mobility and ambulation were evaluated by Bleck's five-point scale. Before therapy, 18 children were able to walk independently (score 4), 13 patients able to walk short distances, with or without aids (score 3), 13

could walk in the household, with or without aids (score 2), 9 patients were able to walk with aids, but not functionally mobile and 11 of them were bed- or wheelchair-bound. Mobility was significantly improved ($p<0.05$) in all but 5 children: with scores of 3 and 2. All five had been taking the drug for less than 2.5 years.

The number of fractures per year (fracture rate) decreased from 8±4 (range 4-11) before treatment, to 0.5±0.5 per year during treatment (range 0-4) ($p<0.05$). After 16 months of treatment, there was significant improvement in bone mineral density (BMD-DEXA) z-scores of the lumbar spine from median of -5.90 (range -7.01 to -4.76) to -2.70 (range -4.46 to -1.98) ($p<0.001$). Serum alkaline phosphatase (ALP) (bone formation marker) decreased from a median of 731.0 U/L (range 438-998 U/L) to 183 U/L (range 95-286 U/L) ($p<0.001$), implying a significant reduction in bone turnover and its resorption and increase in bone mineralization (Table 2).

Table 2. Results after pamidronate therapy in 64 children with osteogenesis imperfecta

Patients	No.	BMD before Rx (z Score)*	BMD after Rx (z Score)	Alkaline Phosphatase before Rx	Alkaline Phosphatase after Rx	Fracture rate before Rx (n/y)†	Fracture rate after Rx (n/y)
Boys	35	-6.3±1.4	-3.3±1.9	782±147	144±48	7±3	0.4±0.5
Girls	29‡*	-5.5±1.1	-2.4±1.1	716±129	209±53	8±3	0.4±0.4
All	64	-5.9±1.5	-2.7±1.3	731±258	183±67	8±4	0.5±0.5

* The BMD z Score was defined as the difference between patient's bone mineral density value (lumbar vertebrae) and the mean value for age and sex-matched healthy children.; † The fracture rate before treatment was defined as the number of fractures during the last year before treatment; ‡ Analyzing by paired t test showed significant ($p<0.001$) changes in some parameters.

Fifty-one patients (80 %) had no fractures during treatment, whereas all of them had had at least 4 fractures in the year before treatment. Fracture healing was not obviously delayed and there was no instance of fracture nonunion during treatment. During therapy, systematic x-ray surveys of the epiphyses showed no evidence of widening or rachitic changes.

There was a flu-like syndrome, at least a temporary increase in body temperature, during the first infusion cycle in 57 (89%) children. Other symptoms were nasal discharge, non-productive coughing, generalized myalgia, and bone pain. These symptoms were easily controlled with 10-15 mg/kg acetaminophen and there was no recurrence during subsequent cycles. There was also a mild and asymptomatic decrease in the serum calcium levels in 23 patients, which occurred on the first day of some pamidronate cycles. Renal function tests were within normal ranges in all 64 children, during the treatment period.

There was no improvement either in patients' weight and height growth velocities or in their standard deviation scores.

Discussion

Osteogenesis imperfecta represents a phenotypically heterogeneous group of conditions that result from a number of genetic defects in the synthesis of type 1 collagen.[1] The clinical expression is primarily that of the osteopenia and bone fragility, the hallmarks of severe osteogenesis imperfecta. They result from structural abnormalities in collagen type I[1, 2, 26] and a reduced rate of osteogenesis.[6] Biochemical studies have indicated that increased resorption of bone also contributes to the disorder.[6, 27, 28] Phenotypes range from a mild form that may cause only a few childhood fractures with no deformity (type I) to the most severe form (type II), which is usu-

ally lethal in the perinatal period due to multiple fractures and marked bony deformities. Types III and IV are both associated with deformity and are the most difficult to manage clinically.[1, 2]

In this study, all children, but 11, had type II or III, the severe forms of the disease.

The study validity increased as the children with less severe types of the disease (having less than 4 fractures per year) were not included in this study. The initial goal of this study was to reduce bone resorption and to increase bone mass in children with this disease. Bisphosphonates are potent inhibitors of bone resorption.[29] These drugs are currently used to treat adults' osteoporosis and increased bone fragility.[19,30-32] However, there are limited experiences available on the efficacy and safety of these compounds in children. Three children have been described who received bisphosphonates before the age of 2 yr,[33, 34] and in another study, nine patients treated under the age of 3 yr.[35] There is a double blind trial of bisphosphonate therapy.[35] This study in an open study design and used a before-after comparison method using paired t test. Placebo compounds were not used in children with severe types of the disease on ethical grounds.

Cyclic administration of intravenous pamidronate resulted in a rapid increase in mineral density of the lumbar vertebrae, resulting from an improvement in the balance between bone formation and bone resorption.[13] Serum concentrations of alkaline phosphatase, a marker of bone resorption significantly decreased in this study (Table 2). This result indicates that the rate of bone turnover declined during therapy as a result of changes in the balance between formation and resorption that favored an increase in bone mass. However, a decrease in resorption shows neither a compromise in bone growth nor a fracture healing independently.[34] The bone mineral density of the lumbar spine, as measured by BMD - DEXA, is an area-related measurement that is affected by both true bone mineral density and the volume of the vertebral body[19,35, 36] Using z scores for bone mineral density, ensured observation of any/all changes in volume caused by the growth.[37] In all children in our study, the z scores improved during therapy, suggesting that pamidronate has a positive effect on bone mineral density. If there was any decrease in vertebral-body size due to crush fracture, which could increase bone mineral density, the bone densitometry was postponed till healing was achieved to get better results. The vertebral area increased in all children, with radiographs showing evidence of new bone formation. Improvement in mobility was considered as an effective factor in producing such changes. Literature shows that the mechanical strain of walking can stimulate new bone formation.[38]

There was an overall decrease in the rate of fractures, even though the risk of fractures may have increased in some individual cases with improved mobility and greater activity for the child. On the other hand, fracture incidence is a weak efficacy parameter in open therapeutic studies of OI patients, as it can be influenced by external factors, *e.g.* mode of handling, mobility, and may spontaneously decrease with age.[39] In spite of the higher risk of injury due to increased mobility, a significant difference compared to the fracture rate in the age-matched control group was noted, implying a direct effect of the therapy.

Besides, there was an improvement in chronic pain in all cases even as early as the first cycle of drug administration. In children with severe osteogenesis imperfecta, the weight and height growth velocities are greatly decreased before the mid-childhood, and growth rate almost stops thereafter,[39] Although some studies indicated that using pamidronate can improve both these,[13, 34] in this study however we were unable to find any significant improvement either in the weight or height growth rates. The sclerotic lines, demonstrating the continued growth of bone during therapy that appear mostly in the metaphyses have no known functional importance.[40] Impairment of mineralization and

widening of the growth plates have been reported.[13, 41] None of these complications however were observed in any of our 64 children during therapy.

Urinary excretion of the *N*-telopeptide of type I collagen, urinary deoxypyridinoline and serum osteocalcin are good markers of bone turnover, and have been used in some studies as an indicator for response to therapy;[26, 27] however, neither were these nor successive radiologic examinations of the thoracic and lumbar regions of the spine and limbs used in this study.

Further Recommendations

This medical therapy cannot be used alone, but should be considered a part of a multidisciplinary approach to the treatment of children with severe osteogenesis imperfecta. To achieve better results, reconstructive surgery, physiotherapy, occupational therapy, and alterations in the child's diet must be considered while defining such an approach. Continued follow-up is needed to show the final outcome of therapy over time.

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