# Low-dose intravenous pamidronate treatment in osteogenesis imperfecta

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**SUMMARY: Gökşen D, Çoker M, Darcan Ş, Köse T, Kara S. Low-dose intravenous pamidronate treatment in osteogenesis imperfecta. Turk J Pediatr 2006; 48: 124-129.**

**Different therapy models have been tried in order to decrease bone resorption in osteogenesis imperfecta. Bisphosphonates are a group of drugs that mainly suppress osteoclast-mediated bone resorption, thus reducing bone turnover. We assessed the effects of low-dose bisphosphonate treatment in children with osteogenesis imperfecta.**

**Sixteen osteogenesis imperfecta patients (12 female, 4 male) with severe deformities were treated with cyclic (3-4 mg/kg/year) intravenous infusions of bisphosphonate (Aredia-Novartis) therapy for a period ranging from 0.6 to 4.7 years (mean 2.50±1.09 years).**

**Bone mineral density increased from 0.304±0.146 g/cm$^2$ to 0.362±0.142 g/cm$^2$ in the first year and to 0.421±0.146 g/cm$^2$ in the second year. A clinical response was shown with a reduction in fracture rate and improvement in mobilization scores. Fracture rates decreased from a median of 4/year (0-30/year) before treatment to 0/year (0-5/year) during treatment. Ambulation improved in 10 children and remained unchanged in three. Two of the children were fully functional before therapy and one was below two years of age. No adverse effects were seen with pamidronate infusions of 7-10 mg/kg/year (monthly) or with 4 cycles/year 3-4 mg/kg/year.**

**Low-dose cyclical pamidronate infusions markedly increased bone density and decreased bone fracture rate and should be considered as a part of a multi-disciplinary treatment.**

***Key words: osteogenesis imperfecta, pamidronate, bone mineral density, children.***

Osteogenesis imperfecta (OI) is a genetic disorder characterized by qualitative and/or quantitative abnormalities in type 1 collagen resulting in bone fragility, osteopenia and recurrent fractures with progressive skeletal deformities[1,2]. Different kinds of drugs have been used in attempts to increase bone mass and to decrease fracture rate but none has resulted in improvement[3].

Bisphosphonates are inhibitors of bone resorption and have beneficial effects in children with OI[2,4-9], but the optimal dose and cycle frequency have not been established. Glorieux[3] used 9 mg/kg/year on three consecutive days with 4-12 cycles of treatment. Plotkin et al.[1] administered 9 mg/kg/year of pamidronate in cycles of three consecutive days every 6-8 weeks to children less than three years of age. In this group, bone pain disappeared and the gain in bone mineral density (BMD) was evident as early as six weeks. Gonzales[10] administered a dose of 2-4 mg/kg/year of pamidronate in three children, who reached the lower limit of the normal range after three years of treatment. Astrom[4] revealed a significant increase in median total body BMD values with monthly infusions of 10-40 mg/m$^2$ pamidronate during two years of treatment.

Our study was designed to show the effects of low-dose bisphosphonate treatment (3-4 mg/kg/year once daily therapy with 4 cycles/year) in children with OI.

## Material and Methods

Patients: Between January 1999 and 2003, pamidronate (Aredia-Novartis) was administered to 16 OI patients (12 female, 4 male), with ages ranging from 1.2 to 11.9 years (Table I) in Ege University Faculty of Medicine, Department of Pediatric Endocrinology and Metabolism. Fourteen had completed one year of treatment, 12 of them two years, five of them three years and one four years of therapy at the time of the evaluation. All but seven had severe restrictions in ambulation because of severe deformities. Nine of them were below the third percentile for height. OI was classified according to clinical findings. Two children were classified as type 1, and 14 as type 3 and type 4. Clinical evaluation was performed and anthropometric variables were recorded at each visit. Height was measured without shoes with a wall-mounted Harpenden stadiometer. Weight was measured without shoes on a standard balance to nearest 100 g. Height and weight SD of patients were determined according to Neyzi[11].

Treatment protocol: Pamidronate disodium (3-amino-1-hydroxypropylidene-bisphosphonate) was given in a dose of 7-10 mg/kg/year monthly to the patients at the beginning. The treatment regimen for all patients was changed (to cyclical therapy 3-4 mg/kg/year once daily therapy with 4 cycles/year) after femur operations in two patients when the surgeon (subjective criteria) observed that the bones were fragile and showed the characteristics of osteopetrosis macroscopically. Three of the patients received pamidronate every month for the first year and then every three months for the second year. Two patients received pamidronate every month for the first eight months and then every three months for the second year. Eleven patients received pamidronate every three months from the start of therapy (Table I). Pamidronate disodium was diluted in 150 ml of isotonic saline and administered by slow infusion over a three-hour period and patients were rehydrated with 150 ml of isotonic saline one hour before and after therapy.

The patient's calcium (Ca) intake was evaluated regularly and was maintained at normal levels with 800 mg/day Ca and 1000 IU/day vitamin D at the beginning, but tapered later according to laboratory changes.

Laboratory evaluation: Fasting blood and urine (from the second morning voiding) and 24-hour urine were obtained before each infusion of pamidronate and blood alone on the third and fifth day of infusion. Serum and urine concentrations of Ca, phosphate, and creatinine and serum concentration of alkaline phosphatase were measured in order to maintain normocalcemia during and after therapy.

**Table I.** Demographical Findings Before and During Treatment and Treatment Data of the OI Patients

| Patient no. | Age/years | Height SDS | | | | Duration of therapy (years) | Treatment cycles |
|---|---|---|---|---|---|---|---|
| | | Start | 1st year | 2nd year | 3rd year | | |
| 1 | 3.90 | 0.27 | -1.26 | -2.67 | | 2.75 | b |
| 2 | 10.15 | | | | | 2.00 | b |
| 3 | 10.30 | -5.90 | -5.18 | -5.5 | -5.50 | 3.75 | a |
| 4 | 5.23 | -2.36 | -2.18 | -2.15 | -1.46 | 3.00 | a |
| 5 | 6.45 | -2.72 | -2.62 | -2.54 | | 2.50 | b |
| 6 | 9.48 | | | | | 3.75 | a |
| 7 | 1.02 | 1.30 | 0.28 | -0.46 | | 2.50 | a |
| 8 | 11.25 | -0.16 | 0.04 | 0.14 | | 2.50 | b |
| 9 | 11.42 | -0.38 | -0.86 | -0.63 | -1.42 | 4.75 | b |
| 10 | 6.35 | -3.13 | -4.25 | -5.32 | | 2.50 | a |
| 11 | 8.87 | -6.34 | -6.96 | -7.02 | | 2.75 | b |
| 12 | 11.93 | -2.56 | -1.57 | -1.95 | | 3.50 | b |
| 13 | 8.51 | -0.17 | -0.31 | -0.40 | | 2.00 | a |
| 14 | 9.98 | -6.10 | -0.60 | | | 1.25 | b |
| 15 | 1.25 | -3.43 | | | | 0.75 | b |
| 16 | 10.91 | -3.96 | | | | 0.50 | b |
| mean±SD | 7.93±3.53 | -2.54±2.48 | -2.12±2.2 | -2.59±2.38 | -2.79±2.3 | 2.54±1.11 | |

a: Every month/year for the first year; every three months/year for the second year.
b: Every three months.
*Height of patients 2 and 6 were not measured because of severe deformities.

Bone densitometry measurements were performed at the beginning and at the end of the first, second and third year of therapy. BMD of the lumbar spine was measured by dual energy X-ray absorptiometry (Hologic QDR 4500A). BMD z-score for age was calculated for each child on each measurement according to normal values calculated for Turkish children. Reference values and z-scores were obtained from a large population of Turkish children[12] consisting of a total of 345 Caucasian children aged between 2 and 18 years (176 girls and 169 boys).

Bone mineral density z-score for patient number 15 was not evaluated because she was below one year of age and we do not have normal values for Turkish children less than two years of age.

Motor performance of the patients was scored at each visit. Mobility and ambulation were assessed using a five-point scale as follows: 0 (bed- or wheelchair-bound), 1 (walking possible but not functional enough to be useful), 2 (household walker), 3 (able to walk short distances), and 4 (able to walk independently, community walker)[6]. Annual fracture incidence was estimated for two years before treatment and throughout the treatment period based on subjective clinical observations from the patients/parents before the treatment period and based on X-rays during treatment.

Since OI is a heterogeneous disease with wide variations between individuals, this study was designed as a comparison in a given patient before and during therapy.

Statistical analyses were performed with paired t-tests and Wilcoxon signed rank test where appropriate with SPSS package program. Variance analyses were performed according to incomplete block design. Whenever the time between the measurements was important, Bonferroni test was used. Since the number of patients were not equal in each visit, incomplete block design was used instead of ANOVA in the analyses of BMD z-scores, height standard deviation score (SDS) and biochemical parameters.

## Results

Effects on growth: Accurate records for growth rate could not be obtained in two patients because of severe deformities (Patients 2 and 6) (Table I). Height SDS before treatment was –2.54±2.48. Height SDS during treatment for the first and second years was –2.12±2.26 and –2.59±2.38, respectively. There was no significant difference between height SDS with univariate analyses of variance (p= 0.44) (Table I).

Biochemical changes: Before treatment all children had normal serum Ca and phosphorus concentrations. There was no change in serum Ca and phosphorus levels after each cycle except for the first treatment cycle. Mean serum alkaline phosphatase values at the beginning, and at the first, second and third year were 512±257.7, 413.5±183.2, 388.2±127.0 and 492.6±182.5 IU (due to fractures in the third year), respectively. Although there were steady decreases in the serum concentrations of alkaline phosphatase in the second and third years, the difference was not statistically significant.

Bone mineral density changes: Mean BMD increased from 0.304±0.146 g/cm$^2$ to 0.362±0.142 g/cm$^2$ in the first year, to 0.421±0.146 g/cm$^2$ in the second year and to 0.457±0.149 g/cm$^2$ in the third year (Table II). BMD z-scores of the patients according to age are given in Table II/Figure 1. Differences between BMD z-scores were important according to variance analyses with incomplete block design.

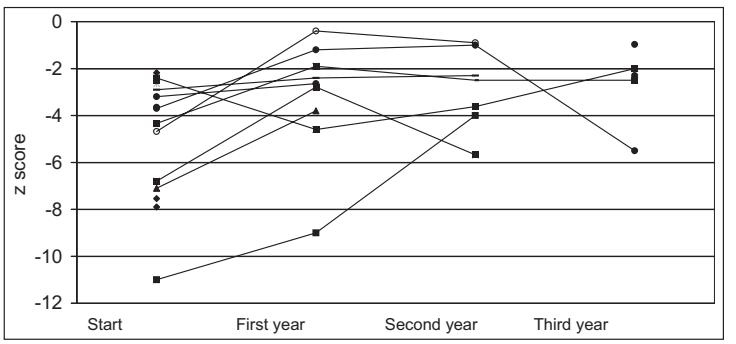


**Fig. 1.** BMD L1-L4 z scores of the children during treatment.

Clinical outcome: Thirteen of the 16 patients were confined to a bed or a wheelchair, whereas two patients used exercise walker. One patient was not included in the evaluation of mobilization because her age was under two years. Ambulation scores increased in 10 children: 4 gained four grades, 6 gained one. In three children, no change was noticed. Before therapy, two children were fully functional. Fracture rates decreased from a median of four per year (range: 0-30) to 0 per year (range: 0-5). Fracture rates decreased in 11 patients, increased in two patients (mobilization scores of these patients increased) and were unchanged in three patients.

The most common side effects of pamidronate, pyrexia and hypocalcemia, were observed in only three patients after first infusion.

**Discussion**

Structural abnormalities of the bone tissue and increased resorption in OI often result in osteopenia and bone fragility[3]. The goal of treatment is to reduce bone resorption and to increase bone mass. Bisphosphonates, potent inhibitors of bone resorption, are used in adults for bone loss and increased fragility and for OI and other childhood osteoporotic conditions[1,5,9]. In this prospective, clinical trial we observed increased areal lumbar spine BMD z-scores, decreased fracture rate and improved mobility with pamidronate therapy.

There are several oral and intravenous bisphosphonate protocols for OI. In this study, Astrom's[4] protocol was chosen because they had shown significant increases in lumbar spine BMD z-scores in two years with one-day monthly therapy. We think that a one-day hospitalization is far more acceptable than the three consecutive days as used in other protocols.

Short stature is frequent in OI and correlates with the type of the collagen defect[7]. Pamidronate therapy is a concern for growing children[1,13]. In our children, height SDS was decreased before treatment and we did not observe any changes in height SDS during therapy. In some studies, height SDS scores in all treated children showed an increase[1,3], whereas in Bambi's study[5] in three children, linear growth continued along the same percentile as at the start of treatment. Zeitlin[14] showed a significant height gain in moderately to severely affected OI patients with four years of cyclical intravenous pamidronate treatment. Although serum concentrations of alkaline phosphatase decreased during treatment, there was no significant difference. This could be due to fractures occurring during the treatment period.

It is known that BMD in growing children increases 3-6% per year before puberty and by 14-16% per year during puberty[7,15]. In Glorieux's[3] study the children received an average of 2.1 years of treatment and had a mean BMD z-score increment of 1.9 with 9 mg/kg/year of intravenous pamidronate therapy. At the end of two years of treatment in our study with 3-4 mg/kg/year with three-month intervals, the increment in lumbar BMD z-score was 2.1. BMD z-scores in the third year were the same as the second year because two of the patients had fractures (Patients 3 and 12) during the third year and were immobile. These fractures were actually a positive effect of treatment. In the third year, these children were able to walk and jump and thus fractures most probably occurred because of increased mobility. Falk[16], using the same treatment protocol as Glorieux[3], demonstrated an increase in areal BMD z-scores by an average of 1.0 annually during a study period of two years. Plotkin et al.[1] experienced a more rapid response to treatment (0.5 mg/kg pamidronate in cycles of 3 consecutive days every 4 months) in infants less than three years of age compared to the older children. In this group, bone pain disappeared and the increase in BMD was evident in as early as six weeks. Although Astrom[4] did not evaluate changes in z-scores with monthly infusions of 10-40 mg/m$^2$ pamidronate, she revealed a significant increase in median total body BMD values of 0.106 g/cm2 ($p<0.001$) and in median lumbar values of 0.248 g/cm$^2$ ($p<0.001$) during two years of treatment. Gonzales[10] achieved the lower limit of the normal range after three years of treatment (2-4 mg/kg/year of pamidronate) and reduced bone pain and fracture rate in three children. It is known that BMD is influenced by height in children, and BMD z-scores should be evaluated according to height or volumetric values. Since height SDS of our patients did not change during evaluation we used BMD z-scores according to age determined for Turkish children[12].

It is known that fracture incidence is a weak efficacy parameter in OI patients as it can be influenced by external parameters (mode of

handling, mobility) and may spontaneously decrease with age[1,2]. In our study, the decrease in fracture rate was significant. Lindsay[17] showed that fracture rates can be reduced by 60% in children with OI with bisphosphonates, and by 80% in older, prepubertal girls. As in our study, Falk[16] observed new fractures during therapy but these occurred in the context of activities that children were previously unable to perform.

At the beginning of therapy we observed that bone pain disappeared and the bedridden children wished to sit up and then later to stand up. The time spent sitting and standing up increased as the treatment evolved. The children who started to stand up wanted to walk. At the end of the second year of therapy, 11 children were able to walk. This was one of our major goals. In the study of Bambi et al.[5], mobility and ambulation improved in 16 children and remained unchanged in 14 of them. The disappearance of bone pain and decreased fracture incidence may contribute to increased mobilization scores[2].

Pamidronate is a symptomatic treatment and it is not clear how long the treatment should be continued. The optimal dose and frequency of intravenous pamidronate have not been established. Glorieux[3] used 9 mg/kg/year on three consecutive days with 4-12 cycles of treatment. Plotkin et al.[1] administered 9 mg/kg/year of pamidronate in cycles of three consecutive days every 6-8 weeks to children less than three years of age. We started in the beginning with a dose of 7-10 mg/kg/year as in other studies[18], but the treatment regimen was changed to 3-4 mg/kg/year after femur operations in two patients revealed bone fragility and showed the characteristics of osteopetrosis macroscopically. In view of the obvious restrictions on the lives of both the child and other family members, we preferred once daily therapy with four cycles/year in contrast to the other therapies requiring three days of hospitalization with 3-4 cycles/year.

In conclusion, cyclical pamidronate infusions markedly increase bone density and decrease bone fracture rate, but should be considered as a part of a multidisciplinary treatment. At present there is no consensus regarding the treatment protocol and dosing regimen in children with OI. Our regimen with a lower dose every third month resulted in increased bone mineral density and mobilization of the children with OI (9 mg/kg/year vs. 3-4 mg/kg/year). The overall positive results and absence of adverse effects may be sufficient to recommend the use of a low-dose treatment protocol for all children with OI. With pamidronate therapy, these children are able to participate more actively in occupational therapy and achieve more independence during daily activities. As there are no long-term safety data available in children and potential side effects are unknown, it is important to follow the patients into late adulthood.

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