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Clinical Characteristics and Treatment Outcomes of Children with Primary Osteoporosis

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What is already known on this topic?

- *Osteogenesis imperfecta (OI) is the commonest cause of primary osteoporosis (POP). The other types are rare.*
- *After bisphosphonate therapy, improvement in bone pain, activation score, and the number of fractures have not been evaluated in all groups of POP.*
- *There is no sufficient clinical experience with zoledronic acid in the pediatric age group.*

What this study adds on this topic?

- *After bisphosphonate therapy (pamidronate/zoledronic acid), we showed improvement in deformity severity score, activation score, fractures, and height-adjusted Z-score in non-OI patients.*
- *Significant improvements in increasing the BMD Z-score, and the activation score, and decreasing the pain, deformity, and fractures were shown in OI and non-OI patients with POP.*

ABSTRACT

Objective: Primary osteoporosis is a rare and essential problem in childhood that can cause severe skeletal deformities. We aimed to reveal the spectrum of primary osteoporosis and assess the effectiveness and safety of bisphosphonates in increasing bone mineral density and reducing fractures.

Materials and Methods: Patients with primary osteoporosis who received at least one course of pamidronate or zoledronic acid were included in the study. Patients were divided into 2 groups, osteogenesis imperfecta and non-osteogenesis imperfecta subjects. We evaluated bone densitometer parameters, activation scores, pain status, deformity status, and the number of fractures per year in all patients.

Results: Of the 31 patients, 21 with osteogenesis imperfect, 3 patients with spondyloocular syndromes, 2 with Bruck Syndrome, and 5 with idiopathic juvenile osteoporosis were included. A total of 21 patients had received pamidronate treatment, while only 4 received zoledronic acid, and 6 of them switched from pamidronate to zoledronic acid. At the end of the treatment, the mean bone mineral density height-adjusted Z-score increased from -3.39 ± 1.30 to -0.95 ± 1.34. The number of fractures per year decreased from 2.28 ± 2.67 to 0.29 ± 0.69. The activation score increased from 2.81 ± 1.47 to 3.16 ± 1.48. The pain decreased significantly. There was no difference in bone mineral density increase in patients treated with pamidronate or zoledronic acid.

Conclusion: Those with osteogenesis imperfecta were diagnosed at an earlier age with severe deformity and fractures. Pamidronate and zoledronic acid increased bone mineral density in all types of primary osteoporosis.

Keywords: Activation score, bisphosphonates, idiopathic juvenile osteoporosis, osteogenesis imperfecta, primary osteoporosis

INTRODUCTION

Childhood osteoporosis is usually defined by a clinically significant fracture (vertebral compression fracture) or a history of significant fracture and low bone mineral density (BMD). The most crucial feature of fractures is the fragility of the bone, where the fracture is seen as a result of minimal trauma.[1,2] Dual-energy x-ray absorptiometry (DXA) is informative about bone.

Two categories of osteoporosis have been identified: primary and secondary. Primary osteoporosis (POP) is prone to bone fractures due to genetic reasons. Osteogenesis imperfecta (OI) is the commonest cause of POP.[1,3,4] Its incidence is 1 in 15 000 to 20 000 births.[5] Osteogenesis imperfecta-like syndromes (Bruck Syndrome, Osteoporosis Pseudoglioma Syndrome, Ehlers–Danlos Syndrome, Marfan Syndrome, Cleidocranial dysplasia, Spondylo-ocular Syndrome,

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Hajdu–Cheney Syndrome) and idiopathic juvenile osteoporosis (IJO) are other causes of POP.[6] Treatment options vary according to the disease's severity and the patients' age. The primary effect of bisphosphonate therapy is to increase BMD and decrease the number of fractures. The secondary effect is a change in biochemical markers of bone and mineral metabolism. However, the underlying hypothesis of treatment is that increased bone volume will benefit bone strength, even if the new bone also contains defective collagen. Bisphosphonates have a long half-life in the bone, and effects on bone density persist for years after discontinuation of therapy.[3,5]

To the best of our knowledge, studies on POP use data from OI patients to define the characteristics of POP. While an increase in bone density has been reported with bisphosphonate treatment, few studies have evaluated features such as improvement in bone pain, change in activation score, and the number of fractures. The fractures might be due to the disease's nature or related to bisphosphonate therapy, which is a matter of debate.

This study aimed to reveal the spectrum of POP in childhood. We also aimed to assess the effectiveness and safety of bisphosphonates in increasing BMD, reducing fractures, and improving clinical function such as activation score, deformity severity score, and pain status in people with POP.

MATERIALS AND METHODS

The retrospective study included 31 children (17 girls and 14 boys) with POP. All patients were categorized into 2 groups in terms of their diagnoses: patients with OI and other types of POP. Three patients with spondyloocular syndromes, 2 with Bruck Syndrome, and 5 with IJO were classified as non-OI group (Figure 1).

This study was approved by the ethical committee of Ankara University (approval number: 2020/226-7).

Inclusion and Exclusion Criteria

All patients (0-18 years old) with POP, treated with at least one course of biphosphonates (pamidronate [PA], zoledronic acid [ZA], or both) and followed up from 2000 to 2020 at our outpatient unit, were included in the study (1 course of ZA 0.1 mg/kg/year and 1 course of PA 9 mg/kg/year).

In all children, the POP diagnosis was based on the International Society for Clinical Densitometry (ISCD) 2013 Pediatric Official Positions algorithm. The following criteria were necessary for diagnosing: the presence of a clinically significant fracture history accompanied by a DXA BMD Z-score ≤−2.0, or ≥1 vertebral compression fracture in the absence of high-energy trauma, or local disease, irrespective of BMD. Clinically significant fracture history is defined as ≥2 long bone fractures by age 10 years or ≥3 long bone fractures at any age up to 19 years in the absence of high-energy trauma.[7]

We excluded patients with secondary osteoporosis or on another bone treatment.

Data

We collected data from electronic and paper-based documents of all patients. We assessed the demographic information, clinical presentations, fracture history, treatment procedures, pre- and posttreatment BMD, number of fractures, and deformity activation score of patients from the medical records. At each visit, patients underwent a comprehensive clinical examination. Adverse events related to treatment were also questioned. The height of all patients was measured with Harpenden stadiometers. Height Z-scores were calculated with the online calculator with reference to the Turkish population.[8,9] All patients' body mass index (BMI) was calculated.

Patients were followed up regularly every 3-6 months. Serum calcium, phosphate, alkaline phosphatase, parathyroid hormone, and 25-OH vitamin D levels were checked according to standard laboratory methods.

Bone ages and anteroposterior and lateral radiographs of the thoracal and lumbar spine were reevaluated yearly. Suspected fractures were located by radiographs. Bone mineral density measurement adjusted for body surface area, age, gender, and height. BMD Z-scores evaluated per year, using DXA devices (Hologic DXA scan) under a standardized protocol. Bone mineral density measurements and height-adjusted LS BMD Z-scores were calculated using age and gender for the Turkish population, and an online calculator was available online at CEDD.[8] We reevaluated all BMD measurements using the ISCD 2013 Pediatric Official Positions algorithm.[7] All measures were assessed during pretreatment, during treatment,

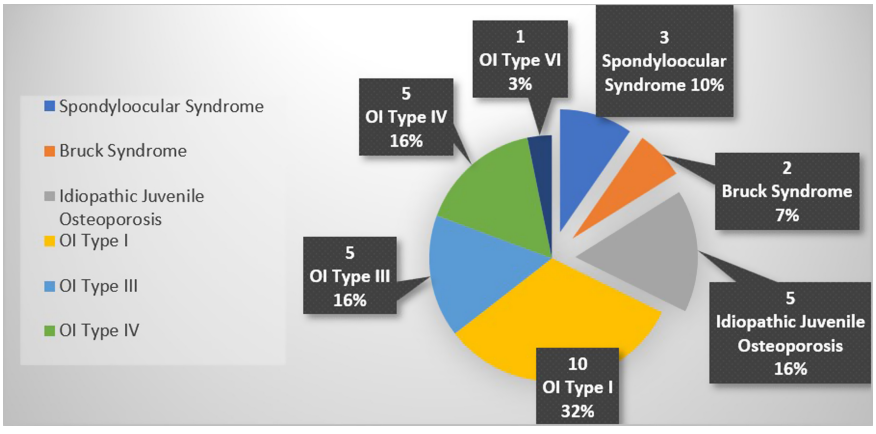

Figure 1. The distribution of patients with primary osteoporosis. OI, osteogenesis imperfecta.

and posttreatment. Z-scores less than −2.0 were accepted as low. In the follow-up BMD, we reduced therapy to maintenance if the height-adjusted Z-score was >0 standard deviation (SD).[2]

All children were on the same treatment protocol. Pamidronate was administered iv 1 mg/kg/day on 3 consecutive days of the treatment course and repeated every 3 months. Zoledronic acid was administered iv 0.05 mg/kg/dose at 6-monthly intervals. Vitamin D and calcium (Ca) status were checked for all patients before the treatment. Calcium supplementation was given for 14 days following the bisphosphonate treatment. 25 OH vitamin D prophylaxis is recommended for all patients. Patients were on no other bone-specific treatment. Treatment responsiveness was evaluated according to an increase in the Z-score of BMD, activity score, and decrease in fracture rate, pain, and deformity score after the initiation of treatment. We defined a decrease in pain with the disappearance of the patient's complaint in the control visits. Activity score was evaluated as followings: "0" for walking impossible, "1" for walking possible but not functional enough to be useful: physical therapy walker, "2" for a household walker, "3" for a walk outside the home but limited to the neighborhood (2 to 3 blocks): neighborhood walker, "4" for community walker.[10] The deformity score was calculated according to the degree of long bones and vertebral deformities, scoliosis, and the presence of fractures. It was scored as follows: no deformity and no fracture were scored as "0," no deformity but the presence of fracture was scored as "1," mild deformities (noticed only by x-rays) and no scoliosis were scored as "2," moderate deformities (noticed by both clinical examination and x-rays affecting isolated long bones/vertebra) ± mild scoliosis were scored as "3," severe deformities (clearly visible by clinical examination and x-rays affecting all long bones/vertebra) and severe scoliosis were scored as "4." We adapted this scoring system from "Proposed scoring system of OI patients."[11] The presence/absence of pain was assessed from patients' follow-up forms.

All data had been recorded on our department's standard case forms, which had been created for patients with osteoporosis. Using the data detailed above, we evaluated changes in the pre- and posttreatment status of the whole group, OI group, and non-OI group.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences, version 21.0 (IBM Corp., Armonk, NY, USA). Data were expressed as the mean ± SD, median [minimum; maximum]. The Shapiro–Wilk test evaluated the normality of variables. Descriptive analyses were presented using means and SDs for normally distributed variables. Paired sample *t*-test was used to compare the mean values of continuous variables. The Wilcoxon signed-rank test with appropriate confidence intervals was used to compare the nonparametric measurements. A *P*-value of less than .05 was considered to show a statistically significant result in all analyses.

RESULTS

Thirty-one patients (F/M = 17/14) were included in the study. The patients included 21 with OI, 3 with spondyloocular syndromes, 2 with Bruck Syndrome, and 5 with IJO (Figure 1). The mean age at diagnosing was 6.95 ± 4.53 [5.29 ± 3.97 for OI]. The follow-up period was 5 ± 4.29 years (Table 1).

Patients with OI were diagnosed at a younger age. They had similar height and BMD (g/cm^2) to the non-OI group. Thirteen of these had a family history of OI. According to the expanded Sillence classification,[12] 10 were type I, 5 were type III, 5 were type IV, and 1 was type VI OI.

Four of the OI group had a pathological variant in *COL1A1.* Two of them had a pathological variant in *COL1A2.* The molecular

Table 1. Characteristics and Laboratory Findings of all Osteogenesis Imperfecta (OI) Patients Before and After Treatment

All Groups	**n**	**Before Treatment**	**After Treatment**	***P***
Age (year)	31	6.95 ± 4.53	11.95 ± 5.55	–
Gender	31	F: 17 (54.8%)	F: 17 (54.8%)	–
		M: 14 (45.2%)	M: 14 (45.2%)	–
Height SD	31	−2.1 ± 2.28	−2.30 ± 2.37	.03
BMI (kg/m^2)	31	17.71 ± 4.39	19.96 ± 5.38	.002
%BMI	31	98.75 ± 23.88%	103.65 ± 22.04%	.74
Puberty stage	31	Prepubertal: 21 (67.7%)	Prepubertal: 9 (29%)	–
		Pubertal: 10 (32.3%)	Pubertal: 22 (71%)	-
Laboratory findings:				
Ca (mg/dL)	31	9.67 ± 0.57	9.64 ± 0.52	0.31*
P (mg/dL)	31	4.86 ± 0.65	4.45 ± 0.66	0,003
ALP (IU/L)	31	240.19 ± 99.14	221.29 ± 94.99	0.55*
25OH-D3 (ng/mL)	26	30.91 ± 15.52	21.26 ± 10.03	0.005*
PTH (pg/mL)	14	33.11 ± 16.45	36.75 ± 13.72	0.10*
Urine Ca/creatinine	24	0.16 ± 0.12	0.12 ± 0.08	0.39*
OI Group	**n**	**Before Treatment**	**After Treatment**	***P***
Age (year)	21	5.29 ± 3.97	10.89 ± 5.72	–
Gender	21	F: 15 (%71.4)	F: 15 (%71.4)	–
		M: 6 (%28.6)	M: 6 (%28.6)	–
Height SD	21	-2.14 ± 2.66	-2.48 ± 2.69	.79
BMI (kg/m^2)	21	15.34 ± 4.07	18.10 ± 3.61	.03
%BMI	21	93.21% ± 18.93%	97.84% ± 14.70%	.26
Puberty stage	21	Prepubertal: 21 (67.7%)	Prepubertal: 9 (29%)	–
		Pubertal: 10 (32.3%)	Pubertal: 22 (71%)	–
Laboratory findings				
Ca (mg/dL)	21	9.76 ± 0.54	9.72 ± 0.55	.32*
P (mg/dL)	21	5.06 ± 0.64	4.48 ± 0.65	<.001
ALP (IU/L)	21	253.76 ± 94.32	235.19 ± 97.41	.60*
25OH-D3 (ng/mL)	18	32.90 ± 17.31	19.92 ± 10.36	.002*
PTH (pg/mL)	8	33.02 ± 17.93	30.5 ± 1.13	.67*
Urine Ca/creatinine	18	0.18 ± 0.12	0.14 ± 0.09	.39*

BMI: body mass index; OI, osteogenesis imperfecta; SD, standard deviation.

analysis of rest has not resulted since they were old patients, and confirmation of the diagnosis by molecular analysis was not routine 20 years ago. Three of spondyloocular syndrome had a pathological variant in *LRP5*. Five of the IJO had no mutation in *COL1A1* and *COL1A2*. All variants were well-known mutations that were defined in the databases. Inborn metabolic errors such as lysinuric protein intolerance were ruled out, and whole exome sequencing was being studied in patients with IJO.

All patients with POP had received bisphosphonate therapy. A total of 21 patients received PA treatment, while only 4 received ZA, and 6 of them switched from PA to ZA. Laboratory results were in normal ranges at the beginning of the treatment, and no significant changes in these levels were observed after treatment (Table 1).

In all, BMD was low at baseline. After 1 course of bisphosphonate therapy, the BMD of all patients significantly increased and reached a higher Z-score. At the end of the treatment, the total BMD increased. The change in BMD was the same in the OI group and all groups (Table 2). Median BMD Z-score ($P <$ .001; 99.9%), and height-adjusted Z-score increased ($P <$ .001; 99.9%) after treatment. After treatment, improvement in BMD of the patients in the non-OI group was shown in Table 3.

Regarding the treatment regimen, PA and PA following ZA therapy caused BMD improvement in POP and OI (Table 2). It could not be proved statistically in the ZA group because of the lack of sufficient patients. Changes in bone mass, expressed as Z-scores, over the first and second course, and total changes at the end of bisphosphonate treatment are shown in Figure 2.

The median age of the first fracture for the OI group was 1 (min: 0.08; max: 10). After treatment, the percentage of fractures decreased from 62.09% to 1.90% in the OI group.

In all groups, low limb fracture (45.02%) was mostly seen and upper limb fracture (42.18%) followed. The femur was the most commonly affected bone before treatment, followed by the tibia. The number of fractures per year decreased from 2.28 ± 2.67 (for OI 3.26 ± 2.66) to 0.29 ± 0.69 (for OI 0.33 ± 0.64) ($P <$ .001; 98.01%). The non-traumatic vertebral fracture was mostly seen in the non-OI group. At baseline, biconcave vertebral deformity and a wedge deformity were found in all children, and at the follow-up visit, a significant improvement was observed (Figure 3). At the time of admission, all patients with other types of POP had vertebral compression (crush) fractures; however, only 3 in the OI group had.

The activation score increased from 2.81 ± 1.47 to 3.16 ± 1.48 in the POP group. After treatment, 74.2% of patients had an

Table 2. Improvement in Bone Mineral Density (BMD) of the Patients in All Imperfecta Osteogenesis (OI) Group

All Groups	**n**	**Pretreatment**	**After Treatment**	***P***	**Power (%)**
Deformity severity	31	1.87 ± 0.79	1.16 ± 1.05	<.001*	99.8
Activation score	31	2.81 ± 1.47	3.16 ± 1.48	.24	–
Number of fractures per a year	31	2.28 ± 0.67	0.29± 0.69	<.001	98.01
Total BMD (g/cm^2)	31	0.31 ± 0.11	0.53 ± 0.13	<.001	99.9
Total BMC (g)	18	8.82 ± 4.93	16.09 ± 8.1	<.001*	90.2
Surface area (cm^2)	18	26.02 ± 9.03	32.2 ± 10.2	.005*	48.2
Height-adjusted total BMD Z-score					
Pretreatment–first end of course	29	−3.33 ± 1.23	−1.89 ± 1.36	<.001*	98.8
Before second course–after second course	22	−2.22 ± 1.06	−1.58 ± 1.29	.12*	-
Pretreatment–end of treatment	31	−3.39 ± 1.30	−0.95 ± 1.34	<.001	99.9
Height-adjusted total BMD Z-score (patients with only PA)					
Pretreatment–end of treatment	21	−3.28 ± 1.17	−1.30 ± 1.07	<.001*	99.9
Height-adjusted total BMD Z-score (patients with PA and PA followed by ZA)					
Pretreatment–End of treatment	27	−3.36 ± 1.35	−1.24 ± 1.23	<.001*	99.9
Osteogenesis imperfecta group	**n**	**Pretreatment**	**After treatment**	***P***	**Power (%)**
Deformity severity	21	1.81 ± 0.79	1.00 ± 0.93	<.001	86.30
Activation score	21	2.62 ± 1.53	3.14 ± 1.42	.03	20.65
Number of fractures per a year	21	5.14 ± 6.02	0.19 ± 0.50	<.001	98.01
Total BMD (g/cm^2)	21	0.29 ± 0.09	0.49 ± 0.11	<.001	99.9
Total BMC (g)	14	8.17 ± 5.11	14.67 ± 7.3	.001	78.2
Surface area (cm^2)	14	24.69 ± 9.19	30.95 ± 9.3	.01	43.3
Height-adjusted total BMD Z-score					
Pretreatment–end of first course	20	−3.29 ± 1.12	−2.06 ± 1.00	<.001	95.6
Before second course–after second course	18	−2.17 ± 0.99	−1.54 ± 1.13	.08	-
Pretreatment–end of treatment	21	−3.25 ± 1.11	−1.04 ± 1.12	<.001	99.9
Height-adjusted total BMD Z-score (patients with only PA)					
Pretreatment–end of treatment	16	−3.21 ± 0.97	−1.40 ± 0.65	<.001	99.9
Height-adjusted total BMD Z-score (patients with PA and PA followed by ZA)					
Pretreatment–end of treatment	18	−3.15 ± 1.11	−1.37 ± 0.90	<.001	99.9

BMC, bone mineral concentration; BMD, bone mineral density; PA, pamidronate; ZA, zoledronic acid.

Table 3. Improvement in Bone Mineral Density (BMD) of the Patients in Non-osteogenesis Imperfecta (Non-OI) Group

Non-osteogenesis Imperfecta Group	n	Pretreatment	n	After Treatment	*P*
Age (year)	10	10.42 ± 3.54	10	14.17 ± 4.40	-
Activation score	10	3.20 ± 1.25	10	3.30 ± 1.42	.79
Deformity severity	10	2.00 ± 0.77	10	1.50 ± 1.20	**.03**
Height SD	10	−2.02 ± 1.07	10	−1.92 ± 1.43	.88
BMI (g/cm²)	10	20.68 ± 5.67	10	23.85 ± 6.34	**.02**
Laboratory findings					
Ca (mg/dL)	10	9.48 ± 0.58	10	9.47 ± 0.39	.68
P (mg/dL)	10	4.44 ± 0.42	10	4.39 ± 0.68	.67
ALP (IU/L)	10	211.70 ± 102.90	10	192.10 ± 82.39	.96
25OH-D3 (ng/mL)	10	32.93 ± 20.24	9	23.23 ± 8.55	.83
PTH (pg/mL)	8	32.55 ± 12.94	7	48.64 ± 18.63	**.03**
Urine Ca/creatinine	10	0.08 ± 0.09	6	0.08 ± 0.04	.75
Total BMD (g/cm²)	10	0.36 ± 0.13	10	0.60 ± 0.13	**.005**
Total BMC (g)	4	11.12 ± 3.32	4	21.07 ± 8.88	.07
Surface area (cm²)	4	30.66 ± 6.57	4	36.32 ± 11.38	.14
Height-adjusted total BMD Z-score					
Pretreatment–end of first course	10	−3.68 ± 1.60	9	−1.51 ± 1.88	**.04**
Before second course–after second course	9	−1.51 ± 1.88	5	−1.20 ± 1.96	.72
Pretreatment–end of treatment	10	−3.68 ± 1.60	10	−0.77 ± 1.77	**.007**
Height-adjusted total BMD Z-score (patients with only PA)					
Pretreatment–end of treatment	5	−3.48 ± 1.63	5	−0.98 ± 1.81	.08
Height-Adjusted Total BMD Z-Score (patients with PA and PA followed by ZA)					
Pretreatment–end of treatment	9	−3.76 ± 1.67	9	−0.96 ± 1.66	.01

BMC, bone mineral concentration; BMD, bone mineral density; PA, pamidronate; ZA, zoledronic acid.

activation score of 4. Physical activity was very low at the baseline, especially in patients with OI. The increase in activation score was evident in the OI group.

Before treatment, 51.6% of patients suffered from pain, and at the end of therapy, only 3.2% still had pain. The pain decreased, and the level of deformity improved in each group ($P_{OI} < .001$; 99.8% and $P_{non\text{-}OI} < .001$; 99.8%).

Adverse reactions were most common in the first treatment episode. None had side effects in any treatment episode. Three pamidronate-treated patients had adverse reactions such as flu-like symptoms, fever, and leukopenia. Three ZA-treated patients had the same adverse effects, flu-like symptoms, and fever (n = 3). In follow-up, no long-term adverse effects were observed with bisphosphonates.

DISCUSSION

Osteogenesis imperfecta has many different presentations. The most well-known manifestation is long bone fractures. Five of our patients with OI type 1 had mild symptoms. Since OI type 2 was lethal, we had no patients in this group. There were 5 patients with severe OI type 3 with multiple fractures, and they had the lowest height SD. Five of the OI type 4 had modest deformities. We noticed that OI type 1 had treatment due to vertebral fractures. The other OI types were diagnosed earlier with long bone fractures and treated earlier.

The 2 major problems encountered by OI are the low amount of bone and low bone quality. Current treatment options increase the amount of bone but do not change the bone quality. Primary osteoporosis treatment options vary depending on the disease's severity and the patients' age. It has been shown that bisphosphonates increase bone densitometry in OI and provide biochemical improvement. Its contribution to the quality of life and fracture rate reduction in OI is unclear.[3] In most children with OI, there were increased regional bone density DXA Z-score gains during the first year of treatment.[13-16] It has been reported that maximum bone density and histology benefits are achieved after 2-3 years of treatment.[5] In the follow-up, although height SD seemed to decrease, several types of OI had multiple operations, and bisphosphonate might have prevented several losses in height SD. The activation score was the lowest in the OI group at the presentation. Vertebral compression fractures were mostly found in patients with spondyloocular syndrome, Bruck Syndrome, and IJO. Other POP seemed to be a self-limiting disease. The fracture rate reduced surprisingly faster after treatment.

In the studies reported in the last Cochrane review, an increase in bone density was reported with bisphosphonate therapy. Still, improvement in bone pain and fracture incidence could not be evaluated.[4] In our study, we showed a reduction in pain, improvement in deformity severity score, and reduction in the fracture in addition to the improvement in BMD.

A total of 80% of patients experience flu-like symptoms (fever, bone pains, myalgia, and nausea/vomiting) within 24–48 hours after the first infusion, and rarely hypocalcemia, iritis, atypical femoral fracture, osteonecrosis of the jaw joint, teratogenic effects, and esophagitis.[2] We found a very low frequency of side effects in our follow-up with regular clinical and laboratory evaluations.

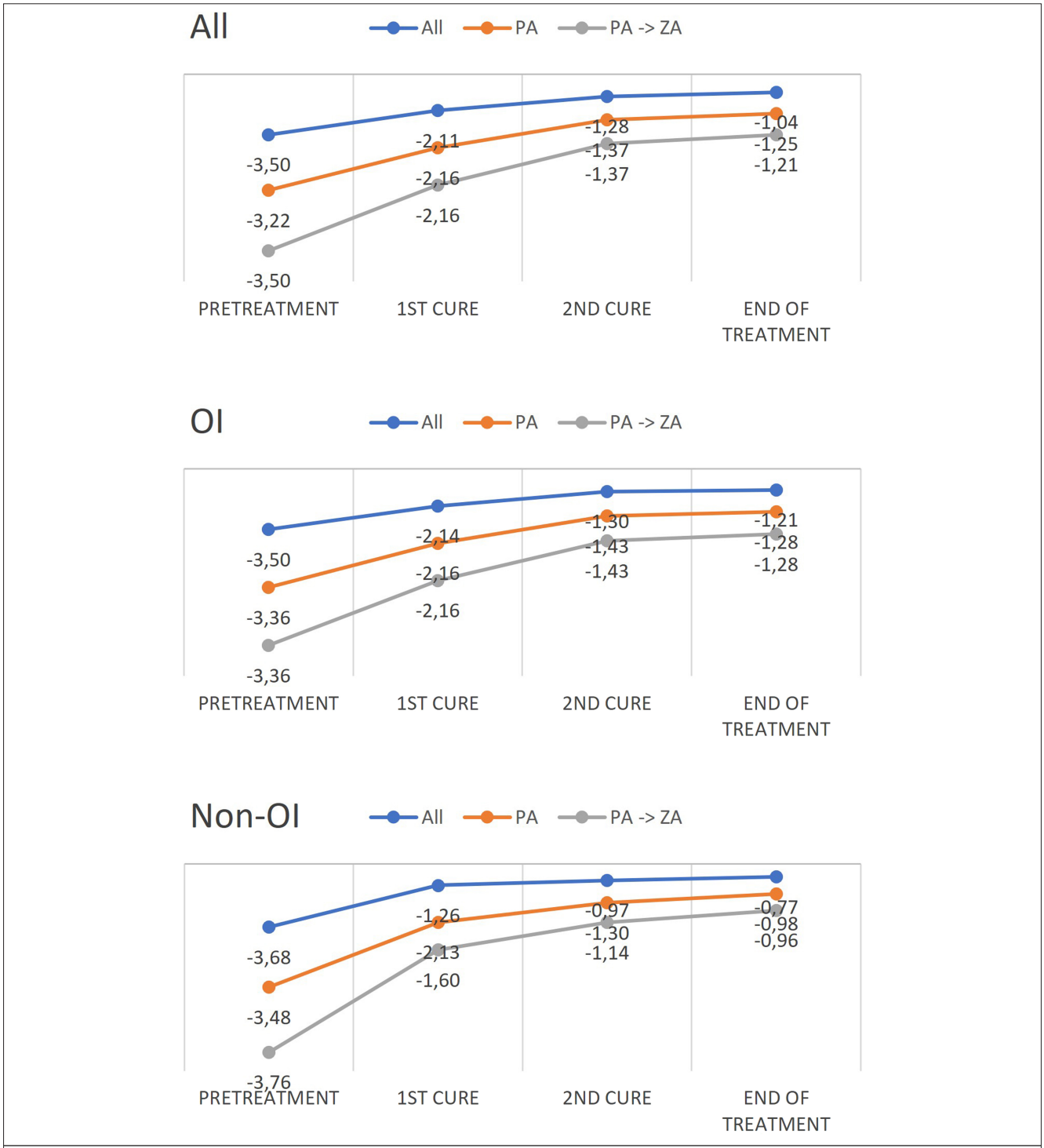

Figure 2. Medians of height-adjusted BMD Z-score of all patients (1) and osteogenesis imperfecta (OI) patients (2). A is for all types of bisphosphonates, B is for only pamidronate (PA), and C is for PA+zoledronic acid (ZA).

In a study, 37 children with OI (OI type I, n = 1; OI type III, n = 14; and OI type IV, n = 22) were assessed on intravenous bisphosphonate treatment (PA or ZA) for approximately 6 years. The mean lumbar BMD Z-score increased; however, fracture rates were not decreased.[17] In our study, children with OI consisted of 10 type I, 5 type III, 5 type IV, and 1 type VI OI. Fracture rates might depend on the patients' OI type. The number of our patients classified in severe type OI was lower.

Baroncelli et al[18] investigated the effect of long-term pamidronate treatment in 9 patients (4 of them were not treated). Bone pain and fracture rate were higher in untreated patients. Lumbar BMD Z-scores improved in the treated group. In our

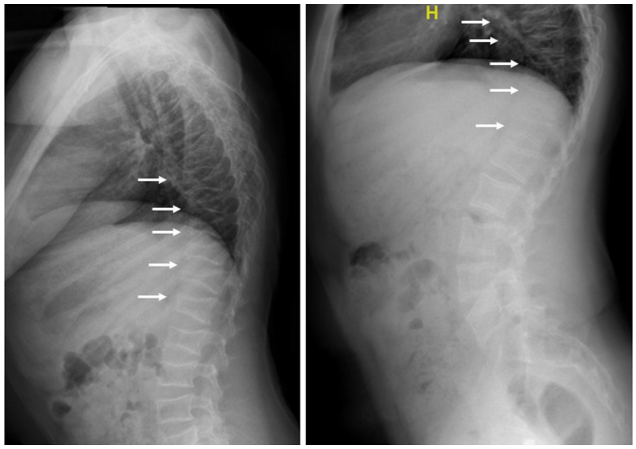

Figure 3. Lateral lumbar spine radiograph of a boy with spondyloocular syndrome. Left panel: At the start of treatment. All vertebrae have compression fractures. Right panel: 3 years of pamidronate treatment.

study, we showed an improvement in deformity severity score, activation score, fractures, and height-adjusted Z-score in 10 non-OI patients.

A study with POP indicated that clinical features, age at diagnosis, and inheritance patterns were different. Most of the parents had low BMD. They emphasized that it is substantial to perform molecular analysis to understand the main mechanism of POP.[19] The limitation of our study is that although most of the patients' diagnoses were genetically confirmed, some of them started to follow-up a long time ago, and their molecular analyses are still being studied. We could not assess the genotype–phenotype correlation. However, other studies with Turkish OI patients could not find a genotype–phenotype correlation.[20] Although the diagnosis is supported by various imaging techniques, histology, and genetic analysis, the diagnosis of POP still depends on the disease history and examination.[1] Since our study was retrospective, we could not share patients' previous bone turnover data.

In our study, we investigated the effect of iv biphosphonate treatment. Although oral alendronate was mentioned in the literature that increased the bone density of OI patients[21] and did not seem adequate for fractures, we could not experience its effect. Zoledronate seemed to have similar effectiveness as pamidronate; we could not prove it statistically. Only 5 patients were on zoledronate from the beginning of the treatment, as zoledronate was found to be easy to administer.

The other limitation of our study was the number of our patients, which was limited even though we included all patients diagnosed in a single center. Although all groups showed standard characteristic features, subtypes had specific features. We believe this pilot study will be a model for prospective national studies, evaluating all subtypes individually.

Our study highlights that POP should be evaluated according to underlying pathology. The OI group was diagnosed earlier, so the treatment was initiated earlier. Although the effects of bisphosphonates in patients with OI are relatively well-known, there is less experience with treatment and results in non-OI POP patients. Bisphosphonates are also effective in non-OI patients, treatment results are satisfactory, and the side-effect profile is no different. Current evidence demonstrated significant improvement in increasing the BMD Z-score and the activation score and decreasing the pain, deformity, and fractures using bisphosphonates in both groups. It should be kept in mind that current treatment options focus on ameliorating signs and symptoms. It does not cure the fundamental problem, which lies in bone formation.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ankara University, (approval no: I7-420-20).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

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