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ORIGINAL ARTICLE

Response to zolendronic acid in children with type III osteogenesis imperfecta

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Abstract Osteogenesis imperfecta (OI) is a common genetic disorder that manifests with intrauterine or pre- or postnatal fractures, blue sclera, and deafness. Various treatments for the management of OI have been tried, of which bisphosphonates (BPs) seem to have the maximum benefit in reducing fracture rate and improving bone density. Zolendronic acid is a newer BP tried for several bone diseases, mainly in adults. The objective of our analysis was to study the response to zolendronic acid in children with type III OI. The case records of subjects with type III OI receiving zolendronic acid in the past 3 years between February 2006 and March 2009 were analyzed. Relevant details were recorded on a predesigned chart. Subjective improvement, reduction in number of fractures, and the DEXA scan Z-score were used to judge improvement. Five OI type III cases were followed up in the Genetic clinic. Presentation was from neonatal period to 7 years of age; M:F ratio was 3:2. Average duration of therapy given was 20.4 months. Improvement was noted in all patients, in the form of reduction in frequency of fractures ($P = 0.002$) and increase in bone density on DEXA scan ($P = 0.01$). Side effects noted were flu-like symptoms and myalgia. No clinical problems due to hypocalcemia were noted in any of the patients. Thus, zolendronic acid is seen as a safe and effective BP in type III OI children. The exact dose for optimal benefit is yet to be determined. The long-term effects of newer BPs need further long-term trials.

Keywords Bisphosphonates · Children · Zolendronic acid · Osteoporosis · DEXA

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Introduction

Osteogenesis imperfecta (OI) is a genetic disease with increased bone fragility and low bone mass. The incidence is 0.4:10,000 live births [1]. Severity of skeletal manifestations in OI varies and typical extraskeletal manifestations include blue sclera, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, hearing impairment, and the presence of wormian bones on skull radiographs [2, 3]. Type III presents with early-onset fractures and is characterized by progressive deformity of the bones. Both inheritance patterns (AR/AD) have been implicated, and are caused by COL1A1 mutations.

Bisphosphonates (BPs), particularly those containing nitrogen, are being increasingly administered to increase bone mass and reduce the incidence of fractures. BPs can be dosed orally (e.g., alendronate) or by intravenous injection/infusion (e.g., pamidronate, zolendronic acid). BP therapy is being used increasingly for the treatment of OI

[4, 5]. Although it decreases fracture rates, there is some concern that prolonged BP treatment may delay the healing of OI fractures, although this effect has not been conclusively demonstrated. Pamidronate is usually administered as an intravenous infusion, lasting about 3 h. The therapy is repeated every 3–6 months. Common side effects include bone pain, low calcium levels, nausea, and dizziness. According to recent results, extended periods of pamidronate use (i.e., 6 years) can actually weaken bones; thus, patients are recommended to get bone density scans every 6 months to 1 year, to monitor bone strength.

Zolendronic acid is the most recent addition to the clinically available BPs. Clinical benefits in metabolic, as well as cancer-related, bone diseases have been observed. Zolendronic acid has been evaluated in randomized, double-blind clinical trials of osteoporosis, Paget's disease of bone, and metastatic, osteolytic, and osteoblastic bone disease [6–8]. Antiosteoclast activity has been demonstrated by reductions in the bone breakdown products N-telopeptide, C-telopeptide, and deoxypyridinoline. Bone mineral density, measured by dual-energy X-ray absorptiometry (DEXA), is increased with administration of zolendronic acid in postmenopausal osteoporosis [6].

Although BPs are presently the most effective form of therapy for OI, there is a lack of studies on zolendronic acid, in OI patients especially. The objective of this study was to examine the efficacy and safety of zolendronic acid in children with type III OI, a potentially debilitating disorder.

Subjects and methods

From February 2006 until March 2009, ten patients with OI were referred for BP therapy. The medical records of each patient with type III OI were reviewed retrospectively, including the history of number of fractures, family history, and other physical manifestations of OI (including deafness, dental abnormalities, and onset of fractures) used to make the diagnosis. Every parent was counseled regarding intravenous zolendronic acid therapy. All patients and/or their parents gave prior, verbal consent to participation in the study.

Before commencement of therapy, all patients underwent a radiographic study and BMD measurement with baseline biochemistry, including serum calcium, phosphorus, alkaline phosphatase, liver and renal function tests, and hemogram. Radiographs were repeated as and when indicated. BMD was undertaken every 6–12 months in lumbar (L1–L4) vertebrae. BMD was measured with dual-energy X-ray absorptiometry using a DPX scanner. Skeletal deformity was analyzed by radiography. Baseline biochemical parameters were recorded initially and then repeated if clinically indicated.

All patients had received intravenous zolendronic acid 2 (<6 months of age) or 4 mg (>6 months of age) over 30 min to 1 h, and this protocol was repeated every 3–4 months. Calcium supplementation (75–100 mg/kg per day) was also given simultaneously. Statistical analysis was performed using the SPSS software (version 13). The paired sample *t* test and the Wilcoxon signed-rank test were used to determine the effect of length of therapy on the fracture risk and the difference in BMD, fracture rate before and after treatment, and change in the Z-score. A P value <0.05 was chosen to indicate significant deviation from the null hypothesis.

Results

The baseline general characteristics of the OI patients at the start of therapy are listed in Table 1.

Response to zolendronic acid

The duration of IV zolendronic acid therapy given ranged from 12 to 32 months with a mean (±SD) duration of 20.4 (±8.98) months. Compliance was good. Three children (60%) were short at the onset of the study, with a mean (±SD) pretreatment height of 84.4 (7.33) cm; mean (±SD) weight was 11.75 (3.5) kg. Four patients (80%) had progressive skeletal deformities, and their mobility was limited: only one patient (20%) was able to walk, two (40%) to sit, and two (40%) to roll over. One patient had hearing defects and another had delayed development (Table 2). The incidence of fractures decreased from 4.4 ± 1.5/year before treatment to 2.2 ± 1.3/year during treatment ($P = 0.002$). All children gained height during therapy, at an average rate of 3.84 cm/year. The increments in growth of two patients who completed more than 2 years therapy are depicted in Fig. 1. None had any progression of their skeletal deformity. Fractures were usually the result of trivial trauma. All fractures sustained during therapy were treated nonsurgically.

Table 1 Baseline general characteristics of the children with osteogenesis imperfecta (OI)

Male:female ratio	3:2
Mean (SD) age	3.5 years (±2.17) (range, 2.5 weeks to 7 years)
Median age	3 years
Sites of fractures	Long bones, ribs
Positive family history	Only 1 patient

Table 2 Clinical characteristics and response to zolendronic acid in type III OI cases

SI. no.	Age at presentation/ sex	Anthropometry (centiles)	Clinical profile	Duration (months)	Number of doses received	Number of fractures 1 year before start of therapy	Number of fractures after start of therapy
1	3 year, F	Height (<3rd) Weight (50th–75th) OFC (normal)	Multiple fractures; blue sclera; fracture of ribs; dysmorphic facies; family history positive	36	11	5	3
2	1.8 year, M	Height (5th–25th) Weight (25th–50th) OFC (normal)	Multiple fractures; blue sclera; high arched palate	19	4	2	1
3	2 year, F	Height (<3rd) Weight (25th) OFC (normal)	Multiple fractures; blue sclera; flared metaphysis; small finger; developmental delay present	18	10	4	1
4	4 year, M	Height (3rd) Weight (50th) OFC (normal)	Multiple fractures; blue sclera; hearing defect	32	8	5	2
5	7 year, M	Height (<3rd) Weight (5th–25th) OFC (normal)	Multiple recurrent fractures; blue sclera	20	6	6	4

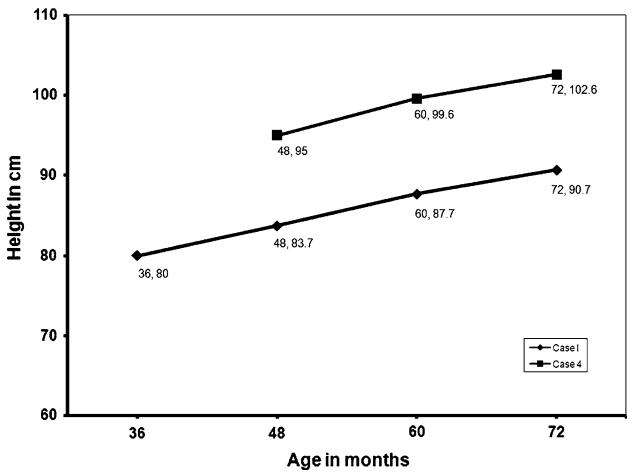

Fig. 1 Showing the rate of height gain (in cm) of two patients in first, second, and third year of zolendronic acid therapy. The *numbers* near the *plotted lines* represent age in months and height in centimeters, respectively

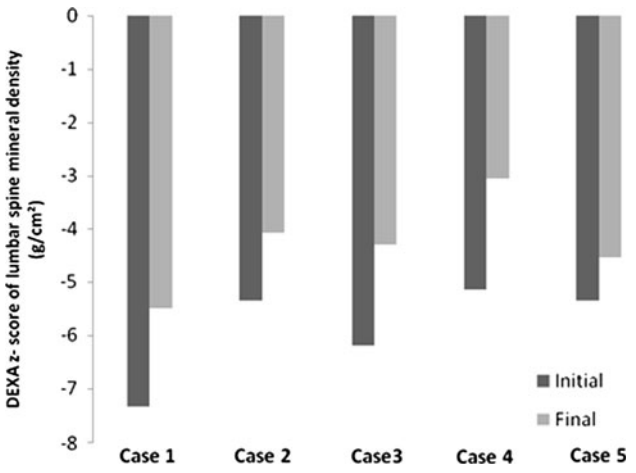

Fig. 2 Initial and final bone mineral density (DEXA Z-score) of the lumbar spine (L1–L4) in all five subjects with OI administered intravenous zolendronic acid

All children had low bone mineral density in the lumbar spine consistent with severe osteoporosis, with Z-scores ranging from –5.34 to –7.32. The mean bone mineral density improved markedly, by 38.04% ± 11.45% per year, and the mean Z-score improved from –5.86 ± 0.81 to –4.28 ± 0.78 ($P = 0.01$) (Fig. 2).

Side effects

Side effects occurred in three patients in total, consisting of flu-like symptoms in two cases (40%) and myalgia in one case (20%). These side effects were transient and noted only during infusion. No clinical problems resulting from hypocalcemia were seen in any patient.

Discussion

Osteopenia and bone fragility, the hallmarks of severe OI, probably result from structural abnormalities in bone tissue [10] and a reduced rate of osteogenesis [11]. The mutations responsible for most cases of OI types II, III, and IV occur

in either the COL1A1 or COL1A2 gene. A defect in the structure of type I collagen weakens connective tissues, particularly bone, resulting in the characteristic features of OI [2]. Mutations in the CRTAP (OI type VII) and LEPRE1 (OI type VIII) are seen in rare autosomal recessive cases. Mutations in either gene disrupt the normal folding, assembly, and secretion of collagen molecules. In cases of OI without identified mutations in the COL1A1, COL1A2, CRTAP, or LEPRE1 gene, the underlying cause is unknown. These cases include OI types V and VI.

BPs (intravenous, oral) are the main group of drugs used currently in treatment of OI. Many trials have been done on the role of intravenous as well as oral BPs in treatment of OI. Zolendronic acid is the newer addition to the BPs, and there have been no trials to date comparing it with other intravenous as well as oral BPs. One study has shown that it is safe and effective in treatment of pediatric osteoporosis including OI [12]. The advantages of zolendronic acid over pamidronate in conditions where both are used include lower dose requirement (4–8 mg, vs. 2–4 mg/kg for pamidronate), short infusion time ($\geq$15 min, vs. 2–4 h for pamidronate), thus causing less venous irritation, and the side-effect profiles of both are similar [13]. Except being convenient for oral administration, oral BPs have no other significant advantage over intravenous BPs [9].

In the present study, cyclic administration of intravenous zolendronic acid resulted in a rapid increase in the mineral density of the lumbar vertebrae. The bone mineral density of the lumbar spine, as measured by X-ray absorptiometry, is an area-related measurement that is affected by both true bone mineral density and the volume of the vertebral body. In growing children, the area-related bone mineral density increases by 3–6% per year before puberty and by 14–16% per year during puberty [14, 15]. In our patients, annualized gains in bone mineral density during zolendronic acid therapy (38.04% $\pm$ 11.45%) substantially exceeded these values. The Z-scores for bone mineral density take into account the changes in volume caused by growth [16]. In all the children in our study, in spite of severe osteoporosis, the Z-scores improved during therapy, suggesting that zolendronic acid has a positive effect on bone mineral density.

In children with severe OI, the growth rate is greatly reduced before the age of 6 or 7 years, and growth almost stops thereafter [17]. In the children in our study, growth was reduced but not arrested before treatment, and during treatment, linear growth proceeded at a slightly increased rate. At least part of this gain was probably the result of increases in the size of the vertebral bodies.

The objective fracture rate is difficult to assess without frequent X-rays, but the use of frequent radiography is not recommended for patients with OI as it can lead over time to a high accumulation of radiation. However, a subjective decrease in symptoms indicates a decrease in fissures or fractures during treatment. Bone density improved in seven patients on long-term treatment. The changes in the lumbar BMD and Z-score were statistically significant. No short-term serious side effects occurred in any of the patients.

This medical therapy does not stand alone; it should be considered part of a coordinated, multidisciplinary approach to the treatment of children with OI, including timely corrective surgery, physiotherapy, and occupational therapy. Continued follow-up will help delineate the response to therapy over time and the limits of the gains that can be achieved.

Within its limitations, this retrospective analysis showed that use of zolendronic acid was associated with clinical as well as radiologic benefit in form of reduction of number of fractures and increase in bone density on DEXA scan in type III OI patients. Thus, zolendronic acid is a safe and effective BP even in children with type III OI. Further research in this area is needed to delineate optimal dose and duration of therapy and to compare with other BPs.

References

1. Romero R, Pilu GL, Jeanty P (1988) Prenatal diagnosis of congenital anomalies. Appleton & Lange, Norwalk
2. Rauch F, Glorieux FH (2004) Osteogenesis imperfecta. Lancet 363:1377–1385
3. Plotkin H, Primorac D, Rowe D (2003) Osteogenesis imperfecta. In: Glorieux FH, Pettifor J, Jueppner H (eds) Pediatric bone. Academic Press, San Diego, pp 443–471
4. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R (1998) Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med 339:947–952
5. Di Meglio LA, Peacock M (2006) Two-year clinical trial of oral alendronate versus intravenous pamidronate in children with osteogenesis imperfecta. J Bone Miner Res 21:132–140
6. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U et al (2002) Intravenous zolendronic acid in postmenopausal women with low bone mineral density. N Engl J Med 346:653–661
7. Reid IR, Miller P, Lyles K, Fraser W, Brown JP, Saidi Y, Mesenbrink P, Su G, Pak J, Zelenakas K, Luchi M, Richardson P, Hosking D (2005) Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 353:898–908
8. Lipton A, Cook R, Saad F, Major P, Garnero P, Terpos E, Brown JE, Coleman RE (2008) Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. Cancer 113:193–201
9. Rauch F, Glorieux FH (2005) Bisphosphonate treatment in osteogenesis imperfecta: which drug, for whom, for how long? Ann Med 37:295–302
10. Sykes B, Ogilvie D, Wordsworth P, Wallis G, Mathew C, Beightn P, Nicolls A, Pope FM, Thompson E, Tsipouras P, Schwartz R, Jensson O, Arnason A, Børresen AL, Heiberg A, Frey D, Steinmann B (1990) Consistent linkage of dominantly inherited osteogenesis imperfecta to the type I collagen loci: COL1A1 and COL1A2. Am J Hum Genet 46:293–307

11. Glorieux FH, Travers R, Chabot G, Lanoue G (1994) Bone histomorphometric analysis in osteogenesis imperfecta. J Bone Miner Res 9:S226 (abstract)
12. Brown JJ, Zacharin MR (2009) Safety and efficacy of intravenous zolendronic acid in paediatric osteoporosis. J Pediatr Endocrinol Metab 22:55–63
13. Li EC, Davis LE (2003) Zoledronic acid: a new parenteral bisphosphonate. Clin Ther 25:2669–2708
14. Plotkin H, Nunez M, Alvarez Filgueira ML, Zanchetta JR (1996) Lumbar spine bone density in Argentine children. Calcif Tissue Int 58:144–149
15. Davie MW, Haddaway MJ (1994) Bone mineral content and density in healthy subjects and in osteogenesis imperfecta. Arch Dis Child 70:331–334
16. Reinus WR, McAlister WH, Schranck F, Chines A, Whyte MP (1998) Differing lumbar vertebral mineralization rates in ambulatory pediatric patients with osteogenesis imperfecta. Calcif Tissue Int 62:17–20
17. Vetter U, Pontz B, Zauner E, Brenner RE, Spranger J (1992) Osteogenesis imperfecta: a clinical study of the first ten years of life. Calcif Tissue Int 50:36–41