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Pamidronate Treatment of Severe Osteogenesis Imperfecta in Children under 3 Years of Age*

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ABSTRACT

Severe osteogenesis imperfecta (OI) is a hereditary disorder characterized by increased bone fragility and progressive bone deformity. Cyclical pamidronate infusions improve clinical outcome in children older than 3 yr of age with severe OI. Because earlier treatment may have potential to prevent deformities and improve functional prognosis in young children, we studied nine severely affected OI patients under 2 yr of age (2.3–20.7 months at entry) for a period of 12 months. Pamidronate was administered iv in cycles of 3 consecutive days. Patients received four to eight cycles during the treatment period, with cumulative doses averaging 12.4 mg/kg. Clinical changes were evaluated regularly during treatment, and radiological changes were assessed after 6–12 months of treatment. The control group consisted of six age-matched, severely affected OI patients, who had not received pamidronate treatment. During treatment bone mineral density (BMD) increased between 86–227%. The deviation from normal, as indicated by the z-score, diminished from -6.5 ± 2.1 to -3.0 ± 2.1 ($P < 0.001$). In the control group the BMD z-score worsened significantly. Vertebral coronal area increased in all treated patients (11.4 ± 3.4 to 14.9 ± 1.8 cm^2; $P < 0.001$), but decreased in the untreated group ($P < 0.05$). In the treated patients, fracture rate was lower than in control patients (2.6 ± 2.5 *vs.* 6.3 ± 1.6 fractures/year; $P < 0.01$). No adverse side-effects were noted, apart from the well known acute phase reaction during the first infusion cycle. Pamidronate treatment in severely affected OI patients under 3 yr of age is safe, increases BMD, and decreases fracture rate. (*J Clin Endocrinol Metab* **85:** 1846–1850, 2000)

OSTEOGENESIS IMPERFECTA (OI) is a heritable disorder characterized by increased bone fragility. Four discrete types are commonly distinguished on the basis of clinical and genetic features (1). Type I OI comprises patients with mild presentation and normal height, whereas type II OI is lethal in the perinatal period. Type III OI is the most severe form in children surviving the neonatal period. These patients have a well defined phenotype, including extremely short stature, growth plate abnormalities, and progressive limb and spine deformities secondary to multiple fractures. Patients with a moderate to severe phenotype who do not fit into one of the above categories are classified as type IV OI. In many, but not all, OI patients, mutations of the genes coding for procollagen type I chains are identifiable (2).

Medical treatment of OI has long been largely ineffective in altering the course of the disease. We recently reported that cyclical iv treatment with pamidronate (3-amino-1-hydroxypropylidene-bisphosphonate) is of benefit to children with severe forms of OI (3). Bone mineral density (BMD) and physical activity increased markedly in these patients, and fracture rate decreased. These children were more than 3 yr of age when treatment was started and already had serious functional disabilities. In an attempt to prevent these functional limitations, we extended the treatment protocol to children less than 3 yr of age. Here we report on the first nine infants with severe OI who completed 12 months of therapy with pamidronate.

Subjects and Methods

The treatment group was made up of nine children with severe OI (Table 1). Eight patients were diagnosed as having type III OI, and one had type IV OI (1). The clinical course in these children during the first 12 months of treatment was compared to corresponding findings in a group of historical controls. The control group consisted of severe OI patients who were first seen at our institution before the age of 2 yr, had a follow-up without pamidronate treatment of at least 12 months, and had a starting BMD z-score below −3. Six children (3 boys), aged 10.7 ± 4.5 months (mean ± SD; $P = 0.95$ compared to baseline age of treated group), fulfilled these criteria (Table 2). These were first examined at our institution between 1991 and 1997, before the current study was started, and received the same multidisciplinary care as the treated patients, including physiotherapy and occupational therapy assessment and intervention.

Treatment

Pamidronate (Aredia, Novartis, Dozval) was administered iv in cycles of 3 consecutive days. As no previous experience with this drug in this age group was available, cycles were initially given every 4 months, as in older children (3), but using a lower dosage (0.5 mg/kg·day). However, it was noted that after 6–8 weeks the patients started to show signs of discomfort, suggesting that the effects of the drug were diminishing. The reason for this could be the more rapid turnover and growth of the skeleton during infancy. The interval between treatments was therefore shortened to 6–8 weeks. For this reason, there was variability

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TABLE 1. Demographical characteristics and treatment data for treated patients and controls

Subject no. (sex)	Type	Age at start (months)	Wt at start (z-score)	Wt after 12 months (z-score)	Ht at start (z-score)	Ht after 12 months (z-score)	Infusion cycles (no.)	Cumulative dose (mg/kg · yr)
Patients								
1 (m)	III	16.6	−4.2	−3.0	−8.1	−6.6	4	10.5
2 (m)	IV	10.0	−2.8	−1.4	−3.0	−1.6	4	8.5
3 (m)	III	2.3	−1.6	−2.3	−4.1	−2.0	8	14.5
4 (f)	III	2.6	−3.6	−4.9	−7.7	−6.8	6	11.3
5 (f)	III	20.7	−5.4	−5.5	−10.6	−9.0	7	15.3
6 (f)	III	6.2	−4.1	−1.6	−9.5	−5.0	6	14.5
7 (m)	III	17.0	−4.1	−3.3	−10.0	−8.2	7	17.5
8 (f)	III	6.0	−4.6	−4.9	−8.5	−6.5	7	10.8
9 (m)	III	14.0	−4.8	−4.6	−8.2	−6.3	5	8.8
Mean		10.6	−3.9	−3.5[a]	−7.7	−5.8[b]	6.0	12.4
SD		6.8	1.1	1.5	2.6	2.5	1.4	3.1
Controls								
1 (m)	III	16.8	−3.5	−1.6	−5.6	−2.6		
2 (f)	IV	7.2	−1.0	−1.1	−3.0	−1.7		
3 (m)	III	10.8	−2.5	−3.7	−5.3	−5.9		
4 (f)	III	13.2	−5.1	−5.0	−7.0	−7.2		
5 (m)	III	12.0	−0.8	0.6	−0.4	−0.8		
6 (f)	IV	4.0	1.4	0.2	−1.0	−2.0		
Mean		10.7	−1.9	−1.8[a]	−4.5	−3.7[a]		
SD		4.5	2.3	2.2	1.2	2.7		
P		0.95	0.04	0.09	0.01	0.09		

The *P* value indicates significance of difference between treated and control groups.
[a] No significant difference compared to baseline ($P > 0.05$).
[b] Significant difference compared to baseline ($P < 0.005$).

TABLE 2. Changes in lumbar spine (L1–L4) bone mineral density, vertebral area, and fracture rate in treated patients and controls

Subject no.	Bone mineral density		Vertebral area		Fracture rate (fractures/yr)
	At start (z-score)	After 12 months (z-score)	At start (cm^2)	After 12 months (cm^2)	
Patients					
1	−7.9	−2.8	14.7	16.7	1
2	−5.5	−1.2	15.5	16.9	1
3	−3.0	−0.4	6.7	16.5	6
4	−4.3	−0.1	7.3	11.8	0
5	−9.0	−4.8	13.6	14.6	6
6	−5.8	−3.0	9.3	15.6	1
7	−9.3	−4.0	15.3	15.9	0
8	−6.3	−6.0	9.9	13.0	4
9	−7.7	−4.8	10.5	13.4	4
Mean	−6.5	−3.0[a]	11.4	14.9[a]	2.6
SD	2.1	2.1	3.4	1.8	2.5
Controls					
1	−5.1	−7.1	18.2	13.7	4
2	−4.4	−6.0	16.5	12.9	7
3	−6.5	−7.6	16.4	11.3	8
4	−4.7	−5.9	13.5	7.7	5
5	−3.1	−3.1	16.2	16.1	8
6	−3.4	−4.0	18.9	17.0	6
Mean	−4.5	−5.6[a]	16.6	13.1[a]	6.3
SD	1.2	1.7	1.9	3.4	1.6
P	0.06	0.02	0.008	0.19	0.005

The *P* value indicates significance of difference between treated and control groups.
[a] Significant difference compared to baseline values ($P < 0.001$).

in the number of infusions and in the cumulative dose each patient received during the first year of treatment (Table 1).

The drug was diluted in normal saline to a final concentration of at most 0.1 mg/mL and was administered over 4 h. Four patients received the drug through a sc Infuse-a-port system (Bard Canada, Missisauga, Ontario, Canada). In the others, a Teflon catheter was inserted in a peripheral vein and left in place for the entire infusion cycle. All patients had a daily intake of vitamin D of at least 400 IU/day, and calcium intake was at least 600 mg/day. All subjects underwent specific physiotherapy and occupational therapy evaluation and intervention, including exercises and provision of special seating devices.

Clinical studies

Fractures were confirmed by radiologists blinded to the treatment status of the subjects. Spine compression fractures were not included in the analysis, because no normative data for vertebral morphometry are available in children; therefore, it is not possible to accurately define vertebral fractures. Due to the spontaneous decrease in fracture rate in OI patients in this age group, the fracture rates before and after treatment were not comparable. Instead, the fracture rates during the 1-yr period of observation for treated patients and controls were compared, considering that age and severity were not significantly different in the two groups. Weight and height measurements were converted to age- and sex-specific z-scores using Canadian reference data (4).

Radiological studies

X-Rays were obtained at baseline and after 6–12 months of treatment. Areal BMD and coronal area in the antero-posterior direction were determined at the lumbar spine (L1–L4) using either a QDR 2000 device (controls) or a 4500A device (patients) (Hologic, Inc., Waltham, MA; entrance radiation dose, <5 mRem). Each subject was studied with the same model of densitometer. All densitometry studies were performed using a pediatric (low density) software. BMD results were transformed to age-specific z-scores combining reference data from Salle *et al.* (5) and data provided by the densitometer manufacturer.

Laboratory studies

Serum calcium was measured before and after each infusion using a colorimetric method (Monarch, Instrumentation Laboratory, Inc., Lexington, MA). Serum PTH levels were determined by RIA (6) before and after the first infusion cycle and before each of the infusion cycles thereafter.

Statistical analysis

Differences between treatment and control groups were tested for significance using unpaired *t* tests. Paired *t* tests were used to analyze changes during treatment. All tests were two-tailed, and a 5% significance level was maintained.

The study was approved by the Shriners Hospital institutional review board, and informed consent was obtained from legal guardians.

Results

Pamidronate infusions lead to a mild drop in serum calcium from normal pretreatment values (2.3–2.6 mmol/L) to levels between 1.8–2.1 mmol/L. These hypocalcemic events were noted in seven patients during the first treatment cycle, but subsequently became less marked and less frequent. There were no associated clinical symptoms.

Serum PTH levels responded appropriately to the decreased calcium concentration to reach values up to twice the upper limit of the reference range (data not shown). However, levels consistently returned to pretreatment values by the time of the next treatment cycle.

Pretreatment BMD was below the lower limit of the reference range in all subjects (Fig. 1). In all treated children BMD had increased by the time of the second infusion cycle. This trend continued thereafter, resulting in a rise between 86–227% during the study period ($P < 0.001$). The increase in absolute BMD values translated into significantly higher BMD z-scores for all infants (Table 2). The control group tended to have a higher BMD z-score than the treated group in the baseline evaluation. During the observation period, a significant decrease in the BMD of controls was noted. Thus, mean BMD z-score in controls was significantly lower than that in the treated group at the end of the observation period (Table 2).

Before treatment, all patients presented severe vertebral body deformities, such as biconcave, flattened or wedged vertebrae, with very thin or undetectable distal plates. No new vertebral compressions were observed during the course of the study, but, rather, an increase in vertebral size on the lateral view of the spine was found (Fig. 2). Similarly, vertebral body area measured as part of the densitometric studies increased significantly during treatment (Table 2). In contrast, a significant decrease in vertebral area occurred in all control subjects ($P < 0.05$; Table 2).

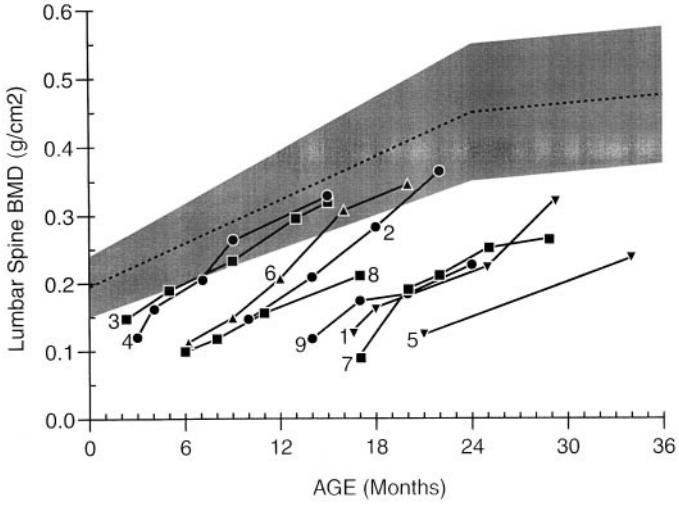

FIG. 1. Changes in BMD of the lumbar spine (L1–L4) in nine children under 3 yr of age affected with severe osteogenesis imperfecta who were treated with cyclic administration of iv pamidronate for 1 yr. The numbers refer to the patient numbers in Tables 1 and 2. The *shaded area* represents the normal range (mean ± 2 SD) for age-matched healthy children.

Other radiological changes included an increase in cortical thickness and decreased deformities of long bones in all patients (Fig. 3). The previously described parametaphyseal dense lines corresponding to each treatment cycle were evident in all patients (3, 7, 8).

Clinical characteristics of individual patients before and during treatment are shown in Table 1. There was a large interindividual variation in weight and height, reflecting the heterogeneity of OI. Compared to measurements obtained at birth, there was a significant decrease in mean z-scores of both weight (-1.2 ± 1.6 to -3.9 ± 1.1) and height (-2.4 ± 1.7 to -7.7 ± 2.6) by the time treatment was started ($P > 0.001$), confirming the delay in physical development typically associated with severe OI (9). All patients were short for age before treatment, and their height z-scores increased significantly during treatment ($P = 0.004$).

All children included in this study had a history of multiple fractures, often without recognizable trauma. During the treatment period, the fracture rate was significantly lower in the treated group. Those fractures occurred after moderate trauma. Pamidronate did not compromise fracture healing.

Signs of bone pain, such as crying during handling and autoimmobilization of a limb, were present in all children before therapy was instituted. Within 1 week after the start of treatment signs of bone pain disappeared. All but one patient acquired head control and the ability to maintain a sitting position by the end of the treatment period.

All patients underwent the well known acute phase reaction after the first infusion, with short term fever up to 38.5 C (10). No other side-effects of treatment were noted.

Discussion

Bisphosphonates are a class of drugs that are potent inhibitors of bone resorption (10). These compounds are widely used to treat adults suffering from bone loss and increased bone fragility (11–13). However, very little experience is available on the effect of these drugs in small children. To our knowledge, only three children have been described who received bisphosphonates before the age of 2 yr (8, 14). Although double blind trials of bisphosphonates have been proposed (8), we judged it unethical to perform placebo infusions in this age group. Therefore, we chose an open study design and compared the results in the treated children to those in a historical control group of patients recently seen in our unit.

In this group of infants under 3 yr of age, the response to treatment appeared to be faster and more pronounced than what we had observed in older children (3). Signs of bone pain disappeared within days, and an increase in BMD was evident as early as 6 weeks after the start of treatment. Without exception, the gain in BMD was greater than the increase expected in healthy children. In contrast, a decrease in BMD occurred in the untreated controls. This strongly suggests

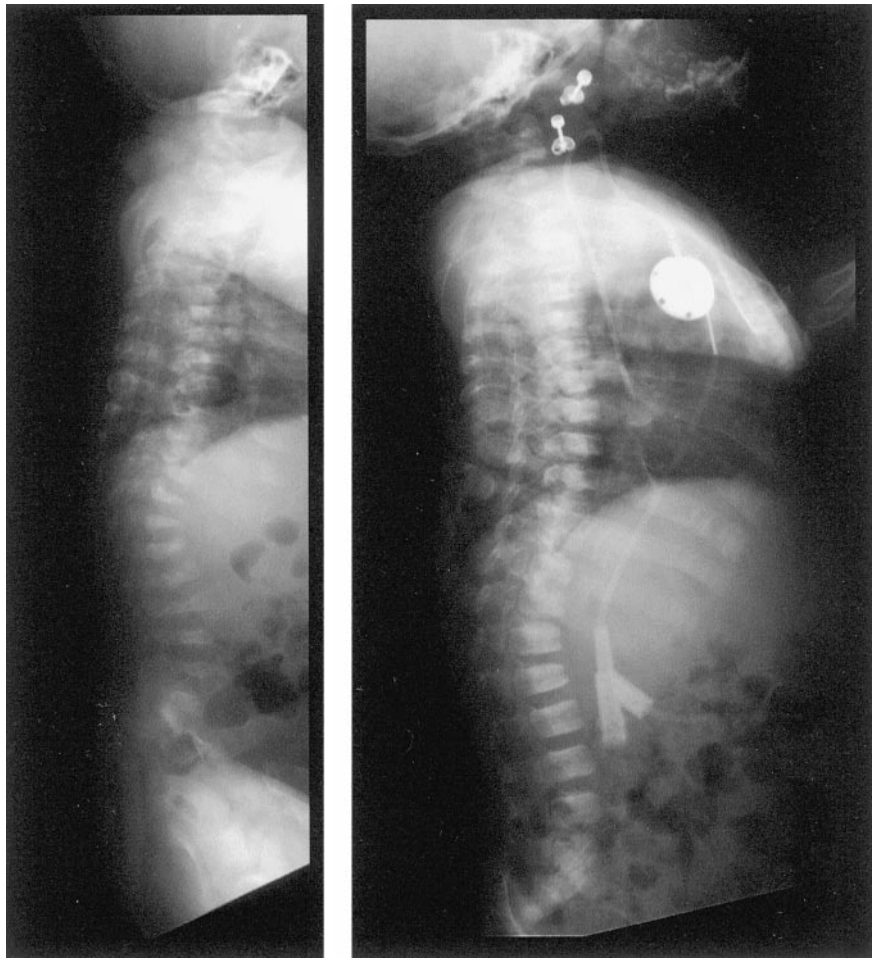

FIG. 2. Radiographs of the lumbar spine (lateral view) of patient 3 before (*left*) and after (*right*) 9.5 months of treatment with pamidronate.

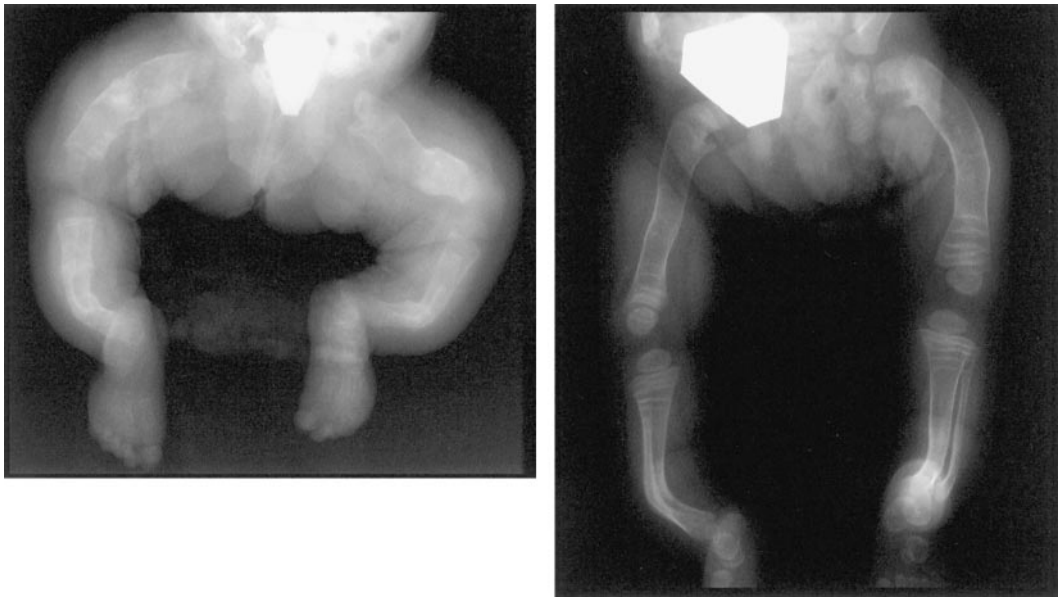

FIG. 3. Radiographs of the lower limbs of patient 3 before (*left*) and after (*right*) 9.5 months of treatment with pamidronate.

that the observed changes reflect a drug effect rather than the passing of time or the natural evolution of the disease.

Vertebral size increased in all treated children, as expected in growing individuals. In contrast, a decrease in vertebral size was noted in all untreated children, indicating that vertebral collapse had occurred in these patients. Thus, it appears that pamidronate infusions not only increased lumbar spine BMD, but also protected bone integrity. This view is

further strengthened by the readily apparent reshaping of both vertebrae and long bones.

Concomitant with these radiological changes, fracture rate decreased significantly. 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 (9). Despite the higher risk of injury due to increased mobility, we noted a significant difference from the fracture rate in the age-matched control group, suggesting a direct effect of the therapy.

During each treatment cycle, a drop in serum calcium induced a transitory increase in PTH levels. The design of the study did not allow us to fully document the time course of these variations. We thus cannot evaluate a possible effect of these bursts of PTH secretion on the increase in BMD. Indeed, PTH has been advocated for treatment of osteoporosis in adults (15, 16).

Although cyclical pamidronate infusions were of clear benefit to our patients, the effect of therapy on growth is an issue of concern in young children. In animal studies, long term treatment with bisphosphonates did not affect growth, unless very high doses were administered (17). In our group of patients, as in the older children recently studied (3), pamidronate did not have a detrimental effect on growth. To the contrary, the data show an increase in z-score in all treated children and no significant changes in the control group.

Pamidronate does not alter the genetic defect underlying OI and therefore is a symptomatic, not a curative, treatment. It is unclear at present how long this treatment should be continued. It is also not known which is the optimal treatment schedule and whether other bisphosphonates have a similar or better effect on the clinical course of the disease. These issues should be addressed in further studies.

In conclusion, cyclical pamidronate infusions markedly improve bone density and decrease fracture rate in severely affected OI patients less than 2 yr of age without causing major adverse side-effects. These encouraging results warrant continuation of the evaluation of this therapeutic approach.

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