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Research Article

ELEVEN-YEAREXPERIENCE WITH ALENDRONATE TREATMENT IN A PREMENOPAUSAL WOMAN WITH OSTEOGENESIS IMPERFECTA TYPE I

Jun Iwamoto, Yoshihiro Sato, Hideo Matsumoto

Institute for Integrated Sports Medicine, Keio University School of Medicine, Tokyo, Japan.

ABSTRACT

We report the 11-year follow-up of a premenopausal woman with osteogenesisimperfecta (OI) who was treated with alendronate. A 41-year-old Japanese premenopausal woman with OI type I who had frequently experienced painful fragility fractures consulted our clinic because of chronic back pain associated with spinal osteoporosis. She had undergone heart surgery (aortic valve replacement) because of aortic regurgitation 5 years before her first consultation with our clinic. After surgery, she began taking warfarin (3 mg/day), and this treatment was continued during our follow-up period. She was treated with alendronate (5 mg/day or 35 mg/week) for 11 years. The patient's urinary cross-linked N-terminal telopeptides of type I collagen and serum alkaline phosphatase levels decreased, while the bone mineral density of her lumbar spine (L2–L4) increased, as measured using dual energy X-ray absorptiometry. The serum calcium and phosphorus levels stayed within the normal ranges. Three non-vertebral fractures occurred at the hip, ankle, and ring finger during the 11-year treatment period, but no adverse effects were observed. Thus, the present case report showed the long-term outcome and safety of alendronate treatment in a premenopausal woman with OI type I.

Keywords: alendronate, fragility fracture, bone mineral density (BMD), osteogenesis imperfect, high bone turnover.

INTRODUCTION

Osteogenesisimperfecta (OI) is a heterogeneous group of genetic disorders that affects the integrity of connective tissue. The hallmark of OI is bone fragility, although other manifestations, including osteoporosis, dentigenesisimperfecta, blue sclera, easy bruising, joint laxity, and scoliosis, are also common among OI patients. The severity of OI ranges from prenatal death to mild osteopenia without limb deformity. Most forms of OI result from mutations in the genes that encode either the pro a1 or pro a2 polypeptide chains that comprise type I collagen molecules, the major structural protein of bone [1].

The fracture rate decreases with maturation in patients with OI [2,3].This clinical stability of the disease may be associated with bone maturation. Despite the reduced fracture rate, the bone mineral density (BMD) usually remains low in adults with OI; however, the optimal long-term strategy for increasing the BMD and subsequently preventing fractures in adults with OI remains uncertain.

Although OI is an inheritable disorder of bone formation, resulting in bone fragility, the activity of cancellous bone remodeling, bone resorption, and/or bone turnover are also increased [3-7].The efficacy of treatment with cyclical intravenous pamidronate for bone fragility in children with OI has been established [8-13], as intravenous pamidronate prevents fragile fractures without inhibiting bone growth. In adults with OI, although the short-term effectiveness of bisphosphonates on the BMD and the incidence of fractures has been suggested [14,15], very few reports have shown the long-term outcome of bisphosphonate treatment in premenopausal women with OI.

Alendronate is generally accepted as a safe, effective, and well-tolerated treatment for postmenopausal osteoporosis [16-18]; it increases the lumbar and femoral neck BMD and prevents new vertebral and femoral neck fractures. Alendronate preferentially binds hydroxyapatite and inhibits osteoclast-mediated bone resorption by suppressing the recruitment and activity of osteoclasts and shortening their life span [19]. Because alendronate is effective for high turnover osteoporosis including postmenopausal osteoporosis, it may be applicable for adult premenopausal women with OI who exhibit a high bone turnover and a history of multiple fractures, although the efficacy of this treatment had not yet been established. We report the 11-year follow-up of a premenopausal woman with OI type I with high bone turnover and a high fracture rate who was treated with alendronate.

Case Report:

Characteristics of the case:

A 41-year-old premenopausal woman consulted our clinic because of back pain. Despite the subjective symptom of chronic back pain lasting for a few years, she had never received treatment for her

pain. Her height was 132 cm, her body weight was 31 kg, and her body mass index (BMI) was 17.7 kg/m^2. She had experienced heart surgery (aortic valve replacement) because of aortic regurgitation 5 years before her first consultation at our clinic. After the surgery, she began taking warfarin (3 mg/day) and continued until her first consultation; this treatment was continued during our follow-up period.

The patient had experienced more than 20 fractures in the femurs, toes, ribs, and scapulae. Of these fractures, 13 occurred in the femurs. Most of the fractures were experienced during infancy, and the fracture frequency gradually decreased with maturation. Three weeks before her first consultation with our clinic, she experienced a fracture of her scapula.

The 3 clinical criteria of OI – history of fractures, blue sclera, and positive family history – were present. Deformities in the legs, such as antero-lateral bowing of the femurs and anterior bowing of the tibiae, and deformity in the thoracic and lumbar spine were observed. The patient was classified as having Sillence Type I OI [20]. The patient had no past history of metabolic bone diseases other than OI and had never taken medicine that affected bone metabolism other than warfarin. Except for leanness (BMI ≤ 18.5 kg/m^2), she did not have any other clinical risk factors for fractures, including a current cigarette smoking habit, a maternal history of hip fractures, an alcohol consumption ≥2 units daily, an age ≥75 years, or a history of steroid use [21].

To understand the pathogenesis of bone fragility and to determine an effective pharmacological treatment, radiographs of the thoracic and lumbar spine were taken, the BMD was measured, and biochemical analyses were performed. Informed consent was obtained from the patient. The radiographs of the thoracic and lumbar spine showed scoliotic deformity. Because of this scoliotic deformity, the vertebral fractures could not be diagnosed precisely according to the Japanese criteria for vertebral fracture [22,23], namely, patients with a BMD<70% of the young adult mean (YAM) and a BMDof 70%-80% of the YAM along with a history of osteoporotic fractures.

Table 1 shows the characteristics of the present patient. The BMD of the lumbar spine (L2-L4) as measured using dual energy X-ray absorptiometry (DXA) with a Norland XR-36 instrument (Norland, Fort Atkison, WI, USA) was 0.579 g/cm^2, which was 55.7% of the YAM. The region of interest was carefully set. The serum calcium and phosphorus levels were within the normal range. The serum alkaline phosphatase (ALP) level and the urinary cross-linked N-terminal telopeptides of type I collagen (NTX) level measured using an enzyme-linked immunosorbent assay (ELISA) were higher than normal. Osteoporosis and bone fragility caused by OI were diagnosed 2 weeks after her first consultation. Blood examinations revealed no other abnormalities. The active form of vitamin D3, vitamin K2, intramuscular elcatonin, etidronate, and alendronate were available for the treatment of osteoporosis, but teriparatide was not available.

	Baseline	Normal ranges
Age (year)	41	
Height (m)	1.32	
Body weight (kg)	31.0	
Bone mass index (kg/m^2)	17.7	
Lumbar spine BMD (g/cm^2)	0.579	
%YAM in BMD	55.7	≧80
Serum		
Calcium (mg/dL)	8.8	8.5 – 10.2
Phosphorus (mg/dL)	3.2	2.8 – 4.6
ALP (IU/L)	394	100 – 320
Urine		
NTX (nmom BCE/mmol Cr)	96.2	9.3 – 54.3

Table 1: Baseline characteristics of the patient

BMD: bone mineral density, YAM: young adult mean, ALP: alkaline phosphatase, NTX: cross-linked N-terminal telopeptides of type I collagen, BCE: bone collagen equivalent, Cr: creatinine.

Outcome of 11 years of treatment:

Treatment with daily alendronate (5 mg/day)was initiated. Five years and 7 months after the start of treatment, the treatment was switched from daily alendronate to weekly alendronate (35 mg/week). The doses indicated in the parentheses above are the doses used in Japan for the treatment of postmenopausal women with osteoporosis and have been recognized as being safe and effective [24-27]. The patient was treated with alendronate for 11 years. The serum calcium, phosphorus, ALP, and urinary NTX levels were evaluated every year during the 11-year period of the treatment. The lumbar spine BMD was measured after 1, 2, 3, and 11 years of treatment. Radiographs of the thoracic and lumbar spine were also taken after 11 years of treatment to identify new vertebral fractures.

Table 2 shows the longitudinal increase in the lumbar spine BMD during the 11-year period of treatment. The increase in the lumbar spine BMD from baseline was 17.1% at 1 year, 26.3% at 2 years, 28.2% at 3 years, and 30.4% at 11 years.

	Baseline	1 year	2 years	3 year	11 year
Lumbar spine BMD (g/cm^2)	0.579	0.678	0.731	0.742	0.755
% changes from baseline	0	17.1	26.3	28.2	30.4

Table 2: Changes in lumbar spine BMD during the 11-year period of treatment

BMD: bone mineral density.

Figure 1 shows the longitudinal changes in the serum calcium, phosphorus, ALP, and urinary NTX levels during the 11-year period of treatment. The urinary NTX and serum ALP levels decreased at 1-3 years after the start of alendronate treatment and were sustained thereafter. The reduction in the urinary NTX level was 66.1% at 1 year, 78.9% at 2 years, 80.4% at 3 years, and 76.1% at 11 years. The reduction in the serum ALP level was 29.9% at 1 year, 40.9% at 2 years, 54.3% at 3 years, and 48.5% at 11 years.The urinary NTX and serum ALP levels were within the normal ranges after 11 years of treatment (Table 3). The serum calcium and phosphorus levels stayed within the normal ranges during the 11-year period of treatment (Table 3). The serum bone-specific alkaline phosphatase (BAP) level, as measured using a chemiluminescent enzyme immunoassay (CLEIA), and the intact parathyroid hormone (PTH) level, as measured using a chemiluminescent immunoassay (CLIA), were within the normal ranges (Table 3).

	Baseline	11 Years	Normal ranges
Age (year)	41	52	
Height (m)	1.32	1.30	
Body weight (kg)	31.0	33.0	
Bone mass index (kg/m^2)	17.7	19.5	
Lumbar spine BMD (g/cm^2)	0.579	0.598	
Serum			
Calcium (mg/dL)	8.8	9.0	8.5 – 10.2
Phosphorus (mg/dL)	3.2	2.9	2.8 – 4.6
ALP (IU/L)	394	203	100 – 320
Bone-specific ALP (I/U)		11.6	9.6 –35.4
Intact PTH (pg/mL)		36	12 – 61
Urine			
NTX (nmom BCE/mmol Cr)	96.2	23.0	9.3 – 54.3

Table 3: Patient data after 11 years of treatment

BMD: bone mineral density, ALP: alkaline phosphatase, PTH: parathyroid hormone, NTX: cross-linked N-terminal telopeptides of type I collagen, BCE: bone collagen equivalent, Cr: creatinine.

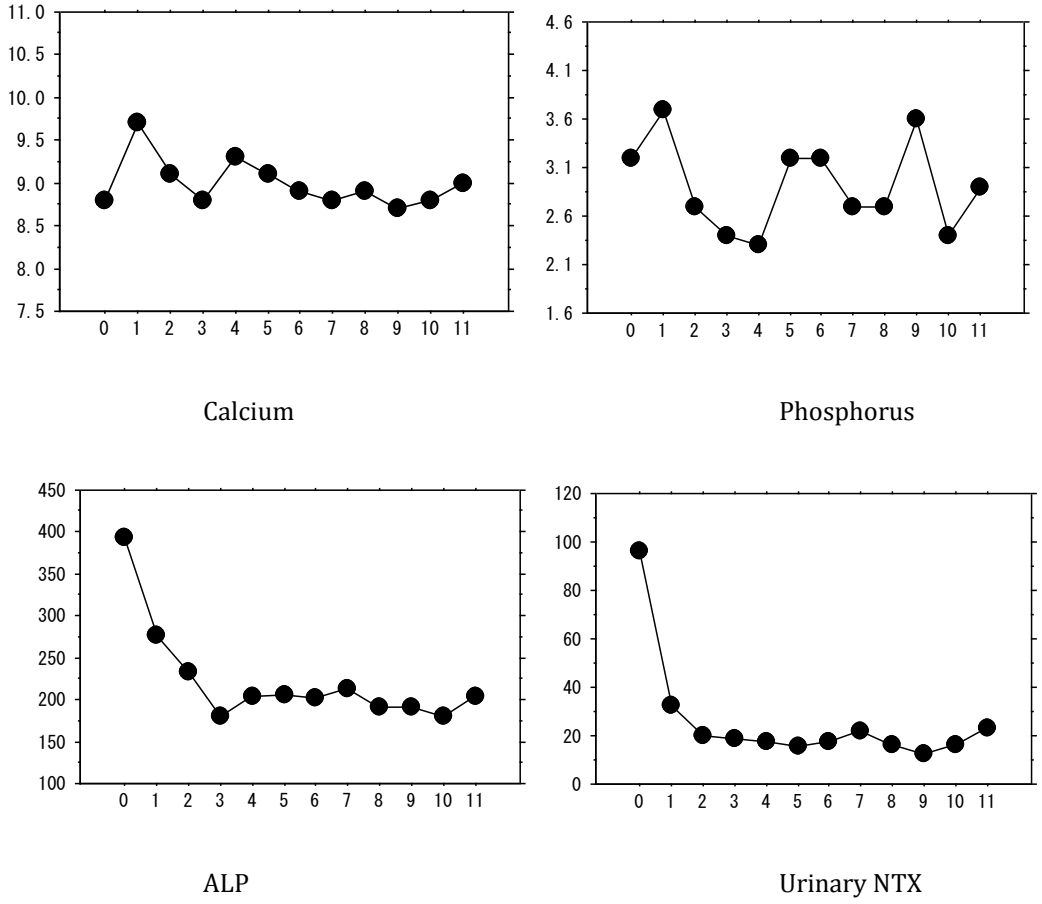

Figure 1: Changes in biochemical markersduring the 11-year period of treatment

The radiographs of the thoracic and lumbar spine obtained after the 11 years of treatment did not show any marked changes in scoliotic deformity and the height of each vertebra, suggesting that no new vertebral fractures had occurred.

Three non-vertebral fractures occurred at the hip, ankle, and ring finger during the 11 years of the treatment period. No adverse events, including upper gastrointestinal tract symptoms, osteonecrosis of the jaw [28], and atypical fractures of the femur [29], were observed.

DISCUSSION

Osteogenesisimperfecta is a congenital disease of which the main characteristic is bone fragility. Although fragile fractures occur frequently in children with OI, the fracture rate decreases after adolescence because of the influences of sex hormones and maturation [2,3].Thus, the clinical stability of OI is usually observed with age, and this is an important characteristic of the disease. The present patient had been experiencing frequent fragile fractures, and the rate of these fractures, especially at the long bones, had decreased with maturation. However, the patient had osteoporosis and had suffered a fracture just before consulting with our clinic. Thus, effective treatment for this condition was considered to be necessary.

The osteoporosis in the present patient was surmised to be associated with a high bone turnover based on high urinary NTX and serum ALP levels. So, an anti-resorptive agent, alendronate, was considered to be the treatment of choice. As a result, the urinary NTX level decreased by 66.1% after 1 year, the serum ALP level decreased by 54.3% after 3 years, and the lumbar spine BMD increased by 30.4% after 11 years. Both the urinary NTX and serum ALP levels were maintained within the normal ranges after 1-3 years of treatment. Furthermore, the serum BAP and intact PTH levels were confirmed to be within the normal ranges after 11 years of treatment. The effect of >10 years of alendronate treatment on BMD and bone turnover markers remains to be established in Japanese patients with osteoporosis. Our previous study showed that alendronate treatment for 7 years increased the lumbar spine BMD by 12.8% in postmenopausal Japanese women with osteoporosis [30]. Thus, alendronate treatment normalized the urinary NTX and serum ALP levels and successfully increased the lumbar spine BMD in the present patient. However, three clinical fractures occurred at the hip, ankle, and ring finger, although no morphometric vertebral fractures occurred at the thoracic spine during the 11-year treatment period. Whether the treatment applied in the present patient was effective remains uncertain from the perspective of fracture prevention.

How long patients with osteoporosis may continue to receive alendronate treatment remains to be established. The prolonged suppression of remodeling is associated with the accumulation of microdamage, advanced glycation products, and an increased tissue mineral density, while stopping treatment results in the reemergence of remodeling [31]. Seeman inferred that stopping anti-resorptive treatment was more likely to do net harm than continuing the treatment [31]. Thus, anti-resorptive treatment should be continued as long as possible in patients with a risk of fractures. Patients with a low BMD and prevalent vertebral fractures after 5 years of alendronate treatment are recommended to continue the treatment for more than 5 years [32-34]. The present patient continued alendronate treatment for 11 years. However, no adverse events, including hypercalcemia, upper gastrointestinal tract symptoms, osteonecrosis of the jaw, or atypical fractures of the femur, were observed, suggesting the safety of long-term treatment with alendronate.

The osteoporosis in the present patient, a premenopausal woman, was associated with a high bone

turnover rate. Available evidence suggests that the classically observed osteopenia in children with OI is associated with increased bone turnover [3–5], supporting our results. However, a histomorphometric study showed that osteoporosis in an adult man with OI was associated with increased bone turnover based on bone marker measurements, with increased bone resorption and decreased osteoblastic activity at the tissue level [35]. Thus, the influence of bisphosphonates on osteoblast activity was a concern. Accordingly, anabolic agents such as teriparatide, which is now available in Japan, might be more effective for increasing the BMD and preventing fractures. Although the effectiveness of teriparatide has not been established in patients with OI, the treatment of the present patient was recently switched from alendronate to teriparatide, and the patient's clinical course is now being carefully observed.

In conclusion, the present case report showed the long-term outcome and safety of alendronate treatment in a premenopausal woman with OI type I who exhibited high bone turnover and a history of multiple fractures. However, three clinical non-vertebral fractures occurred during the 11-year treatment period. Currently, we are examining the effectiveness of an anabolic agent, teriparatide, on the BMD and fracture incidence in the present patient, since OI is a basically an inheritable disorder of bone formation that results in bone fragility.

DISCLOSURES

We have no funding sources. We have no conflict of interest.

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