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Zoledronic Acid Treatment in Children with Osteogenesis Imperfecta

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Key Words

Osteogenesis imperfecta · Bisphosphonates · Fracture · Bone mineral density · Bone turnover

Abstract

Background: Intravenous disodium pamidronate has become an established treatment in osteogenesis imperfecta (OI). Another bisphosphonate, zoledronic acid, has been indicated for the treatment of adult osteoporosis. We studied its efficacy and safety in children with mild OI. ***Methods:*** Patients were treated for 1.0–3.2 years with 0.05 mg/kg zoledronic acid intravenously every 6 months as part of their clinical care. They were carefully followed for clinical and biochemical parameters, side effects, bone mineral densities (BMD) and compression fractures. ***Results:*** The study included 17 patients (age 1.5–16.8 years) with type I OI. They had sustained altogether 73 fractures; 9 had compression fractures. During the treatment, 6 patients suffered in total 10 new long-bone fractures. The median lumbar spine areal BMD z-score increased from –2.0 to –0.7 during 2 years of treatment. The infusions were associated with a transient decrease in serum calcium and phosphate and a significant increase in serum PTH. Two patients developed symptomatic hypocalcemia. Bone turnover markers decreased during the treatment. ***Conclusions:*** Intravenous zoledronic acid is an effective mode of treatment in children with OI. The treatment response is comparable to pamidronate but the infusion protocol is more convenient. Further studies are needed to establish optimal dosing and long-term safety.

Introduction

Osteogenesis imperfecta (OI) is an inherited disorder with skeletal fragility and is usually caused by mutations in one of the two genes encoding type I collagen *(COL1A1*, *COL1A2)*. The mutations result in decreased synthesis of type I collagen or formation of abnormal protein. OI is classically divided into four subtypes reflecting its wide range of clinical severity [1]. Type I OI is the mildest form and presents with increased fracture rate but no significant deformity or height deficit. Type II is lethal during the neonatal period. The most severe form in patients surviving the neonatal period is type III OI, which causes severe limb and spinal deformities and short stature secondary to multiple fractures. Type IV comprises patients with phenotype intermediate to types I and III. Recently, new types of OI (V–IX) have been described. Although they phenotypically resemble types I–IV, they are not associated with type I collagen mutations [2–5].

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Cyclic intravenous therapy with bisphosphonates, mainly disodium pamidronate, has become an established part of the treatment of moderate to severe OI. Its beneficial effects on bone mineral densities (BMD) in the lumbar spine, hips and whole body have been reported in several studies [6–11]. There is also increasing evidence for its beneficial effects on patients' growth, well-being and bone pain [7, 12, 13]. Despite published reports on decreasing fracture incidence during treatment, there are also inconsistent results and overall the evidence for fracture prevention is scarce [8, 14, 15]. Most studies have involved mainly patients with OI type III and IV, and it is yet unclear whether bisphosphonates are also useful in the treatment of patients with type I OI.

Another intravenous bisphosphonate, zoledronic acid, has recently been indicated for the treatment of adult osteoporosis [16, 17]; there is only little experience of its use in pediatric patients [18–22]. The major advantages of zoledronic acid are its superior potency compared to other bisphosphonates and long-lasting efficacy in suppressing bone turnover, allowing less frequent administration. The purpose of the present study was to assess the efficacy and short-term safety of intravenous zoledronic acid in the treatment of pediatric patients with OI.

Patients and Methods

Study Population

Since 2004, zoledronic acid has been the predominant bisphosphonate used in the treatment of children with OI at our institution. This study evaluated in a retrospective manner the treatment results in children and adolescents with OI who had received intravenous zoledronic acid treatment as part of their normal clinical care at the Hospital for Children and Adolescents, Helsinki University Hospital. The treatment decision was made individually and based on the patient's clinical features and symptoms, including number of peripheral and spinal fractures, BMD, estimated risk for future fractures (based on age, musculature, joint laxity, hypotonia and fracture history in other affected family members) and bone pain. Usually the patients were eligible for zoledronic acid treatment if they had (1) a history of frequent fractures, (2) vertebral compression fractures, (3) chronic disabling bone pain, and/or (4) their vulnerability to fractures was estimated high. The inclusion criteria for the present study were: (i) diagnosis of mild OI, (ii) treatment with intravenous zoledronic acid between the years 2004 and 2009, (iii) a minimum treatment duration of 12 months, and (iv) no prior bisphosphonate treatment before zoledronic acid. Altogether 17 patients fulfilled these criteria (8 boys and 9 girls). At the start of treatment their median age was 10.1 years (range 1.5–16.8). The study protocol was approved by the Research Ethics Committee, Hospital for Children and Adolescents, Helsinki University Hospital.

Treatment Protocol

Prior to treatment onset, the patients and their parents were informed about the potential common side effects such as hypocalcemia and fever and about rare complications observed in adults, e.g. osteonecrosis of the jaw. Zoledronic acid (Zometa®; Novartis, Basel, Switzerland) infusions were administered intravenously (0.05 mg/kg up to 4.0 mg/day) over 45 min once every 6 months. After the first infusion the patients were hospitalized overnight and during the following infusions, followed at the hospital for a few hours and then discharged. All the patients received oral vitamin D_3 (20 μg/day) and calcium supplements (500 mg 1–2 times daily) for the duration of the treatment, starting 1–3 months prior to the first infusion to ensure that none of the patients were vitamin D insufficient at the start of the treatment. The treatment duration was usually 2 years but was in some patients shortened or extended based on treatment response, which was evaluated yearly. The median treatment duration in the present cohort was 1.9 years (range 1.0–3.2). The patients were carefully followed during the infusions and were seen at the Metabolic Bone Clinic at baseline and once a year during the treatment for clinical evaluation, BMD and radiography.

Clinical Evaluation

The patient's history of fractures was recorded at each clinic visit. Height and weight were measured at baseline and every 6–12 months thereafter; the height measurements were converted to age- and sex-standardized SDS scores by comparing them with values of healthy Finnish children [23, 24]. The weight was used to determine the dose of zoledronic acid.

Radiology

Bone densitometry was performed at baseline and then annually by dual energy X-ray absorptiometry (DXA) (Hologic Discovery A, pediatric software, version 12.4); changes in bone area (cm^2), bone mineral content (g) and areal BMD (aBMD) (g/cm^2), measured at the lumbar spine (L1-L4), femoral neck and whole body, were included in the analyses. These aBMD values were transformed to z-scores using the equipment-specific age- and sex-adjusted reference data for US Caucasian children. The validity of these references was tested in a cohort of 199 healthy Finnish children (125 girls and 74 boys; age range 7.4–18.8 years, median 13.1 years) who where assessed with the same DXA equipment as part of an ongoing study, which evaluates bone health in healthy schoolchildren in Helsinki area. Their median aBMD z-scores in the lumbar spine, proximal femur and whole body were 0.0, +0.1, and 0.0, respectively, confirming that the use of equipment-specific reference data in the present study is justified [25]. Since aBMD does not take into account the anterior-posterior dimension of the lumbar spine, an additional lateral projection of the lumbar vertebrae L2-L4 was obtained with the DXA scanner to obtain volumetric BMD (vBMD). The vBMD values were automatically calculated with the scanner; no pediatric reference values were available. Femoral neck and whole-body BMD could not be measured for 2 patients because of intramedullary rods in femur and tibia. In addition, 3 patients were too young for BMD measurement.

Conventional postero-anterior and lateral radiographs of the thoracic and lumbar spine were obtained at baseline and at 2 years. The morphology of each lumbar and thoracic vertebra was assessed using a standardized pediatric scoring system; a 20% or

Table 1. Clinical characteristics of the 17 patients with OI at baseline

Patient No.	Age years	Sex	Height z-score	Peripheral fractures	Spinal fractures		LS aBMD z-score
					n	grade	
1	16	M	–1.0	3	0		–0.8
2	11	M	–0.6	6	6	2a, 3b	–3.6
3	16	M	–1.3	4	0		–0.6
4	12	F	–2.0	4	0		–2.4
5	1	F	–0.4	0	5	3a	NA
6	3	M	0.0	5	7	3a, 3b	–4.0
7	10	F	0.1	9	3	2a, 3a	–0.8
8	15	M	–1.4	10	2	3a	–2.9
9	15	F	–1.0	0	0		–1.5
10	10	M	–0.7	4	4	3b	–2.9
11	10	M	NA	12	0		–2.2
12	10	F	–0.7	5	10	3a, 3b	–1.8
13	10	F	0.1	5	0		–1.2
14	6	M	–2.0	0	5	3a, 3b	–1.1
15	12	F	–1.6	1	0		–2.4
16	2	F	–1.4	3	0		NA
17	2	F	–0.4	2	2	3a, 3b	NA

The spinal fractures were classified as mild (2a) or severe (2b) anterior wedge deformities, or mild (3a) or severe (3b) compression deformities. LS = Lumbar spine; NA = not assessed.

greater reduction in the vertebral height was regarded abnormal [26]. The spinal fractures were classified as mild (2a; 20–49% anterior vertebral height reduction) or severe (2b; ≥50% anterior height reduction) anterior wedge deformities, or mild (3a; 20–49% mild height reduction) or severe (3b; ≥50% middle height reduction) compression deformities [26]. The improvement and deterioration of spinal changes was determined by comparing the grades assigned to each vertebra at baseline and at follow-up. All X-ray images were evaluated by a pediatric radiologist (S.T.-S.).

Biochemical Measurements

Blood and urine samples for parameters of calcium homeostasis, bone turnover, liver and renal function and blood count were obtained at the onset of each bisphosphonate infusion and 6 months after the last infusion. In addition, plasma concentration of calcium (P-Ca) was measured 2 h after every infusion and P-Ca, phosphate (P-Pi) and parathyroid hormone (P-PTH) 2 days later to evaluate the acute effects of infusion. All blood and urine samples (except P-Ca at 2 h) were obtained between 9:00 and 11:00 a.m. using second morning void for urine samples. The blood counts, P-Ca, P-Pi, magnesium, creatinine (P-Crea), alkaline phosphatase (P-ALP), alanine aminotransferase (P-ALT) and urine concentrations of creatinine (U-Crea), calcium (U-Ca) and phosphate (U-Pi) were measured by standard methods. P-PTH was measured by immunochemiluminometry and 25-hydroxyvitamin D (S-25-OH-D) by high-performance liquid chromatography. Bone turnover was determined by P-ALP, serum concentrations of procollagen I N-terminal peptide (S-PINP) (UniQ PINP RIA®; Orion Diagnostica, Espoo, Finland), collagen I C-terminal telopeptide (S-ICTP) (UniQ PINP RIA®; Orion Diagnostica) and urine concentration of collagen I N-terminal telopeptide (U-NTX) (Vitros ECi®; NTx Reagent Pack, Ortho-Clinical Diagnostics, N.Y., USA).

Side Effects

The patients were followed overnight after the first infusion and few hours after the subsequent infusions and all side effects during this time were recorded. Side effects occurring between the infusions were registered by the patient and/or the parents and recorded to the patient's health record at clinic visits. Bone pain and other symptoms were also inquired and recorded at each clinic visit.

Statistical Analysis

Descriptive data are reported as median and range. Comparisons between data at two time points were carried out using Student's paired t test; linear regression was used for correlations. All tests were two-tailed and a p value <0.05 was considered statistically significant. All the analyses were performed with StatView software (StatView 5.0.1; 1992–1998©; SAS Institute Inc.).

Results

Clinical Characteristics

The study group comprised 17 patients (8 boys and 9 girls), ranging in age from 1.5 to 16.8 years at treatment onset (median 10.1 years) (table 1). All were diagnosed with type I OI. Twelve patients received zoledronic acid for at least 2 years, 1 patient discontinued treatment at 12 months with good treatment response and 4 continued on treatment after the first treatment year. Prior to the therapy, the patients had sustained altogether 73 fractures (average 0.52/year) (table 1). After the treatment onset, 6 patients suffered in total 10 new long-bone fractures (0.28 fractures/year for the whole cohort). Five of these 6 patients were pubertal and in 3 of them the fractures occurred during pubertal growth spurt. The fracture incidence during the 2 years preceding the treatment onset was 6.5/year (in total 13 fractures) and during the first treatment year, 4 fractures/year. Half of the fractures occurred immediately before or after the infusion and others were evenly spread throughout the infusion cycle. Fracture healing was normal. One patient suffered a tibial refracture with a 2-month interval despite normal callus formation and healing of the first fracture in X-rays. The median height z-score was –0.9 (range –2.0 to +0.1) at baseline and remained unchanged during the follow-up (table 1).

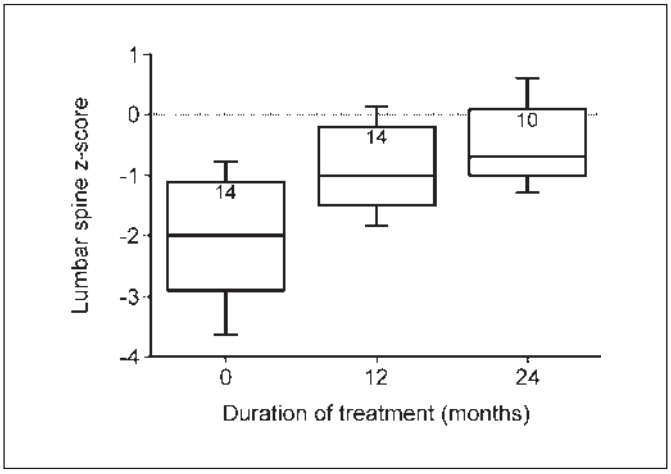

Fig. 1. Lumbar spine BMD z-scores at baseline and at 12 and 24 months of zoledronic acid treatment. Plots show median, quartiles, and 5th and 95th percentiles. The numbers within the plots refer to the number of observations at each time point.

Radiological Findings

At baseline the median lumbar spine aBMD z-score in the 15 patients, for whom it could be measured, was –2.0 (range –4.0 to –0.6). During the first year of treatment, aBMD increased by median 29.6% ($p < 0.001$) and the median z-score improved to –1.0 ($p < 0.001$) (fig. 1). The median vBMD increased by 19.8% ($p < 0.001$). Parallel but somewhat milder improvement was seen in femoral neck and whole-body aBMD values, which increased by 12.2% ($p < 0.001$) and 12.6% ($p < 0.001$), respectively. The respective z-scores improved from –1.3 to –0.9 ($p = 0.001$) and from –1.4 to –0.7 ($p < 0.001$).

During the second treatment year, aBMD increased much more moderately. In those 10 subjects who continued treatment after the first year, the lumbar spine aBMD increased 14.6% ($p = 0.003$ for the difference between 12- and 24-month values) as compared to 30.9% ($p < 0.001$) from baseline to 12 months. Their median aBMD z-score improved by 0.5 units, to –0.7 at 24 months ($p = 0.011$); the baseline value was –2.3. Femoral neck and whole-body aBMD increased 12.3% ($p = 0.005$) and 6.4% ($p = 0.015$), respectively, from 12 to 24 months. Their corresponding changes during the first year were 13.2 and 12.6% (both $p < 0.001$). The median z-score improved 0.5 units to –0.8 ($p = 0.005$) for femoral neck but decreased 0.1 units to –0.8 for the whole body ($p = 0.44$).

At baseline, 9 of the 17 patients (53%) had compressed vertebral bodies in spinal radiographs (table 1). Follow-up radiographs were available for 9 patients who had completed 2 years of treatment; 5 of them had compression fractures at baseline. At 2 years there was 1 additional patient with 1, and 1 patient with 2 new compressions. However, 3 patients had fewer compressions than at baseline (table 1). Overall, there was only a slight tendency to normalization in the vertebral compressions.

Biochemical Changes

All patients received vitamin D supplements; S-25-OH-D was satisfactory (mean 62.5 nmol/l) at treatment onset, none had vitamin D deficiency and no significant change was observed during the treatment. Before treatment, 16 patients had normal S-Ca and 1 had a slightly elevated value. S-Ca measured 2 h after the infusion was also normal (fig. 2). However, S-Ca values measured 2 days after the first infusion were significantly decreased (mean decrease 9%, $p < 0.001$) and 12 patients (71%) had subnormal values (fig. 2). Two of them had clinical symptoms and were treated with intravenous calcium. Similar decrease without symptoms was seen with subsequent infusions (7–10%, $p < 0.001$). Only 1 patient had a slightly supranormal P-PTH at infusion onset. The values measured 2 days later had increased by mean of 500% ($p < 0.001$) (fig. 2). A similar change was seen after every infusion (range 250–480%, $p < 0.01$). The rise in P-PTH was associated with a significant decrease in P-Pi (mean 41%, $p < 0.001$) during the first infusion; the decrease was between 20 and 32% during the subsequent infusions ($p < 0.001$). All the changes in S-Ca, Pi and PTH were transient and normalized by the following infusion (fig. 2).

Both the markers of bone formation (P-ALP, S-PINP) and bone resorption (S-ICTP, U-NTX) decreased during the treatment; these changes were statistically significant except for S-ICTP. P-ALP decreased on average 17% during the first 6 months ($p = 0.008$) and 26% during the first year ($p = 0.001$); at 2 years of treatment the total reduction was 26% from baseline ($p = 0.02$). For S-PINP the corresponding values were 43% ($p < 0.001$), 54% ($p < 0.001$) and 52% ($p = 0.03$), and for U-INTP 46% ($p = 0.002$), 63% ($p = 0.001$) and 52% ($p = 0.02$), respectively. All other blood values, including renal function tests, remained normal throughout the treatment. No correlation between bone turnover markers and aBMD could be observed.

Side Effects

Despite consistent decrease in P-Ca levels, only 2 patients had mild clinical symptoms of hypocalcemia after their first dose, mainly fatigue, dizziness, nausea and

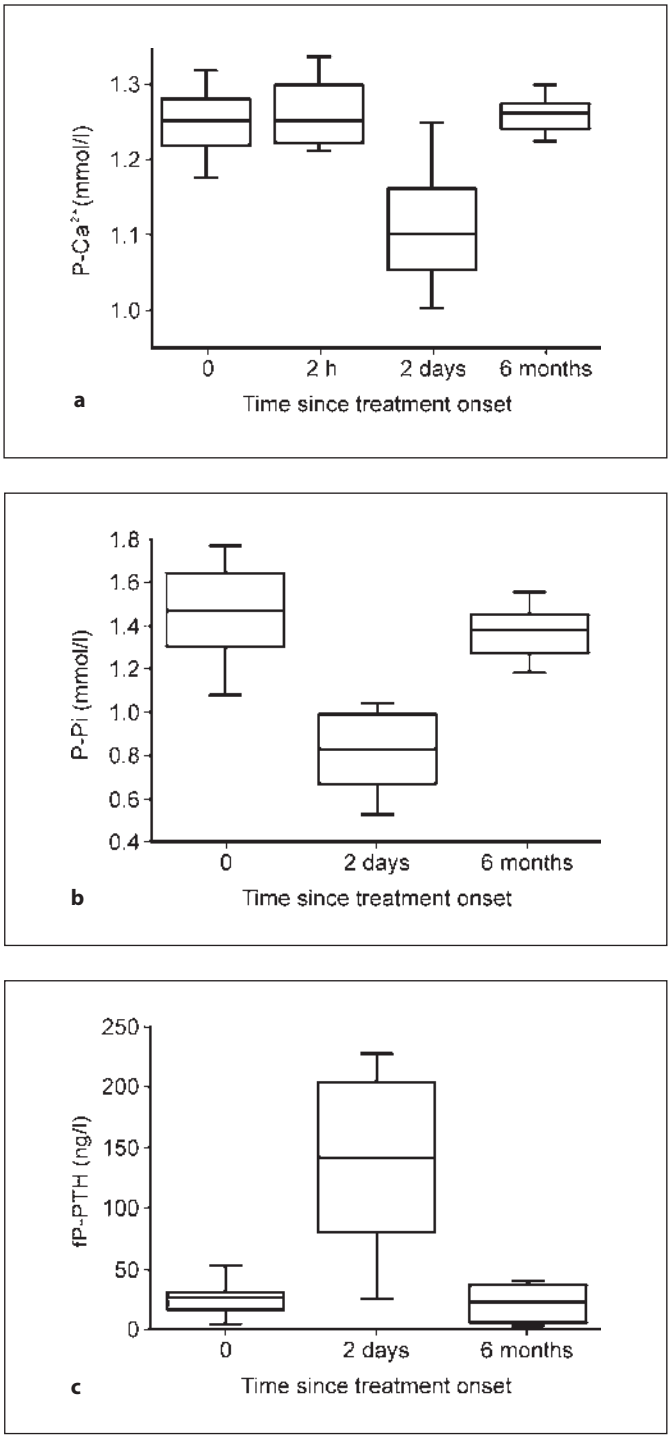

Fig. 2. Acute effects of the first zoledronic acid infusion on calcium (**a**), phosphate (**b**) and PTH (**c**) concentrations. The values were taken immediately prior to the first infusion, 2 h and 2 days after the infusion and immediately before the next infusion. Plots show median, quartiles, and 5th and 95th percentiles. The numbers within the plots refer to the number of observations at each time point.

mild muscle tremor. Their pretreatment S-25-OH-D levels were normal. The patients were treated with intravenous calcium and the symptoms alleviated. To avoid similar side effects their second zoledronic acid dose was reduced to 0.025 mg/kg and third dose was again normal; hypocalcemia did not recur. None of the patients had symptoms of hypophosphatemia. The most common (65%) side effect was transient flu-like reaction after the first infusion. Among those 11 patients who had the reaction, 5 had also bone pain. Only 1 patient had the same reaction after the second infusion. Other side effects were not reported.

Overall the treatment was well tolerated. Three of the patients suffered from daily bone pain before treatment onset; 2 of them reported disappearance of pain after the onset of treatment. In addition, their parents reported marked increase in social and physical activity. In 1 patient (No. 11) the infusion interval was shortened to 3 months in order to prevent pretreatment bone pain. An attempt to stop his treatment after 2.5 years failed because of recurrence of severe bone pain. The treatment was not discontinued because of side effects in any of the patients.

Discussion

The results of the present study confirm that intravenous zoledronic acid treatment has beneficial effects on bone health in children and adolescents with OI. aBMD and BMD z-scores increased significantly already during the first year of treatment and a more moderate increase was seen during the second treatment year. Bone turnover markers decreased during the treatment indicating suppression of bone resorption.

Compared with previously reported findings during pamidronate treatment, the changes in BMD were slightly more moderate in our study [6–8]. However, previous studies have usually included patients with OI type III or IV and this may contribute to their greater improvements in BMD. This explanation is supported by the reported positive correlation between disease severity and benefits of the treatment: the more severe the disease, the more dramatic the response to pamidronate treatment seems to be [6, 10]. The decrease in bone turnover markers was similar or slightly less pronounced than in previous studies [6, 8]. These findings are consistent with a significant effect on bone turnover and subsequent increase in bone mass during zoledronic acid treatment. Our findings are similar to those reported by Glorieux et al. [20] in a par-

allel efficacy trial between zoledronic acid and pamidronate. They observed that compared to pamidronate, the patients treated with zoledronic acid had a significantly greater increase in LS BMD (42.7 vs. 34.7%; p = 0.013) and significantly greater reductions in serum biomarkers of bone resorption and formation at 12 months. The proportion of patients with clinical fractures was similar between groups. Both treatments significantly reduced clinical fractures [20].

One third of the patients continued to fracture during the treatment. All but 1 patient were pubertal and it is likely that this contributed to the fractures. The frequency of fractures was lower than during the years preceding the treatment: the fracture incidence during the 2 pretreatment years was 6.5/year and during the first treatment year, 4 fractures/year. Since fracture rate varies with age, and fractures overall were not very prevalent in our cohort, it is not possible to draw any definite conclusions based on this relatively short observational study. We observed also a slight but not significant trend of recovery in vertebral shape during zoledronic acid treatment. This observation is similar to previous studies with pamidronate, showing slower or no progression in compression fractures and some bone regeneration [7, 15, 27]. Some patients developed new compression changes during the treatment. As the evaluation of vertebral bodies in patients with OI is often challenging due to low BMD it is also possible that some of the deformities only became visible during the treatment.

Three of our patients reported daily bone pain at treatment onset; in 2 of them pain disappeared during the treatment. Their parents also reported marked increase in social and physical activity. A reliable assessment of pain and well-being was not possible because of the lack of standardized method for assessment and the retrospective nature of the present study.

The most common side effect was a transient flu-like reaction, often associated with bone pain. This reaction only appeared with the first infusion except in 1 child. Significant changes in mineral homeostasis were commonly observed. However, symptomatic hypocalcemia was seen in only 2 patients who required intravenous calcium treatment. The subsequent zoledronic acid dose was reduced and hypocalcemia was avoided. Although the magnitude of changes in serum calcium levels did not differ from those associated with pamidronate treatment, equally severe clinical symptoms were not reported in those studies. It is important to ensure adequate calcium and vitamin D supplements before and during intravenous zoledronic acid treatment. Another interesting acute biochemical change was the increase in plasma PTH secondary to decrease in serum calcium levels. This increase was remarkable (500% after the first dose) and significantly greater than observed during pamidronate treatment (up to 115%) [10, 28]. It has been suggested that this transient increase in plasma PTH could have a beneficial, stimulatory effect on osteoblasts, similar to the anabolic effect seen with PTH treatment in postmenopausal osteoporosis [29]. In all patients, PTH levels normalized before the following infusion. It is possible that even lower doses of zoledronic acid (0.025 or 0.0125 mg/kg) could be used in the treatment, to avoid these significant biochemical changes and to avoid oversuppression of bone turnover [19].

We used a 6-month interval between the infusions; no modifications were made based on the patient's age. Bone turnover markers remained suppressed during the treatment and bone mass increased significantly, suggesting that the dosing was appropriate. The distribution of new fractures along the infusion cycle may suggest that the interval is too long as several fractures occurred immediately before or after the infusion. In addition, in 1 of the patients the infusion cycle had to be reduced to 3 months because of reappearance of bone pain. In the treatment of adult osteoporosis, 5 mg zoledronic acid once yearly has proven to be effective in prevention of hip, vertebral and other fractures [30]. Our study was not designed to examine the relationship between fractures and drug interval; more studies in larger patient populations are required to optimize the dosing, infusion interval and treatment duration in the pediatric age group. Longer follow-up is also necessary to monitor the consequences of discontinued treatment.

One of the limitations of our study is that the patient group was heterogenous with regard to age, BMD and fracture history. However, all patients had OI type I and none had the more severe forms, type III or IV. The patient group is representative of the general OI type I patient population seen in pediatric OI clinics and thus the findings can be extended to normal clinical settings. The treatment decision was based on several parameters, not only on BMD or number of peripheral fractures; this caused further heterogeneity to the study population. Ideally a placebo group should have been included to strengthen data analysis; in mild OI this would not have caused ethical problems [31]. Lack of standardized bone pain evaluation my have prevented us from observing the anticipated significant pain reduction.

In conclusion, the present study shows that intravenous zoledronic acid treatment, given once every 6 months, is an effective mode of treatment in children and adolescents with OI. The treatment response and short-term safety are comparable to that seen with pamidronate. However, the infusion protocol presented here is much more convenient to the family, with only 2 hospital visits per year as compared to the standard 3 days every 4 months with pamidronate therapy. Therefore, zoledronic acid should be considered in the treatment of children with OI. Since the number of subjects was small, follow-up short and no placebo or comparison group was included, further studies are needed to confirm the results and to establish optimal dosing, long-term outcomes and adverse effects.

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