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Effects of monthly intravenous ibandronate on bone mineral density and microstructure in patients with primary osteoporosis after teriparatide treatment: The MONUMENT study

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ABSTRACT

Purpose: To investigate the effects of sequential therapy with monthly intravenous ibandronate on bone mineral density (BMD) and microstructure in patients with primary osteoporosis who received teriparatide treatment.
Methods: Sixty-six patients with primary osteoporosis who had undergone teriparatide treatment for more than 12 months (mean 18.6 months) received sequential therapy with 1 mg/month intravenous ibandronate for 12 months. The patients were evaluated using dual-energy X-ray absorptiometry (DXA), quantitative ultrasound, bone turnover markers, and high-resolution peripheral quantitative computed tomography (HR-pQCT) at baseline and 6 and 12 months after beginning administration.
Results: At 12 months after beginning sequential therapy, the bone resorption marker, tartrate-resistant acid phosphatase-5b, decreased by 39.5%, with 82.3% of the patients exhibiting levels within the normal limit. DXA revealed that the BMD of the lumbar spine increased by 3.2%, with 79.0% of the patients exhibiting a response, and 40.3% experiencing an increase in BMD over 5%. HR-pQCT revealed that the cortical thickness of the distal tibia was increased by 2.6%. The cortical area increased by 2.5%, and the buckling ratio (an index of cortical instability) decreased by 2.5%. Most parameters of the trabecular bone showed no significant changes. These changes in the cortical bone were observed in both the distal radius and tibia and appeared beginning 6 months after treatment initiation.
Conclusions: Sequential therapy with monthly intravenous ibandronate increased the BMD and improved the cortical bone microstructure of osteoporotic patients who had undergone teriparatide treatment.

1. Introduction

Teriparatide is now commonly used for patients with severe osteoporosis [1–4]. However, when osteoporosis treatment is discontinued after completion of teriparatide, the increased bone is not maintained but decreases. Therefore, sequential therapy with a bone resorption inhibitor is recommended [5–12].

Although denosumab possesses strong osteoclastic inhibitory effects, because of the risk of intense acceleration of bone resorption after discontinuation [13–15], caution is required, especially in elderly

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patients for whom reliable follow-up is challenging.

In contrast, bisphosphonates are long-acting drugs that retain their effects after treatment is discontinued [16,17]. Accordingly, switching to a bisphosphonate following teriparatide treatment has become a viable option [5–7,10,12].

Oral bisphosphonates for elderly patients are effective, but problematic in terms of compliance, polypharmacy, and a concern with sustainability [18]. Once-yearly intravenous administration of zoledronate may induce renal damage [19].

In North America and Europe, ibandronate, a nitrogen-containing bisphosphonate, is approved for oral use of 150 mg monthly and intravenous preparations of 3 mg once every 3 months [20]. In Japan, monthly intravenous preparations of 1 mg are approved and used for many elderly patients due to the reliable bioavailability and minimal adverse reactions [21–26]. To treat elderly patients with severe osteoporosis, sequential administration of teriparatide followed by ibandronate is frequently performed. However, evidence is not sufficient regarding the efficacy of this regimen.

High-resolution peripheral quantitative computed tomography (HR-pQCT) has the highest resolution (voxel size: 60.7 μm) among all available clinical CT methods and enables non-invasive analysis of changes in bone microstructure in osteoporotic patients [27–29]. In 2014, second-generation HR-pQCT technology was developed, providing faster scan times and higher resolution [30,31]. To date, no previous studies have used HR-pQCT to analyze the effects of monthly intravenous ibandronate [32].

The purpose of this study is to investigate how sequential therapy with monthly intravenous ibandronate affects the bone mineral density (BMD) and microstructure in patients with primary osteoporosis who have undergone teriparatide treatment.

2. Methods

2.1. Study design

This study examined the effects of monthly intravenous injections of ibandronate (Bonviva Syringes for Intravenous Injection, Chugai Pharmaceutical Co.) for 12 months for osteoporotic patients who had undergone teriparatide treatment. The study was conducted as a single-arm, open-label, multi-center joint trial (Fig. 1) (Effects of MOnthly intravenous ibaNdronate on bone mineral density and MicrostrUcturE in patieNts with primary osteoporosis after Teriparatide treatment: MONUMENT study). This study was approved by the Nagasaki University Clinical Research Review Board and was registered in the Japan Registry of Clinical Trials (jRCT) (jRCTs071180086).

2.2. Subjects

The study involved patients with primary osteoporosis who had received teriparatide treatment for more than 12 months. The inclusion criteria were age of 55 years or older, female sex, and a compliance rate of at least 75% for teriparatide treatment. The exclusion criteria were serious cardiac disease, serious hepatic disease, serious renal disease, active malignant tumor, endocrine metabolic disease affecting bone metabolism, secondary osteoporosis (steroids, rheumatoid arthritis, immobility, etc.), previous history of steroid use at 5 mg and above for 3 months or longer, previous history of drug use affecting bone metabolism, oversensitivity to bisphosphonate preparations, hypocalcemia, and three or more vertebral fractures in the first to fourth lumbar vertebrae.

2.3. Intervention

Within 8 weeks after the final use of teriparatide, the subjects started receiving monthly intravenous ibandronate (Bonviva® Intravenous Injection 1 mg Syringe, Chugai Pharmaceutical Co., Ltd.) for 12 months and a medical compound of calcium (610 mg/day), natural vitamin D (400 IU/day), and magnesium (30 mg/day) (New Calcichew, Takeda Pharmaceutical Co.). A notebook was handed to each subject to keep track of oral ingestion every morning to confirm drug compliance. During the administration period, information on adverse events was collected.

2.4. Dual-energy X-ray absorptiometry (DXA) and quantitative ultrasound (QUS)

At baseline and 6 and 12 months after beginning administration, bone density was assessed with DXA and QUS. Using DXA (Lunar Prodigy Advance, GE Lunar, Madison, WI), the areal bone mineral density (aBMD) and T-scores of the lumbar spine (L1–4), proximal femur (total hip and femoral neck on both sides), and radius (radius 1/3) were measured. Measurements of the lumbar spine were strictly excluded if a high aBMD due to degenerative changes and fractures was confirmed in images. The speed of sound (SOS) in the calcaneus was measured using QUS (CM200, Furuno Electric Co., Ltd., Nishinomiya, Japan).

Regarding reproducibility, root-mean-square coefficient of variation (RMS%CV) was 0.99% for aBMD of the lumbar spine (L1–4), 0.42% for the total hip, 0.76% for the femoral neck, and 0.48% for the SOS of the calcaneus.

2.5. Bone turnover markers

At baseline and 6 and 12 months after beginning administration, bone metabolism was evaluated with the bone resorption marker, tartrate-resistant acid phosphatase-5b (TRACP-5b) and the bone formation marker, total type I procollagen-N-propeptide (total P1NP). In addition, general biochemical levels of corrected calcium, phosphorus, and intact parathyroid hormone were also examined. At baseline only, levels of 25-hydroxyvitamin D (25(OH) vitamin D) and pentosidine were measured.

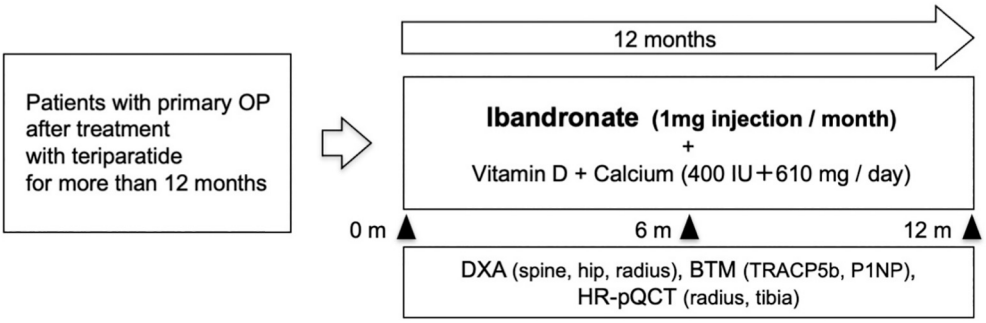

Fig. 1. Study protocol of the MONUMENT study.

2.6. HR-pQCT scan

At baseline and 6 and 12 months after beginning administration, the volumetric bone mineral density (vBMD), bone microstructure, and estimated bone strength were assessed with HR-pQCT. With the non-dominant forearm and lower leg of each patient fixed with a specialized cast, the distal radius and tibia were scanned with second-generation HR-pQCT (XtremeCT II, SCANCO Medical AG, Brüttisellen, Switzerland). Based on the guidelines for the HR-pQCT assessments, the scanned regions were set at a 10.2-mm width of the distal radius 4% proximal of the forearm length from the hand joint and a 10.2-mm width of the distal tibia 7.3% proximal of the lower leg length from the talocrural joint [33,34]. The scan conditions were as follows: tube voltage: 68 kVp; tube current: 1470 μA; integration time: 4.3 ms; number of projections: 900; field of view: 140 mm; matrix: 2304 × 2304; voxel size: 60.7 μm; number of images: 168; scan time: 2.0 min; exposed dose: CTDIvol 10.8 mGy, DLP 11.0 mGy·cm; and effective dose: 5 μSv.

2.7. Bone microstructure analysis

Three-dimensional registration of the HR-pQCT images was performed for the datasets at baseline and 6 and 12 months after beginning administration. vBMD and bone microstructures were analyzed for the common domain of the three datasets (TRI/3D-BON, Ratoc System Engineering Co., Ltd.) [35]. Measurement items were divided into the following three categories [36]:

1) Trabecular bone: Trabecular volumetric bone mineral density (Tb.vBMD, mg/cm^3); trabecular bone volume fraction (BV/TV, %); trabecular thickness (Tb.Th, mm); trabecular number (Tb.N, 1/mm); trabecular separation (Tb.Sp, mm); structure model index (SMI): an index for quantifying the trabecular shape, whether it is plate-shaped (SMI = 0) or rod-shaped (SMI = 3); connectivity density (Conn.D): an index for quantifying trabecular connection; and degree of anisotropy (DA): an index for quantifying the trabecular direction.

2) Cortical bone: Cortical volumetric bone mineral density (Ct.vBMD, mg/cm^3); cortical volumetric tissue mineral density (Ct.vTMD, mg/cm^3); cortical porosity (Ct.Po, %); cortical perimeter (Ct.Pm, mm); cortical area (Ct.Ar, mm^2); cortical thickness (Ct.Th, mm); minimum cortical thickness (Ct.Th.Min, mm); and buckling ratio (BR): an index for resistance to buckling calculated from the maximum distance from the bone axis to the cortical bone and the cortical thickness.

3) Total bone: Total volumetric bone mineral density (Tt.vBMD, mg/cm^3); stiffness (kN/mm); and failure load (FL, kN).

vBMD values were converted from the X-ray attenuation values using a regression line created from phantom images. Bone microstructure analysis was performed on binarized images with a threshold of 320 mg/cm^3 for trabecular bone and 450 mg/cm^3 for cortical bone. Tb.Th, Tb.Sp, and Ct.Th were directly measured [37].

Stiffness and failure load were analyzed using the finite element method (IPL, SCANCO Medical AG). With a Young's modulus of 10 GPa and a Poisson ratio of 0.3, bone stiffness when a load is applied to the bone axis direction was predicted. Failure was defined as more than 2.0% of all voxels becoming strained by at least 0.7%.

Regarding reproducibility, RMS%CV at the radius and tibia, respectively, were: 1.86% and 1.48% for Tb.vBMD, 1.42% and 1.11% for BV/TV, 0.94% and 0.84% for Tb.Th, 1.75% and 2.45% for Tb.N, 2.31% and 3.27% for Tb.Sp, 3.25% and 5.20% for SMI, 5.76% and 5.79% for Conn.D, 3.56% and 2.05% for DA, 0.59% and 0.57% for Ct.vBMD, 0.59% and 0.57% for Ct.vTMD, 6.08% and 6.02% for Ct.Po, 0.10% and 0.10% for Ct.Pm, 0.92% and 1.34% for Ct.Ar, 0.99% and 1.38% for Ct.Th, 1.73% and 1.32% for Ct.Th.Min, 1.02% and 1.50% for BR, and 0.90% and 1.01% for Tt.vBMD.

2.8. Endpoints

The primary endpoint of this study was the percent change in DXA-measured aBMD values in the lumbar spine (L1–4) from baseline to 12 months after the first administration. The percent change at 12 months was calculated as a proportion of the change: measurement at 12 months – measurement at baseline/measurement at baseline The secondary endpoints were the percent change of all other evaluation items from baseline to 6 and 12 months after beginning administration.

2.9. Statistical analysis

The sample size was determined based on the result from our power analysis. Referring to a previous report [5], we postulated that the mean and standard deviation of the standardized change in aBMD at 12 months from the switch in medication to a bisphosphonate from teriparatide are 2.5% (5.5%). According to this assumption, we calculated that 53 was the minimum sample size with a statistical power over 80% to detect a standardized change at 12 months >0 using the Student's *t*-test with the alpha of 0.05 (two-sided). Further, 13 patients were added based on the estimation of a 20% dropout rate. Therefore, we decided to recruit 66 patients as subjects in our study.

For the primary analysis, we used the Student's t-test to test the null hypothesis that the mean of the primary endpoint is 0 on the full analysis set (FAS). The FAS consisted of all subjects who received at least one protocol treatment and who had results of aBMD measurement at baseline and month 6, month 12, or both. Another analysis set was the per protocol set (PPS), which consisted of subjects in the FAS who received administration of ibandronate over 80% of the planned protocol treatment, who showed adherence to treatment with the medical compound of calcium, natural vitamin D, and magnesium over 60% for every month during the observation period, who had measurement results for aBMD for all time points (baseline, 6 and 12 months), and who had no major protocol deviations that could affect the efficacy assessment. As for FAS, missingness in the measurement results at 12 months was complemented by addition of the result at 6 months and the least change between 6 and 12 months among the FAS. Also, missingness in the measurement results at 6 months was complemented by the arithmetic mean of the results at baseline and 12 months for the FAS. The same analysis on the PPS was conducted for supportive purposes.

The measured values, changes, and percent change were summarized by the arithmetic mean, standard deviations, 95% confidence intervals (95% CI), and *p*-values from the two-sided Student's *t*-test. The program source code for analyses is available at the GitHub repository (https://mrmtshmp/proj.MONUMENT).

3. Results

3.1. Subjects

As shown in Fig. 2, 66 patients were enrolled in this study. Overall, three patients withdrew within 6 months after beginning administration, and one patient discontinued within 12 months, resulting in a dropout rate of 6.1%. In the FAS, one patient had no measurement results at 12 months, and the missingness was complemented as described in the statistical analysis section.

As listed in Table 1, the analysis subjects (63 in the FAS) had a mean age of 77.3 years. They were mostly elderly, with 69.8% over the age of 75 years. They were small women with a mean height of 147.7 cm and body mass index of 22.6 kg/m^2.

Among the participants, 61.9% had a previous history of fragility vertebral fractures (11 thoracic, 15 lumbar, and 13 thoracolumbar vertebrae) and received teriparatide treatment for an average of 18.6 months. The median DXA T-scores were −2.7 for the lumbar spine, −2.0 for the total hip, and −2.5 for the femoral neck; 74.6% of the patients were diagnosed with osteoporosis (T-score <−2.5). The median TRACP-5b value was 469 mU/dL, and that of total P1NP was 62.5 μg/L. The level of 25(OH) vitamin D was 12.3 ng/mL, indicating vitamin D deficiency.

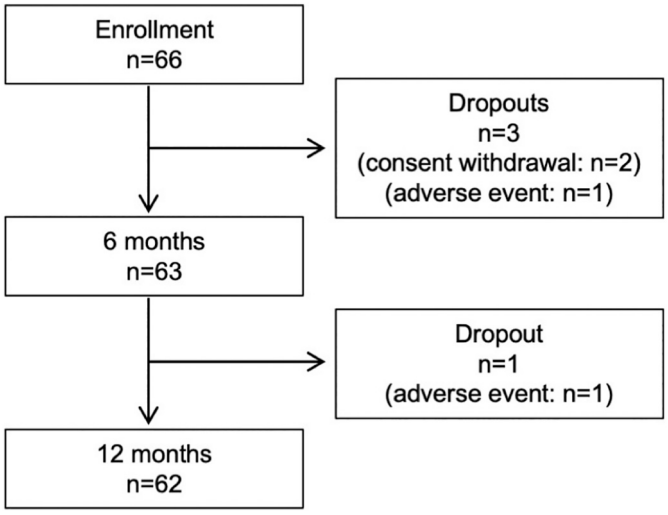

Fig. 2. Consort diagram of the MONUMENT study.

Table 1
Background data of the patients included for the analysis ($n = 63$).

			Study population (n = 63)
Age		(years)	77.3 ± 7.3 (58, 90)
Age > 75 years		(n, %)	44 (69.8)
Height		(cm)	147.7 ± 6.6 (131.7, 160.7)
Weight		(kg)	49.3 ± 7.6 (32.0, 70.0)
BMI		(kg/m^2)	22.6 ± 2.8 (15.2, 30.2)
History of fragility fracture	Vertebra	(n, %)	39 (61.9)
	Proximal femur	(n, %)	5 (7.9)
	Distal radius	(n, %)	9 (14.3)
	Others	(n, %)	2 (3.2)
History of OP treatment	Duration of teriparatide	(months)	18.6 ± 4.9 (12, 24)
FRAX	Major OP fracture	(%)	29.0 (22.0, 36.0)
	Hip fracture	(%)	11.0 (7.5, 18.5)
DXA T-score	Lumbar spine		−2.7 (−3.4, −1.8)
	Total hip		−2.0 (−2.5, −1.4)
	Femoral neck		−2.5 (−3.1, −2.0)
	Radius 1/3		−3.8 (−4.6, −3.2)
	Osteoporosis	(n, %)	47 (74.6)
	Osteopenia	(n, %)	13 (20.6)
Blood test	TRACP-5b	(mU/dL)	469 (390.5, 617.5)
	total P1NP	(μg/L)	62.5 (42.0, 76.3)
	25(OH) vitamin D	(ng/mL)	12.3 (9.4, 17.3)
		(nmol/L)	30.8 (23.5, 43.3)
	Pentosidine	(pmol/mL)	33.1 (25.8, 41.6)
	Corrected Calcium	(mg/dL)	9.5 (9.3, 9.8)
	Phosphate	(mg/dL)	3.4 (3.0, 3.8)
	intact PTH	(pg/mL)	52.4 (36.6, 67.9)

BMI: body mass index, OP: osteoporosis, DXA: dual-energy x-ray absorptiometry, TRACP-5b: tartrate-resistant acid phosphatase 5b, P1NP: Procollagen type 1 N propeptide, 25(OH) vitamin D: 25-hydroxyvitamin D, PTH: parathyoid hormone.
Mean ± SD (Min, Max), Number (%), Median (25%, 75%).

3.2. DXA and QUS

As listed in Table 2, the aBMD in the lumbar spine increased by 2.2% after 6 months and 3.2% (95% CI: 1.8 to 4.6%) after 12 months ($p < 0.0001$) (primary endpoint). Fig. 3 shows that 79.0% of the patients were responders, and 40.3% exhibited an increase of at least 5% after 1 year. The aBMD of the total hip increased by 1.1% after 6 months and 1.2% after 12 months, with 80.6% of the patients being responders. The radial 1/3 aBMD and calcaneal SOS values exhibited minimal changes. We confirmed that the effect of complementation for missingness (described in the statistical analysis section) was trivial by checking the mean after removal of the complemented data.

Table 2
Changes in aBMD measured by DXA, SOS measured by QUS, and bone turnover makers.

				Baseline (n = 63)	6 months (n = 63)	12 months ($n = 62$)
				Value	Change (%)	Change (%)
DXA	Lumbar Spine	aBMD	(g/cm^2)	0.803 (0.708, 0.902)	**2.2 ± 4.6****	**3.2 ± 5.5****
	Total Hip	aBMD	(g/cm^2)	0.700 (0.640, 0.777)	**1.1 ± 2.0****	**1.2 ± 2.2****
	Femoral Neck	aBMD	(g/cm^2)	0.652 (0.588, 0.707)	**1.0 ± 2.4***	**1.3 ± 2.6****
	Radius 1/3	aBMD	(g/cm^2)	0.513 (0.442, 0.566)	0.6 ± 4.6	0.9 ± 6.0
QUS	Calcaneus	SOS	(m/s)	1470 (1457.5, 1480)	**0.3 ± 0.7****	0.0 ± 0.8
BTM	TRACP-5b		(mU/dL)	469.0 (390.5, 617.5)	**−43.4 ± 22.2****	**−39.5 ± 23.8****
	total P1NP		(μg/L)	62.5 (42.0, 76.3)	**−58.9 ± 24.9****	**−60.2 ± 25.9****

DXA: dual-energy x-ray absorptiometry, aBMD: areal bone mineral density, QUS: quantitative ultrasound, SOS: speed of sound, BTM: bone turnover maker, TRACP-5b: tartrate-resistant acid phosphatase 5b, P1NP: Procollagen type 1 N propeptide.
Median (25%, 75%), Mean ± SD, * $p < 0.01$, ** $p < 0.001$ vs baseline. Bold font indicates significant differences.

3.3. Bone turnover markers

As listed in Table 2, the TRACP-5b decreased by 43.4% after 6 months and 39.5% after 12 months. Fig. 4 shows that 82.3% of the patients exhibited levels of TRACP-5b within the normal limit after 12 months. Likewise, the total P1NP decreased by 58.9% after 6 months and by 60.2% after 12 months; 73.8% of the patients exhibited levels of P1NP within the normal limit after 12 months.

3.4. HR-pQCT

As listed in Tables 3 and 4 and shown in Fig. 5, no significant changes were observed in most of the trabecular bone parameters except for decreased Tb.vBMD in the tibia.

In the cortical bone, Ct.vBMD and the cortical porosity did not change significantly. In the tibia, Ct.Th increased by 2.8% after 6 months and by 2.6% after 12 months. Consequently, Ct.Ar also increased by 2.7% after 6 months and by 2.5% after 12 months. Meanwhile, BR decreased by 2.8% after 6 months and by 2.5% after 12 months, indicating an improvement in cortical stability. Similar changes were observed in the radius. As shown in Fig. 5B, 82.3% and 93.4% of the patients exhibited increased Ct.Th in the radius and tibia, respectively. An increase over 2% was noted in 38.7% and 54.1% of the patients, respectively. No significant differences were found in Tt.vBMD and estimated bone strength in the radius and tibia.

Fig. 6 shows images of bone microstructural changes in a responder patient. 3D images show bone formation (yellow) on the surface of the endocortical and trabecular bone (Fig. 6E and F). In this 3D registration method, bone formation is defined as voxels with a mineral density above 450 mg/cm^3 of the threshold at 12 months due to an increase in

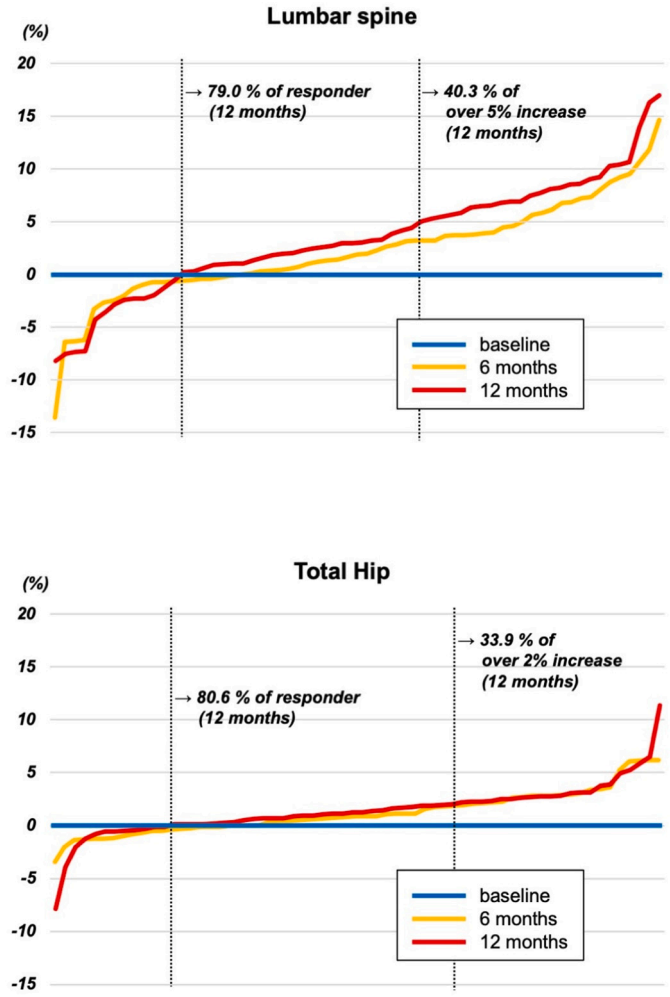

Fig. 3. Cumulative distribution of the change in aBMD of the lumbar spine and total hip after sequential therapy with ibandronate. In the lumbar spine, 79.0% of the patients were responders, and 40.3% of the patients showed an increase of over 5% in 12 months. In the total hip, 80.6% of the patients were responders, and 33.9% of the patients showed an increase of over 2% in 12 months.

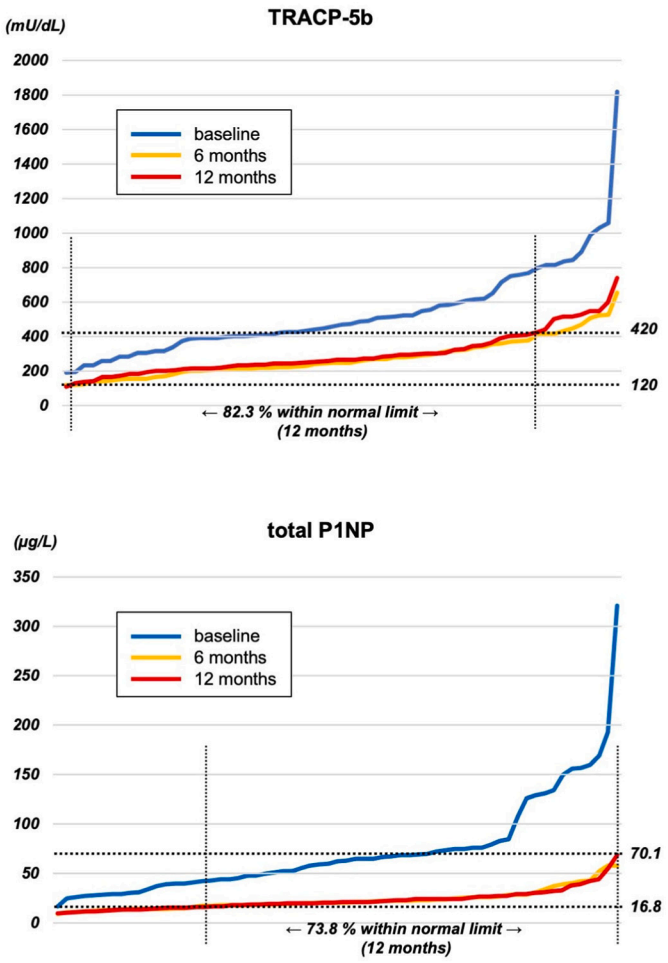

Fig. 4. Cumulative distribution of the values of TRACP-5b and total P1NP before and after sequential therapy with ibandronate. The ranges of the normal limit are depicted with dashed lines. Among the patients, 82.3% (TRACP-5b) and 73.8% (total P1NP) were within the normal limit in 12 months.

calcification. Therefore, this case shows that new bone on the endocortical and trabecular surface that was generated by teriparatide treatment was further calcified by sequential therapy with ibandronate and was eventually recognized as bone.

3.5. Adverse events

Two patients withdrew because of adverse events (Fig. 2). One had a history of angina pectoris and dropped out when the disease recurred. The other developed a fever of unknown origin and general pain and was consequently excluded.

4. Discussion

In this study, we investigated how 12-month sequential therapy with intravenous ibandronate (1 mg/month) affected BMD and microstructure of patients with primary osteoporosis who had undergone teriparatide treatment for more than 12 months.

4.1. Bone turnover markers

The bone turnover markers showed a state of high bone turnover at baseline, due to the effects of teriparatide treatment (Table 1). Six months after switching to ibandronate, the bone turnover markers rapidly declined (Table 2). Contrary to the common belief that bisphosphonates induce non-physiological suppression of bone metabolism, the majority of the patients exhibited levels within the normal limit (Fig. 4).

4.2. DXA

This study confirmed that ibandronate has the effect of adding to aBMD (lumbar spine 3.2%, total hip 1.2%, femoral neck 1.3%) after teriparatide treatment (Table 2, Fig. 3). Several previous studies have been conducted with sequential therapy with bisphosphonates, denosumab, and raloxifene after teriparatide [5–12,38–43].

Niimi et al. reported that 12 months of sequential therapy with oral alendronate (35 mg/week) after 24 months of teriparatide increased aBMD in the lumbar spine by 1.3% and femoral neck by 0.7% in 100 patients (mean 78 years) [41]. Ebina et al. reported that 12 months of sequential therapy with oral bisphosphonates (alendronate 35 mg/week $n = 19$, risedronate 17.5 mg/week $n = 12$, minodronate 50 mg/month $n = 5$) after 24 months of teriparatide increased aBMD in the lumbar spine by 2.6%, total hip by 1.1%, and femoral neck by 1.4% in 36 patients (mean 73.5 years) [39]. Monthly intravenous ibandronate may have equivalent or better effects than oral bisphosphonates.

Burkard et al. reported that 24 months of zoledronic acid after 24

Table 3
Changes in volumetric bone mineral density, bone microstructure, and estimated bone strength at distal radius.

Distal radius			Baseline (n = 63)	6 months (n = 63)	12 months (n = 62)
			Value	Change (%)	Change (%)
Trabecular	Tb.vBMD	(mg/cm^3)	99.8 (80.4, 115.7)	−0.3 ± 2.4	−0.4 ± 2.7
	BV/TV	(%)	10.5 (8.1, 13.0)	−0.1 ± 2.9	0.2 ± 3.5
	Tb.Th	(μm)	197.3 (185.9, 204.4)	0.0 ± 1.4	0.0 ± 1.8
	Tb.N	(/mm)	1.05 (0.94, 1.18)	1.0 ± 4.2	1.7 ± 5.5
	Tb.Sp	(μm)	755.0 (661.6, 874.8)	−1.0 ± 5.1	−1.7 ± 6.4
	SMI		2.35 (2.17, 2.48)	0.5 ± 2.6	0.5 ± 3.7
	Conn.D		1.22 (0.77, 1.70)	−0.4 ± 8.0	0.5 ± 8.4
	DA		1.79 (1.68, 1.92)	0.1 ± 6.1	0.0 ± 5.3
Cortical	Ct.vBMD	(mg/cm^3)	807.2 (776.9, 840.9)	−0.3 ± 1.5	−0.1 ± 1.9
	Ct.vTMD	(mg/cm^3)	812.6 (786.5, 846.0)	−0.3 ± 1.4	−0.1 ± 1.8
	Ct.Po	(%)	0.98 (0.82, 1.37)	0.7 ± 16.2	1.9 ± 17.1
	Ct.Pm	(mm)	65.1 (62.3, 68.8)	0.0 ± 0.2	−0.1 ± 0.2
	Ct.Ar	(mm^2)	36.9 (33.6, 41.4)	**1.7 ± 2.2****	**1.4 ± 2.7****
	Ct.Th	(μm)	613.3 (540.1, 687.3)	**1.8 ± 2.2****	**1.5 ± 2.6****
	Ct.Th. Min	(μm)	394.5 (373.4, 463.3)	**1.5 ± 1.9****	**1.4 ± 2.6****
	BR		21.6 (19.2, 24.8)	**−1.7 ± 1.9****	**−1.5 ± 2.3****
Total	Tt.vBMD	(mg/cm^3)	210.8 (187.1, 242.6)	−0.0 ± 1.8	−0.0 ± 2.4
	Stiffness	(kN/mm)	32.4 (28.4, 39.1)	1.2 ± 6.0	0.7 ± 7.6
	Failure load	(kN)	1.71 (1.46, 2.13)	1.5 ± 7.2	1.2 ± 9.0

Tb.vBMD: trabecular volumetric bone mineral density, BV/TV: trabecular bone volume fraction, Tb.Th: trabecular thickness, Tb.N: trabecular number, Tb.Sp: trabecular separation, SMI: structure model index, Conn.D: connectivity density, DA: degree of anisotropy, Ct.vBMD: cortical volumetric bone mineral density, Ct.vTMD: cortical volumetric tissue mineral density, Ct.Po: cortical porosity, Ct.Pm: cortical perimeter, Ct.Ar: cortical area, Ct.Th: cortical thickness, Ct.Th.Min: minimum cortical thickness, BR: buckling ratio, Tt.vBMD: total volumetric bone mineral density.
Median (25%, 75%), Mean ± SD, * $p < 0.01$, ** $p < 0.001$ vs baseline. Bold font indicates significant differences.

Table 4
Changes in volumetric bone mineral density, bone microstructure, and estimated bone strength at distal tibia.

Distal tibia			Baseline (n = 63)	6 months (n = 63)	12 months (n = 62)
			Value	Change (%)	Change (%)
Trabecular	Tb.vBMD	(mg/cm^3)	148.1 (122.6, 166.2)	−0.8 ± 1.9*	−0.9 ± 2.4*
	BV/TV	(%)	17.0 (13.1, 19.6)	−0.1 ± 2.0	−0.2 ± 2.7
	Tb.Th	(μm)	210.5 (199.8, 226.0)	−0.1 ± 1.1	0.0 ± 1.3
	Tb.N	(/mm)	1.05 (0.96, 1.14)	−0.4 ± 3.1	−0.9 ± 3.2
	Tb.Sp	(μm)	749.9 (646.6, 830.4)	0.8 ± 4.0	1.4 ± 4.5
	SMI		1.88 (1.63, 2.04)	−1.3 ± 4.9	−2.0 ± 6.0
	Conn.D		2.25 (1.82, 2.88)	−1.7 ± 5.8	−2.6 ± 6.8*
	DA		1.98 (1.89, 2.05)	0.6 ± 2.9	0.7 ± 3.6
Cortical	Ct.vBMD	(mg/cm^3)	767.1 (720.1, 817.4)	0.4 ± 1.7	0.3 ± 2.7
	Ct.vTMD	(mg/cm^3)	782.3 (729.8, 831.2)	0.3 ± 1.8	0.3 ± 2.8
	Ct.Po	(%)	2.51 (2.17, 3.23)	−3.3 ± 11.0	−1.6 ± 12.3
	Ct.Pm	(mm)	95.3 (91.4, 99.9)	**−0.1 ± 0.1****	−0.1 ± 0.2*
	Ct.Ar	(mm^2)	71.2 (64.5, 77.4)	**2.7 ± 2.2****	**2.5 ± 2.3****
	Ct.Th	(μm)	780.1 (719.3, 862.0)	**2.8 ± 2.3****	**2.6 ± 2.4****
	Ct.Th. Min	(μm)	702.8 (657.8, 752.4)	**1.8 ± 1.9****	**1.6 ± 1.9****
	BR		22.5 (19.0, 24.2)	**−2.8 ± 2.2****	**−2.5 ± 2.3****
Total	Tt.vBMD	(mg/cm^3)	226.2 (186.5, 246.5)	−0.2 ± 1.8	−0.4 ± 2.5
	Stiffness	(kN/mm)	104.5 (87.2, 114.6)	1.1 ± 3.6	0.5 ± 4.9
	Failure load	(kN)	5.86 (4.91, 6.30)	1.1 ± 3.6	0.5 ± 4.7

Tb.vBMD: trabecular volumetric bone mineral density, BV/TV: trabecular bone volume fraction, Tb.Th: trabecular thickness, Tb.N: trabecular number, Tb.Sp: trabecular separation, SMI: structure model index, Conn.D: connectivity density, DA: degree of anisotropy, Ct.vBMD: cortical volumetric bone mineral density, Ct.vTMD: cortical volumetric tissue mineral density, Ct.Po: cortical porosity, Ct.Pm: cortical perimeter, Ct.Ar: cortical area, Ct.Th: cortical thickness, Ct.Th.Min: minimum cortical thickness, BR: buckling ratio, Tt.vBMD: total volumetric bone mineral density.
Median (25%, 75%), Mean ± SD, * $p < 0.01$, ** $p < 0.001$ vs baseline. Bold font indicates significant differences.

months of teriparatide resulted in a 1.8% increase in aBMD in the lumbar spine and a 1.1% decrease in the femoral neck in 20 patients (mean 65.8 years) [12]. In the same study, 24 months of denosumab showed an increase in aBMD in the lumbar spine by 5.7% and femoral neck by 4.9% in 26 patients (mean 72.4 years). Although these results cannot be directly compared with the results in this study because the periods of sequential therapy were different (24 vs. 12 months), monthly intravenous ibandronate may have a higher effect on aBMD than zoledronic acid and a lower effect than denosumab.

Eastell et al. reported that 12 months of sequential therapy with raloxifene (60 mg/day) after 12 months of teriparatide resulted in a 0.3% decrease in aBMD in the lumbar spine and a 1.5% increase in aBMD in the femoral neck in 97 women (mean 69.4 years) [9]. Adami et al. reported that 12 months of sequential therapy with raloxifene (60 mg/day) after 12 months of teriparatide resulted in a 1.2% decrease in aBMD in the lumbar spine and a 2.3% increase in aBMD in the femoral neck in 157 women (mean 66.7 years) [8]. Although these results cannot be directly compared with the results in this study because the periods of the teriparatide treatment were different (12 vs. 19 months), monthly intravenous ibandronate may have a better effect on aBMD than raloxifene in the lumbar spine.

Compared to many previous studies, this study consisted of elderly

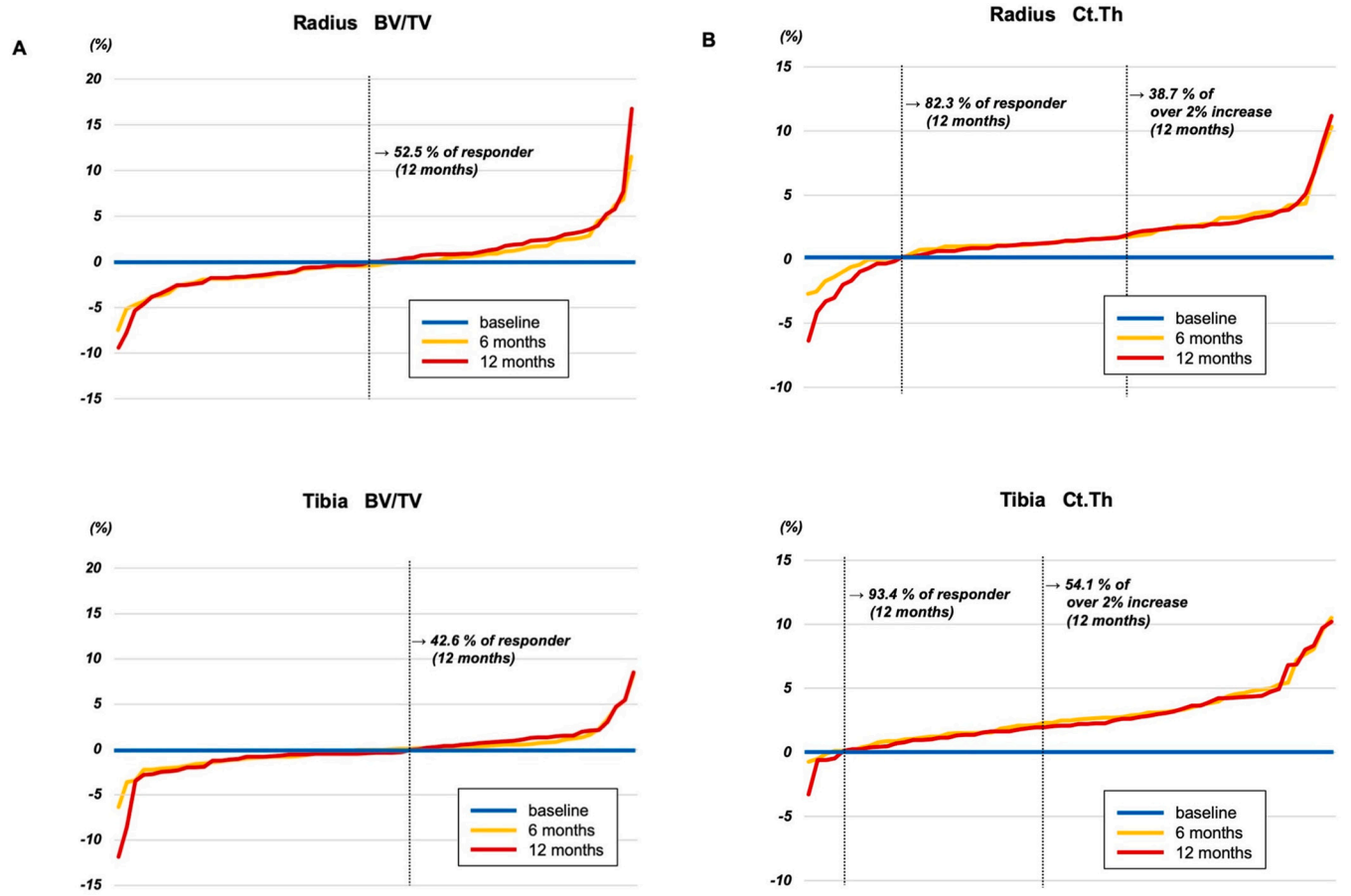

Fig. 5. A Cumulative distribution of the change in trabecular bone volume fraction (BV/TV) in the distal radius and tibia after sequential therapy with ibandronate. Among the patients, 52.5% (distal radius) and 42.6% (distal tibia) were responders in 12 months.
B Cumulative distribution of the change in cortical thickness (Ct.Th) in the distal radius and tibia after sequential therapy with ibandronate. In the distal radius, 82.3% of the patients were responders, and 38.7% of the patients showed an increase of over 2% in 12 months. In the distal tibia, 93.4% of the patients were responders, and 54.1% of the patients showed an increase of over 2% in 12 months.

patients who were about 10 years older (mean 77.3 years) than in the above studies and with decreased activity due to fragility fractures. Simple comparisons of the results are not possible. However, the incidence of vertebral and proximal femoral fractures increases after the age of 70, and this study shows real-world results.

4.3. HR-pQCT

The cortical thickness (Ct.Th) increased in both the radius and tibia (1.5% and 2.6%, respectively) with ibandronate (Tables 3 and 4, Fig. 5B). Consequently, an increase in the cortical area (Ct.Ar) and a decrease in cortical instability (BR: an index of cortical instability) were observed. We also measured the minimum cortical thickness (Ct.Th. Min) to evaluate the most fragile part of the whole circumference of the cortical bone, and the results indicated significant improvements. These effects were greater in the tibia than in the radius, perhaps because the tibia is a weight-bearing bone. In contrast, no significant changes were noted in the density and porosity of the cortical bone (Ct.vBMD and Ct. Po) in this study. Although we initially predicted that the cortical porosity induced by teriparatide would be reduced by ibandronate, this study yielded no such findings.

HR-pQCT did not detect significant changes in most trabecular bone parameters (Tables 3 and 4). As shown in Fig. 5, the trabecular bone showed different changes from patient to patient, with some patients maintaining, some increasing, and others decreasing the trabecular bone.

Only one previous report used HR-pQCT to investigate the effects of sequential therapy after teriparatide treatment [43]. Leder et al. reported that 24 months of teriparatide followed by 24 months of denosumab increased Ct.Th in the tibia by 4.7% (as read from the graph), and Ct.vBMD increased by 3.0% in 27 women (66.1 years). On the other hand, Ct.Po and trabecular bone microstructure did not change significantly. Although these results cannot be directly compared with the results in this study because the average age of the participants was 11 years younger and the duration of sequential therapy was 12 months longer than those of this study, the results seemed to reflect the strong bone resorption inhibitory effect of denosumab.

Three previous reports have described HR-pQCT analysis of the effects of ibandronate in osteoporotic patients [44–46]. All these studies used oral ibandronate (150 mg/month), and one was a randomized clinical trial using ibandronate and a placebo. Over a 24-month observation period, the study showed that ibandronate leads to an increase in cortical vBMD [45]. The design of this study differed from that of the present study in many ways: younger age (63 vs. 77 years), not osteoporotic (Lumbar −1.4, Femoral neck −1.5 vs. Lumbar −2.4, Femoral neck −2.5), use of an oral preparation (oral 150 mg vs. 1 mg i.v.), administration period (24 months vs. 12 months), osteoporosis treatment naïve (naïve vs. teriparatide sequential treatment), and use of different HR-pQCT devices (XtremeCT vs. XtremeCT II). The remaining two reports were a study on patients with glucocorticoid-induced osteoporosis (systemic lupus erythematosus) and a study on combined therapy with ibandronate and teriparatide (PICS), respectively [44,46].

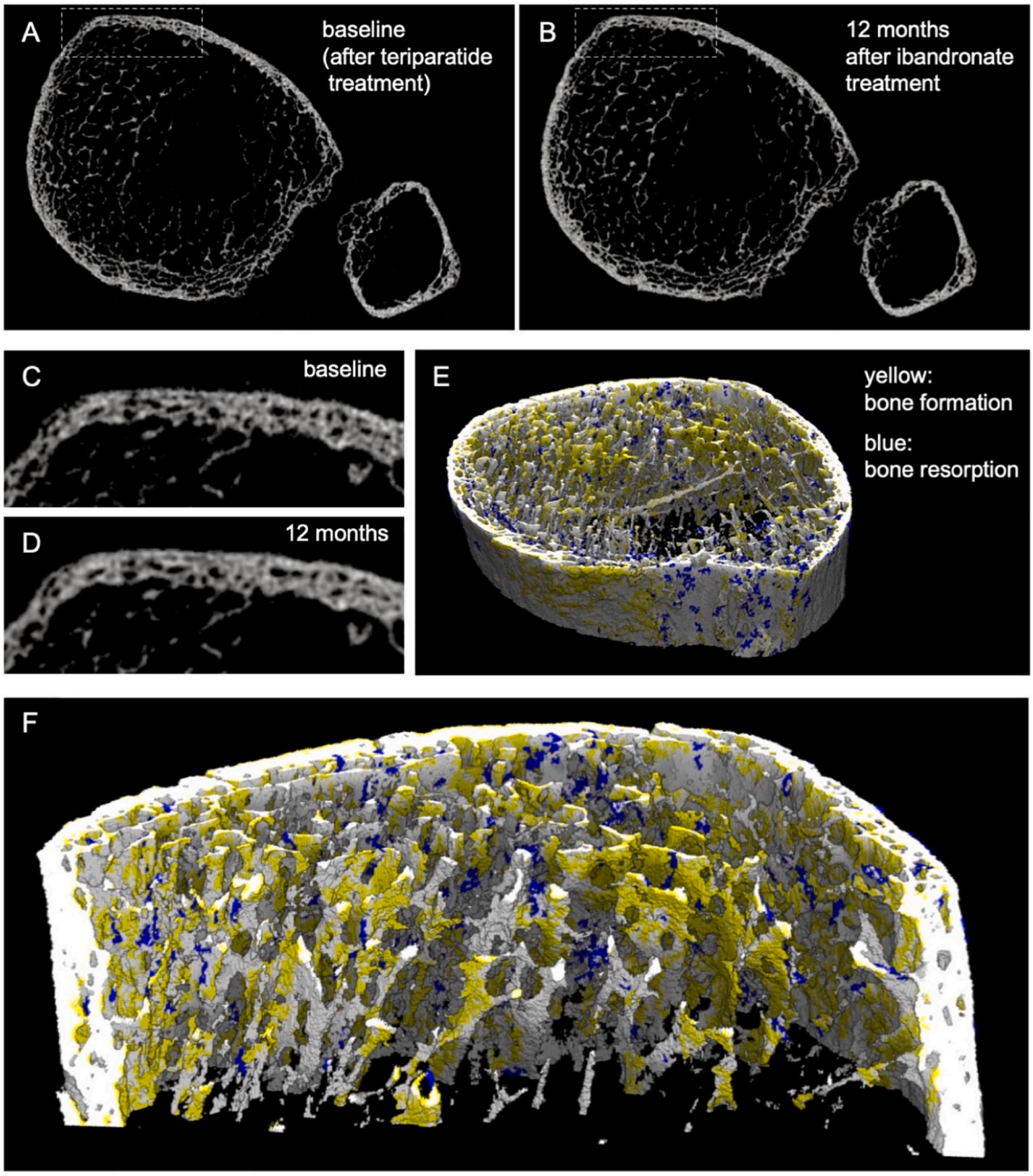

Fig. 6. HR-pQCT images of a responder patient following sequential therapy with ibandronate. A 67-year-old woman with vertebral fractures was treated using teriparatide 20 μg/day for 24 months followed by ibandronate 1 mg/month for 12 months. 2D images show the increase in bone mineral density at 12 months (B and D) compared with baseline (A and C). 3D superimposed images (E and F) clearly show that bone formation has occurred on the surfaces of endocortical and trabecular bones.

5. Strengths & limitations

The strength of this study is the fact that the analysis involved various parameters, was detailed, used various techniques such as DXA, blood testing, HR-pQCT, and a 3D registration method, and tested sequential therapy, which is now a critical topic in current osteoporotic medical care.

A limitation of this study was that it was a single-arm study that did not involve comparison with an untreated control cohort or cohorts treated with other drugs. Another limitation was that this study started observations not from the time of initial treatment with teriparatide but beginning with the switch to ibandronate. Changes due to teriparatide treatment remain unclear. Also, the relatively small sample size may have affected the statistical non-significance. Moreover, Vitamin D and pentosidine were evaluated at baseline only and were not assessed after ibandronate treatment.

6. Conclusions

Sequential therapy with monthly intravenous ibandronate following teriparatide treatment resulted in a 39.5% decrease in the bone resorption marker, TRACP-5b, and a 3.2% increase in the aBMD of the lumbar spine in patients with primary osteoporosis. In addition, HR-pQCT revealed that cortical thickness increased by 2.6%, and the BR, which is an index of cortical instability, decreased by 2.5% in the tibia. These results demonstrate the positive effects of sequential therapy with

monthly intravenous ibandronate on BMD and cortical bone microstructure.

CRediT authorship contribution statement

Ko Chiba: Conceptualization, Methodology, Resources, Writing - original draft, Visualization, Project administration, Funding acquisition. **Shuta Yamada:** Project administration. **Itaru Yoda:** Resources. **Makoto Era:** Resources. **Kazuaki Yokota:** Resources. **Narihiro Okazaki:** Resources. **Shingo Ota:** Investigation. **Yusaku Isobe:** Investigation. **Satsuki Miyazaki:** Investigation. **Shigeki Tashiro:** Data curation. **Sawako Nakashima:** Methodology, Project administration. **Shimpei Morimoto:** Formal analysis, Writing - review & editing. **Shuntaro Sato:** Methodology. **Tomoo Tsukazaki:** Resources. **Tsuyoshi Watanabe:** Resources. **Hiroshi Enomoto:** Resources. **Yoshihiro Yabe:** Conceptualization. **Akihiko Yonekura:** Supervision. **Masato Tomita:** Supervision. **Masako Ito:** Conceptualization, Supervision. **Makoto Osaki:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

Declaration of competing interest

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