

# Alendronate Treatment in Children with Osteogenesis Imperfecta

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## ABSTRACT

**Background:** Recent studies reported beneficial effect of cyclical intravenous administration of pamidronate in children and adolescents with osteogenesis imperfecta (OI). However, this treatment requires frequent hospital admissions and is relatively expensive. Alendronate is an oral bisphosphonate effectively used in adults with osteoporosis. Experience with alendronate treatment in children with OI is limited. **Aims:** To report our experience with alendronate in children with OI. **Methods:** 12 children with OI (7 with type I, 4 with type III and 1 with type IV; 7 boys, 5 girls) aged 1.8 to 15.4 years (7.9±4.4 yrs) were included in this retrospective study. The patients were treated with alendronate in a dose of 5-10 mg/day along with calcium (500 mg/day) and vitamin D (400-1000 IU/day) supplements for 19.8±11.3 months (range: 7-46 months). Serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), osteocalcin (OC), pyrilinks-D and urinary Ca/Cr ratio were studied 3 monthly and bone mineral density (BMD) by DXA on 6-12 monthly basis. **Results:** Fracture rate of the patients significantly decreased after treatment (1.2±1.5 vs. 0.16±0.32 per year,  $P<0.05$ ). Treatment improved bone density in each individual case. Z-scores of lumbar DXA (L2-L4) significantly increased during treatment ( $-4.60 \pm 1.30$  vs  $-2.47 \pm 1.52$ ,  $P<0.05$ ). Urinary pyrilinks-D decreased with treatment (90.8±136.3 vs. 35.1±29.9,  $P<0.05$ ). Serum Ca, P, ALP, OC and urinary Ca/Cr did not change significantly during treatment. **Conclusion:** We conclude that alendronate is effective, safe and practical alternative to intravenous bisphosphonates in treatment of children with OI.

**Key words:** Alendronate, Bisphosphonates, Osteogenesis imperfecta.

## INTRODUCTION

Osteogenesis imperfecta (OI) is a heterogeneous group of inherited disorders of connective tissue, characterized by bone fragility. Severity varies widely, ranging from intrauterine fractures and perinatal lethality to very mild forms without fractures(1-3).

Many types of pharmacological treatment have been tried for the severe forms of OI, including sodium fluoride(4), calcium(5), magnesium oxide(6), anabolic steroids(6), vitamin C(7), growth hormone(8), and calcitonin(9), without consistent benefit. In recent years, bisphosphonates have been used in children for treatment of a growing number of disorders associated primarily with generalized or localized osteoporosis(10-12). Bisphosphonate compounds are synthetic analogues of pyrophosphate,

an endogenous inhibitor of bone resorption. Bisphosphonates may restore a more normal balance between osteoblast-mediated bone synthesis and osteoclast-mediated bone resorption in OI, a disease that has high bone turnover(13). The benefits of treatment with intravenous bisphosphonate, pamidronate, in osteogenesis imperfecta have recently been reported(14,15). Intravenous (IV) therapy is more expensive and requires frequent hospitalization. Alendronate is an oral bisphosphonate successfully used in adults with osteoporosis. The efficacy of oral bisphosphonates in treatment of OI has not been well established. Nevertheless, we have been using oral alendronate in these patients since 2000 because of difficulties in availability of IV bisphosphonates in Turkey. We report our experience with oral alendronate treatment on clinical and biochemical parameters in children with osteogenesis imperfecta.

## METHODS

Hospital records of patients with OI followed at Marmara University, Pediatric Endocrinology Clinic, treated with oral alendronate from 2000 to 2004 were reviewed retrospectively. The diagnosis was based on clinical and radiological findings and family history of OI. 5 girls and 7 boys aged 1.8 to 15.4 years (mean  $7.9 \pm 4.4$ ) were included in the study. The type of the OI was type I in 7 patients, type III in 4 patients, and type IV in one patient according to the classification of Silience, *et al.*(3). None of them had prior treatment with any form of bisphosphonates. All of them had previous history of fractures. Three patients were non-ambulatory due to severe deformities, 9 patients had milder deformities and were ambulatory.

After obtaining informed consent from the parents, alendronate in a dosage of 5-10 mg/day (up to 2003) or 35-70 mg/week (after 2003) were started according to patients' weight (5 mg/day or 35 mg/week for <30 kg, 10 mg/day or 70 mg/week for  $\geq 30$  kg) (mean dosage:  $0.37 \pm 0.07$  mg/kg/day). Parents and patients were informed about giving the medication at least 60 min before breakfast with 100 mL water and keep the child in upright position after taking pill for at least one hour to prevent possible gastroesophageal reflux, a known side effect of the medication. All children received daily supplements of 500 mg elementary calcium and 400-1000 IU cholecalciferol to avoid hypocalcaemia. Renal functions were checked before starting the drug.

Serum calcium (Ca), phosphorus (P), total alkaline phosphatase (ALP), osteocalcin (OC), intact parathyroid hormone (PTH); and urinary deoxypridinolines (Pyrilinks-D), urinary calcium excretion and calcium/creatinine ratio (Uca/Ucr); and stool guaiac test were obtained at entry and at 3 months intervals during follow-up. Plasma OC levels, serum intact PTH and urinary pyrilinks-D measurements were performed by Immulite 2000 system which is a solid-phase, two-site chemiluminescent enzyme-labelled immunometric assay.

The effect of treatment on fracture rate per year as well as on bone mineral density (BMD) in 6 to 12 months intervals, and biochemical parameters (3 monthly) were investigated. The BMD of lumbar

vertebrae (L2-L4) and whole body were measured with dual-energy X-ray absorptiometry (DXA) using either Hologic or Lunar densitometer. Longitudinal evaluation of each patient was done by the same method. The BMD measurement and Z-scores according to the pediatric reference data given by the manufacturers were compared before and after treatment.

All statistical analyses were performed using Jandel Sigmastat statistics program. For biochemical parameters, paired *t* tests were used before and after treatment. Results were considered significant at  $P < 0.05$ .

## RESULTS

The mean duration of treatment was  $19.8 \pm 11.3$  months (range: 7-46 months) (**Table I**). The treatment improved bone density in each individual case. The pre- and post-treatment parameters evaluated are shown in the **Table II**. No clinically apparent side effect of alendronate was observed during the follow-up period except slight bone pain at the beginning of the treatment, which disappeared in all patients.

Although, we did not formally assess the ambulatory capacity in non-ambulatory patients, notable improvement in ambulatory capacity was observed in all three patients such as being able to sit up independently from supine position. The parents of all children (ambulatory and nonambulatory) reported improvement in ambulatory capacity and decrease in bone pain 3 months after beginning of the treatment.

We observed no metaphyseal banding in the patients treated with alendronate in contrast to cyclic pamidronate treatment. Vertebral X-rays of the patients also demonstrated improvement in density and height of the vertebrae.

## DISCUSSION

In this study, oral alendronate treatment was effective in preventing fractures and improving BMD and decreasing bone resorption markers in patients with various type of OI. The efficacy of alendronate in OI was demonstrated in a placebo-

**TABLE I** CLINICAL CHARACTERISTICS OF THE PATIENTS

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Type	III	IV	I	I	I	III	I	I	III	I	III	I
Gender	F	F	M	F	F	M	M	F	M	M	M	M
Age (year)	6.7	10.9	5.7	1.8	9.3	9.0	1.8	11.4	5.9	3.8	15.4	14.1
Duration of treatment (mo)	38	18	22	20	46	20	14	7	16	14	12	11
Fracture rate/yr (before therapy)	3	4.5	0.3	1	0.2	3.3	0.9	0.1	0.66	0.24	0.33	0.14
(after therapy)	0.32	1	0	0.6	0	0	0	0	0	0	0	0
Ambulatory status	A	A	NA	NA	NA	NA	A	NA	NA	A	NA	NA

A: ambulatory; NA: non-ambulatory

**TABLE II** COMPARISON OF THE STUDY PARAMETERS BEFORE AND AFTER ALENDRONATE TREATMENT

	Reference ranges	Pre-treatment (mean±SD)	Post-treatment (mean±SD)	P
Fracture rate per year		1.2 ± 1.5	0.16±0.32	<0.05
BMD L2-L4 Z-score (n = 10)		-4.6 ± 1.3	-2.47±1.52	<0.05
Serum calcium (mg/dL)	8.4-10.5	9.9 ± 0.4	10.0±0.5	NS
Serum phosphorus (mg/dL)	2.5-4.9	4.1 ± 1.4	4.2±1.0	NS
Alkaline phosphatase (U/L)	250-1000	495.8 ±347.2	399.0±169.2	NS
Urinary Ca / Cr	<0.2	0.2 ± 0.21	0.30±0.29	NS
Pyrilinks-D (nM/mMCre)	3-7.4	90.8 ±136.3	35.1±29.9	<0.05
Osteocalcin (ng/mL)	3.1-13.7	43.0 ±46.8	42.8±33.1	NS
Serum iPTH (pg/mL)	10-69	29.0 ±18.9	40.4±26.1	NS

controlled animal study(16). It considerably reduced the number of fractures in severe OI. Studies examining the efficacy of oral bisphosphonates in children are limited, in contrast to experience in adult practice where they are primary means of treatment for osteoporosis. Earlier limited studies demonstrated that oral pamidronate or oral olpadronate were effective in reducing fracture rates and improving BMD in children with severe osteoporosis and OI(17).

In a recent clinical trial by DiMeglio, *et al.*(18), comparison of oral alendronate to intravenous pamidronate in 12 children with OI yielded results similar to ours. Bone mineral density increased in both oral and intravenous groups equally and all children had a decrease in biochemical markers of

bone turnover and increased PTH. We found decrease only in PTH and not in ALP and OC in contrast to DiMeglio's findings. The reason for no significant change in PTH, ALP and OC in our group might be the addition of vitamin D and oral Ca in our treatment protocol. The decrease in bone resorption markers is more pronounced than that of bone formation markers following treatment with bisphosphonates. However, the decrease of bone formation markers might also be related to decrease in number of fractures in OI after treatment. It is well known that bone turn-over markers are increased in patients with recent fractures.

One of the limitations of our study and similar studies is the reliability of BMD measurements.

### What Is Already Known?

- Intravenous bisphosphonates have beneficial effects in children with Osteogenesis imperfecta.

### What This Study Adds?

- Alendronate, an oral bisphosphonate, is also effective and safe for treating children with osteogenesis imperfecta.

Available *z*-score references are based on limited normative data from healthy, normal-sized children. Since they are based on areal densities, there may be falsely low results in OI children who are small for age or who have deformities. However, overall, the DXA, X-ray findings, laboratory, and clinical responses of patients on oral bisphosphonates were impressive compared with pretreatment values.

The dosage of alendronate and periodicity varies among the centers. In this study we used very low dose of alendronate (0.37 mg/kg/day) compared with DiMeglios's study (1 mg/kg/day), similar to study of Vyskocil, *et al.*(19). It seems that lower doses of alendronate are as effective as higher dose in improving fractures, BMD and bone resorption. It will be reasonable to use lower doses of alendronate in the context of long term side effect of bisphosphonates in children.

Numerous questions have been raised regarding bisphosphonate therapy in childhood(20-23). As bisphosphonates accumulate in the bone and might continue to exert effects as they are gradually released from bone even after treatment is discontinued, the long-term safety of bisphosphonate therapy is unknown(23,24). Cyclic bisphosphonate therapy results in distinctive radiographic findings in the growing skeleton, such as metaphyseal bands and increased BMD(21). Excessive doses of pamidronate may result in osteopetrosis-like syndrome(22). We did not observe such findings in our patients. Continuous oral therapy with bisphosphonates does not appear to result in metaphyseal bands and/or osteopetrosis in a duration of up to 4 years of treatment. Alendronate appeared to be safe in children with osteogenesis imperfecta in our study. No child on active treatment complained

of gastrointestinal discomfort and the stool tests for occult blood remained negative. There was no impairment of renal or hepatic function.

Finally, there are significant financial reasons to explore the benefits of oral bisphosphonates as well. According to 2003 average wholesale price data, one month of treatment with pamidronate is about 10 times costly than for one month of alendronate(25).

In conclusion, this study provides evidence that oral alendronate therapy is effective and safe up to four years of treatment and is a viable option in treatment of osteogenesis imperfecta.

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