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## Original article

## Effects of treatment interruption due to patient convenience on treatment of once a week teriparatide

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## ABSTRACT

**Objectives:** Once-weekly teriparatide (W-TPTD) is an effective drug for patients with osteoporosis; however, some patients discontinue W-TPTD owing to its adverse drug reactions (ADRs). Sequential treatment with W-TPTD and antiresorptive therapy may be effective in treating such patients. In this study, we evaluate the efficacy of this sequential treatment regimen.

**Methods:** This retrospective study was conducted at a single institution in Japan. The target subjects were patients with osteoporosis who started W-TPTD treatment. The subjects who received W-TPTD for 6 months or more were divided into 3 groups: TTT (W-TPTD for 18 months); TBT (sequential treatment of W-TPTD/bisphosphonates/W-TPTD; each for 6 months); and TET (sequential treatment of W-TPTD/elcatonin/W-TPTD, each for 6 months) groups. The efficacy endpoints were bone mineral densities (BMD) in the lumbar spine and femur.

**Results:** Lumbar spine BMD in group TBT increased significantly by 1.6% ( $P = 0.023$ ), 2.9% ( $P = 0.001$ ), and 4.4% ( $P < 0.001$ ) after 6, 12, and 18 months, respectively, compared with baseline values. In group TET, it increased by 2.1%, ( $P = 0.001$ ), 1.3% ( $P = 0.066$ ), and 3.0% ( $P = 0.015$ ) after 6, 12, and 18 months, respectively. A significant increase was observed only after 6 and 18 months. In group TTT, it increased significantly by 3.3% ( $P = 0.023$ ), 5.1% ( $P = 0.019$ ), and 7.1% ( $P = 0.010$ ) after 6, 12, and 18 months, respectively. However, no significant difference in total hip BMD was observed among all three groups. No serious ADRs were reported.

**Conclusion:** In patients who discontinue treatment with W-TPTD due to ADRs, sequential treatment with W-TPTD and antiresorptive therapy would be beneficial.

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## 1. Introduction

Teriparatide (TPTD) is an osteogenic agent showing potent effects by increasing bone mineral density (BMD) and reducing the incidence of fracture. Therefore, it is clinically useful to treat osteoporosis in patients with high risk of fracture [1].

The risk of developing vertebral fracture was lowered by 73% in subjects treated with once-weekly TPTD (W-TPTD) compared with placebo group, and by 78% in female subjects alone. However, in

clinical setting, some patients have difficulty in continuing W-TPTD treatment for osteoporosis owing to various reasons, including necessity of once-weekly visit, high price of the drug, and high incidence of adverse drug reaction (ADR). In addition, only few reports have verified the clinical efficacy of W-TPTD.

The maximum approved duration of W-TPTD treatment is 24 months. Even in cases where W-TPTD administration is temporarily discontinued and then resumed, the total duration of administration must not exceed 24 months. Although sequential treatment requires caution, it is expected to be a potential treatment option for patients unable to complete long-term W-TPTD administration, taking advantage of the effect of W-TPTD in increasing BMD.

In the present study, we analyzed the pooled data in our hospital and examined the increase in BMD by W-TPTD to show its therapeutic effects in patients with osteoporosis receiving sequential

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treatment with W-TPTD and bone antiresorptive drug (bisphosphonate [BP] or elcatonin [EL]). We also examined the clinical response obtained by both continuous W-TPTD alone and the sequential administration of W-TPTD + bone antiresorptive drug (BP or EL) to report more practical clinical results for investigating the efficacy of the sequential treatment regimen and the safety of W-TPTD.

To examine the efficacy of sequential treatment, we analyzed the changes in BMD in the lumbar spine and femur neck by dual energy X-ray absorptiometry (DXA), bone turnover markers, hip structural analysis (HSA) [2,3], and trabecular bone score (TBS) [4]. As EL is indicated for pain in osteoporosis, the present study focused mainly on sequential treatment with BP.

## 2. Methods

### 2.1. Study design

The present study was designed as a single institution, retrospective study in Japan. We only included existing data in the analysis without collecting any new data. Therefore, we adopted an opt-out policy to use the existing data.

This study was conducted with the approval of the 2nd Institutional Review Board of Adachi Kyosai Hospital (September 28, 2017) (approval number: 2189). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### 2.2. Study subjects

The target subjects were those who met all the following criteria:

- 1) Efficacy assessments (rationale)
  - (1) Subjects with osteoporosis who started treatment with W-TPTD (56.5 µg/dose) between April 2013 and October 2015 (to collect data from those receiving treatment for 18 months or longer at the start of the study)
  - (2) Subjects previously untreated with teriparatide (to evaluate the effect of the drug precisely)
  - (3) Subjects who were available to follow up data up to 18 months after the start of administration (to analyze subjects completing the sequential administration upon comparing differences in treatment regimens)
- 2) Safety assessment (rationale)

Subjects meeting criteria (1) and (2) of efficacy assessment and receiving W-TPTD at least once (to include all patients who received W-TPTD to evaluate safety).

### 2.3. Treatments

We performed BMD measurement and bone turnover marker assay using DXA (QDR-4500, Hologic, Inc., Marlborough, MA, USA) approximately every 6 months in patients receiving treatment for osteoporosis, providing detailed explanation on the outcome of ongoing treatment to continue it. In patients receiving W-TPTD, we ensured their willingness to continue the treatment. When they indicated their strong intention to discontinue the drug, W-TPTD was switched to bone antiresorptive drug to continue treatment for osteoporosis. The drug of choice for patients expressing difficulty in scheduled visits was BP and for those without any problem in clinic

visits but complaining of pain was EL. During BMD measurement 6 months after switching the regimen, we reconfirmed the patients' intention to continue the therapy and asked to resume treatment with W-TPTD.

We assigned subjects who received W-TPTD for 6 months or more into one of the following three groups: treatment with W-TPTD for 18 months (group TTT); sequential treatment with W-TPTD for 6 months and a BP agent, followed by treatment with W-TPTD again for 6 months (group TBT); and sequential treatment with W-TPTD for 6 months and EL for 6 months, followed by treatment with W-TPTD again for 6 months (group TET).

### 2.4. Evaluation

#### 2.4.1. Efficacy assessments

2.4.1.1. *Primary endpoint.* Change in BMD measured by DXA (lumbar spine BMD (L2-4) after 12 months of treatment).

#### 2.4.1.2. Secondary endpoints

- 1) Changes in BMD measured by DXA (lumbar spine BMD (L2-4) after 6 and 18 months, and total hip BMD after 6, 12, and 18 months)
- 2) Changes in bone turnover markers (procollagen type I N-terminal propeptide (P1NP), type I collagen cross-linked N-telopeptide (NTX), and tartrate-resistant acid phosphatase-5b (TRACP-5b) after 6, 12, and 18 months)
- 3) Changes in HSA (outer diameter, cortical bone inner diameter, cortical bone thickness (CBT), cross-sectional area (CSA), section modulus (SM), and buckling ratio (BR) in narrow neck of the femur, intertrochanteric region, and femoral shaft after 6, 12, and 18 months). Beck reported that the HSA method was introduced to extract geometric strength information from archived DXA scans acquired in large research studies.
- 4) Changes in TBS (after 6, 12, and 18 months)

#### 2.4.2. Safety assessments

ADRs occurred during 18 months of treatment with teriparatide (treatment-related adverse events)

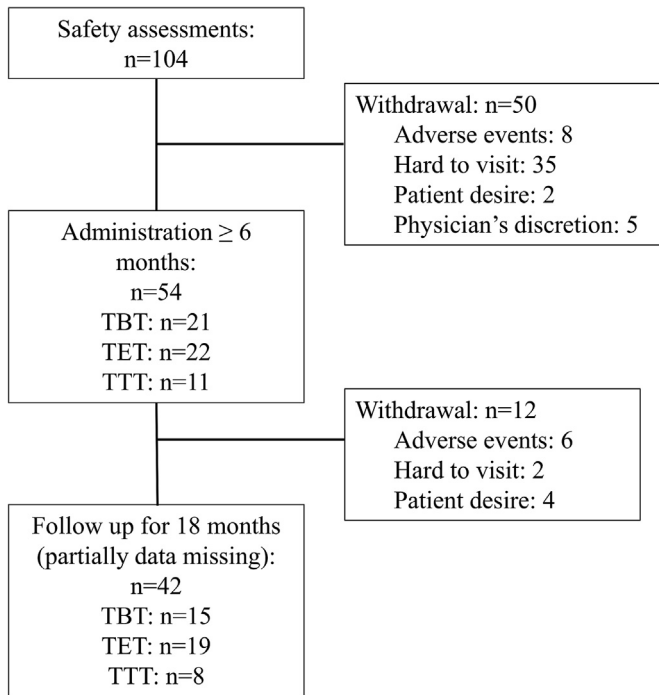
### 2.5. Statistical analysis

Changes in each efficacy assessment from baseline were evaluated by paired *t*-test. However, because, too small number of patients were included in this study, we performed Kolmogorov-Smirnov test for each group and tested the normality. For items for which normality cannot be confirmed, we performed Wilcoxon signed rank test, respectively. For the analysis of each assessment, the data for a subject were included only if all the measured values until 18 months from treatment initiation were available. Continuous variables were shown as mean ± SD (standard deviation) and nominal scale as n (%). The 2-sided significance level was 5%. R software product (R Core Team, Vienna, Austria) was used for statistical analysis.

## 3. Results

### 3.1. Participant flow

Fig. 1 shows the participant flow. Among 104 subjects included



**Fig. 1.** Participant flow. TTT, treatment with once-weekly teriparatide (W-TPTD) for 18 months; TBT, sequential treatment of W-TPTD/bisphosphonates/W-TPTD, each for 6 months; TET, sequential treatment with W-TPTD for 6 months and EL for 6 months, followed by treatment with W-TPTD again for 6 months.

for safety assessments in the study, 50 subjects dropped out. The remaining 54 subjects continued W-TPTD administration for more than 6 months. Among them, 42 subjects continuing the treatment until 18 months were included in the efficacy assessments. There were 15 subjects in group TBT, 19 patients in group TET, and 8 patients in group TTT.

### 3.2. Patients' characteristics

**Table 1** presents demographic data of each group at baseline. All subjects received treatment with BP until immediately before the start of W-TPTD administration. The BP used in all cases was only minodronic acid.

**Table 1**  
Baseline characteristics of patients in each group.

	TBT		TET		TTT		P-value
	n		n		n		
Age, yr	15	76.9 ± 5.2	19	75.4 ± 6.5	8	81.1 ± 4.3	0.067
Height, cm	15	146.8 ± 4.6	19	148.3 ± 5.3	8	149.9 ± 2.1	0.311
Body weight, kg	15	51.2 ± 7.5	19	48.6 ± 6.8	8	51.4 ± 10.1	0.549
BMI, kg/m <sup>2</sup>	15	23.7 ± 3.1	19	22.2 ± 3.6	8	22.8 ± 4.2	0.482
Lumbar spine BMD, g/cm <sup>2</sup>	15	0.745 ± 0.111	19	0.657 ± 0.111	8	0.682 ± 0.124	0.092
Femoral neck BMD, g/cm <sup>2</sup>	15	0.615 ± 0.078	19	0.589 ± 0.102	8	0.594 ± 0.125	0.742
TBS	15	1.21 ± 0.12	19	1.21 ± 0.09	8	1.19 ± 0.07	0.889
P1NP, ng/mL	15	26.1 ± 20.0	18	26.8 ± 18.5	3	57.4 ± 32.7	0.054
NTX, nmol BCE/mmol Cr	15	28.3 ± 14.2	18	29.3 ± 13.7	—	—	0.838
TRACP-5b, mU/dL	15	338.7 ± 164.1	18	339.1 ± 145.0	2	539.5 ± 0.7	0.207
Previous treatment with BP		15 (100%)		18 (100%)		8 (100%)	1
Previous treatment with EL		6 (40%)		8 (42.1%)		0 (0%)	0.083

Values are presented as mean ± standard deviation or number (%).

TTT, treatment with once-weekly teriparatide (W-TPTD) for 18 months; TBT, sequential treatment of W-TPTD/bisphosphonates/W-TPTD, each for 6 months; TET, sequential treatment with W-TPTD for 6 months and EL for 6 months, followed by treatment with W-TPTD again for 6 months; BMI, body mass index; BMD, bone mineral density; TBS, trabecular bone score; P1NP, type I procollagen N-terminal propeptide; NTX, type I collagen cross-linked N-telopeptides; TRACP-5b, tartrate-resistant acid phosphatase-5b; BP, bisphosphonate; EL, elcatonin.

### 3.3. Bone mineral density

**Fig. 2a** shows the change in lumbar spine BMD per group at each time-point of measurement. The absolute value for test parameters is shown in **Supplementary Table 1**. The change in lumbar spine BMD in group TBT was 1.6% ( $P = 0.023$ ), 2.9% ( $P = 0.001$ ), and 4.4% ( $P < 0.001$ ) after 6, 12, and 18 months, respectively. Significant increases were observed at all time-points compared to baseline. In group TET, change in lumbar spine BMD was 2.1% ( $P = 0.001$ ), 1.3% ( $P = 0.066$ ), and 3.0% ( $P = 0.015$ ) after 6, 12, and 18 months, respectively. There was no significant difference between baseline and 12 months; however, it increased significantly after 18 months. In contrast, no significant difference was observed in total hip BMD in all 3 groups from baseline to 18 months (**Fig. 2b**). In group TBT, there was no significant difference between 6 and 12 months ( $P = 0.153$ ), as well as between 12 and 18 months ( $P = 0.464$ ).

### 3.4. Bone turnover markers

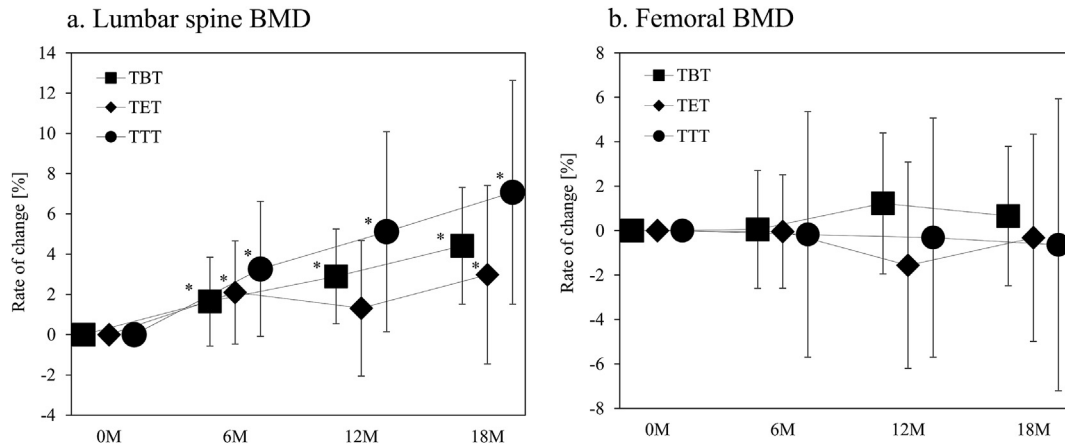
**Fig. 3** shows the changes in bone turnover markers. A significant increase in P1NP and NTX was observed only after 6 months in group TBT compared to baseline. A significant increase from baseline was observed after 6, 12, and 18 months in group TET. A significant increase in TRACP-5b was observed in group TET after 12 months compared to baseline. However, a significant decrease in TRACP-5b was observed in group TBT after 12 months.

### 3.5. Hip structural analyses

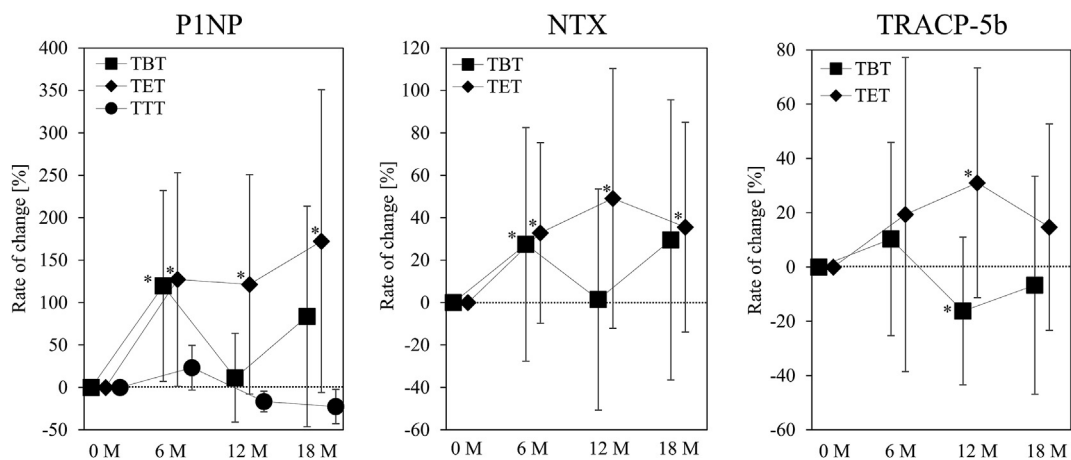
**Table 2** shows the changes in HSA. In group TBT, a significant decrease from baseline was observed in CBT, CSA, and SM at the narrow neck, and a significant increase was observed in BR. At intertrochanteric region, a significant increase was observed in CBT, CSA, and SM. No significant change was observed in femoral shaft. In addition, no significant change in TBS was observed in the 3 groups (**Supplementary Table 2**).

### 3.6. Safety

Fourteen ADRs (13.5%) were observed. The most commonly observed event was “feeling bad (5 events)” (**Table 3**).



**Fig. 2.** Changes in lumbar spine and total hip bone mineral density (BMD). TTT, treatment with once-weekly teriparatide (W-TPTD) for 18 months (18 M); TBT, sequential treatment of W-TPTD/bisphosphonates/W-TPTD, each for 6 months (6 M); TET, sequential treatment with W-TPTD for 6 months and EL for 6 months, followed by treatment with W-TPTD again for 6 months. 12 M, 12 months. \* $P < 0.05$  vs. 0 month (0 M), paired t-test.



**Fig. 3.** Changes in bone turnover markers. No data in group TTT for NTX and TRACP-5b. TTT, treatment with once-weekly teriparatide (W-TPTD) for 18 months (18 M); TBT, sequential treatment of W-TPTD/bisphosphonates/W-TPTD, each for 6 months (6 M); TET, sequential treatment with W-TPTD for 6 months and EL for 6 months, followed by treatment with W-TPTD again for 6 months; P1NP, procollagen type I N-terminal propeptide; NTX, type I collagen cross-linked N-telopeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b. 12 M, 12 months. \* $P < 0.05$  vs. 0 month (0 M), paired t-test.

#### 4. Discussion

In the present study, we analyzed the changes in BMD to evaluate the efficacy of sequential treatment with W-TPTD and anti-resorptive therapy.

In groups TBT and TET, a significant increase in lumbar spine BMD was observed after 18 months, which is the time-point after the sequential administration of W-TPTD, compared to baseline. This result suggests that discontinuation of W-TPTD treatment once to switch to bone antiresorptive drug does not impair the therapeutic effect of subsequent treatment with W-TPTD on osteoporosis.

When the group treated with daily teriparatide for one year followed by BP administration for one year was compared with the group treated with combination therapy of BP and daily teriparatide for one year followed by BP administration for one year, lumbar spine BMD increased more in the former [5]. Black et al. [5] suggested that sequential treatment was more effective than simultaneous combination treatment.

In our present study, we included subjects who received W-TPTD for 6 months, followed by either BP or EL for 6 months, and

W-TPTD again for 6 months. Although this is the first report to describe sequential treatment using W-TPTD and/or antiresorptive therapy in every 6 months period, our study demonstrates the usefulness of sequential treatment, including W-TPTD.

Porosity in cortical bone has been reported after administration of once-daily teriparatide [6–8]. In addition, when patients treated with bone antiresorptive drug switched to once-daily teriparatide, BMD in the femur or femoral neck decreased after 6 months [9].

All the subjects included in our study were treated with BP before starting W-TPTD, i.e., the all patient at baseline switched the treatment from BP to W-TPTD. However, no significant decrease was observed in the rate of change in total hip BMD after 6 months in all groups. In group TBT, no significant decrease in total hip BMD was observed during 12–18 months even switching from BP, which was used for 6–12 months.

Boonen et al. [10] reported that 2 years of teriparatide treatment were stratified by previous predominant antiresorptive treatment and BMD at the lumbar spine and hip was determined after 6, 12, 18, and 24 months. They showed that the administration of once-daily teriparatide for 2 years followed by switching to BP resulted in a significant decrease in BMDs in the femur and femoral neck

**Table 2**  
Change in HSA in each group.

		TBT (n = 11)						TET (n = 18)						TTT (n = 8)																							
		NN	P	IT	P	FS	P	NN	P	IT	P	FS	P	NN	P	IT	P	FS	P																		
Outer diameter (mm)	0 M	3.25 ± 0.30		5.31 ± 0.50		2.98 ± 0.34		3.24 ± 0.18		5.26 ± 0.23		2.93 ± 0.17		3.34 ± 0.24		5.54 ± 0.40		2.99 ± 0.28																			
	%Δ6 M	1.1 ± 3.7	0.409	0.4 ± 1.2	0.414	-0.1 ± 0.6	0.452	-0.3 ± 2.3	0.56	0.7 ± 3.2	0.335	0.1 ± 1.1	0.836	0.6 ± 3.1	0.584	-0.6 ± 4.2	0.633	0.3 ± 2.4	0.809																		
	%Δ12 M	0.7 ± 3.4	0.659	2.2 ± 2.1	0.008	0.0 ± 1.7	0.876	0.9 ± 4.1	0.424	0.5 ± 2.7	0.467	0.3 ± 2.2	0.531	-0.9 ± 2.7	0.332	-1.8 ± 3.6	0.176	0.6 ± 2.2	0.500																		
Cortical bone inner diameter (mm)	0 M	1.7 ± 4.3		0.5 ± 1.8		0.396		-0.2 ± 1.5		0.519		1.0 ± 4.2		0.325		0.7 ± 2.3		0.221		0.3 ± 1.9		0.558		0.9 ± 3.2		0.407		0.4 ± 5.2		0.922		0.7 ± 2.3		0.436			
	%Δ6 M	3.02 ± 0.31		4.84 ± 0.50		2.22 ± 0.45		3.01 ± 0.18		4.79 ± 0.23		2.21 ± 0.3		3.13 ± 0.26		5.06 ± 0.35		2.27 ± 0.45																			
	%Δ12 M	1.5 ± 4.5	0.322	0.1 ± 1.4	0.759	-0.2 ± 2.5	0.753	0.0 ± 2.7	0.978	0.8 ± 3.6	0.314	0.9 ± 2.3	0.134	1.1 ± 3.4	0.379	-0.6 ± 4.3	0.615	1.0 ± 5.2	0.699																		
CBT (mm)	0 M	1.0 ± 3.9		0.533		2.0 ± 2.4		0.024		0.2 ± 4.6		0.863		1.5 ± 4.7		0.209		0.7 ± 3.0		0.296		1.6 ± 4.1		0.109		-0.6 ± 3.2		0.579		-2.2 ± 3.8		0.146		2.2 ± 5.8		0.288	
	%Δ6 M	2.4 ± 4.5	0.141	0.3 ± 2.1	0.692	-0.6 ± 2.9	0.408	1.6 ± 4.7	0.184	0.9 ± 2.6	0.140	1.6 ± 3.7	0.078	1.7 ± 3.3	0.199	0.2 ± 5.4	0.976	1.4 ± 5.4	0.529																		
	%Δ18 M	0.11 ± 0.01		0.24 ± 0.03		0.38 ± 0.09		0.12 ± 0.02		0.24 ± 0.05		0.36 ± 0.08		0.11 ± 0.02		0.24 ± 0.06		0.36 ± 0.10																			
CSA (cm <sup>2</sup> )	0 M	-5.4 ± 9.4		0.091		2.1 ± 5.4		0.206		0.0 ± 5.4		0.940		-5.3 ± 6.2		0.002		-0.7 ± 7.0		0.775		-2.9 ± 5.0		0.029		-7.0 ± 5.3		0.006		0.1 ± 7.0		0.907		-1.0 ± 5.1		0.579	
	%Δ6 M	-3.6 ± 5.5	0.066	4.1 ± 5.1	0.022	0.7 ± 5.9	0.860	-8.2 ± 6.9	<0.001	-2.5 ± 7.6	0.189	-4.6 ± 7.2	0.018	-5.9 ± 7.6	0.061	1.2 ± 6.4	0.608	-3.4 ± 6.5	0.192																		
	%Δ12 M	-7.7 ± 6.3	0.002	2.7 ± 4.1	0.039	1.2 ± 5.2	0.499	-6.2 ± 6.7	0.001	-2.0 ± 6.4	0.189	-4.2 ± 6.6	0.014	-10.1 ± 4.3	<0.001	1.4 ± 8.9	0.596	-1.1 ± 6.6	0.746																		
SM (cm <sup>3</sup> )	0 M	1.86 ± 0.20		3.01 ± 0.45		3.05 ± 0.54		1.89 ± 0.28		2.95 ± 0.51		2.87 ± 0.47		1.79 ± 0.21		3.02 ± 0.68		2.87 ± 0.59																			
	%Δ6 M	-4.5 ± 7.2	0.061	1.8 ± 5.0	0.303	-0.3 ± 4.3	0.904	-5.5 ± 5.9	0.001	-0.6 ± 6.2	0.802	-2.5 ± 4.3	0.024	-6.4 ± 5.0	0.008	0.3 ± 7.5	0.908	-0.5 ± 3.6	0.674																		
	%Δ12 M	-3.0 ± 5.1	0.089	4.0 ± 4.4	0.017	0.6 ± 3.7	0.662	-7.4 ± 5.6	0.000	-2.1 ± 6.6	0.176	-3.8 ± 6.0	0.017	-6.8 ± 6.1	0.013	1.6 ± 5.6	0.463	-2.3 ± 4.6	0.156																		
BR (-)	0 M	-6.0 ± 7.7		0.031		2.3 ± 4.0		0.098		0.7 ± 4.4		0.608		-5.1 ± 6.2		0.002		-1.7 ± 6.0		0.230		-3.5 ± 5.7		0.016		-9.0 ± 5.1		0.001		2.0 ± 8.9		0.479		-0.3 ± 4.9		0.943	
	%Δ6 M	0.89 ± 0.18		2.57 ± 0.71		1.75 ± 0.47		0.86 ± 0.17		2.49 ± 0.57		1.58 ± 0.22		0.82 ± 0.17		2.80 ± 0.65		1.66 ± 0.35																			
	%Δ12 M	-7.5 ± 9.0	0.011	9.2 ± 8.5	0.003	-0.2 ± 5.0	0.947	-10.9 ± 9.4	<0.001	7.3 ± 12.6	0.035	-1.9 ± 4.7	0.119	-6.2 ± 7.0	0.031	9.5 ± 13.0	0.126	2.6 ± 5.0	0.280																		
BR (-)	0 M	-6.6 ± 5.6		0.004		14.2 ± 10.8		0.001		1.9 ± 4.3		0.382		-11.1 ± 9.6		<0.001		7.6 ± 13.1		0.033		-3.0 ± 6.2		0.071		-6.7 ± 7.0		0.029		8.8 ± 6.0		0.002		-0.4 ± 7.0		0.727	
	%Δ6 M	-9.1 ± 6.8	0.003	11.1 ± 7.7	<0.001	1.7 ± 5.3	0.391	-8.6 ± 9.0	<0.001	6.7 ± 13.3	0.057	-1.4 ± 5.0	0.307	-8.0 ± 10	0.017	10.4 ± 12.0	0.048	3.0 ± 3.0	0.017																		
	%Δ18 M	16.37 ± 2.81		13.66 ± 2.60		4.33 ± 1.3		16.24 ± 2.61		13.72 ± 3.23		4.55 ± 1.33		18.19 ± 3.52		13.93 ± 3.84		4.86 ± 1.94																			
BR (-)	0 M	10.8 ± 18.6		0.094		-4.0 ± 5.5		0.062		-0.2 ± 6.4		0.899		7.3 ± 9.3		0.004		-0.5 ± 7.7		0.709		2.9 ± 6.2		0.053		11.6 ± 9.0		0.014		-2.1 ± 7.0		0.459		0.6 ± 8.0		0.894	
	%Δ6 M	6.5 ± 9.1	0.049	-4.0 ± 6.6	0.082	-0.8 ± 7.8	0.531	12.8 ± 13.1	0.001	0.5 ± 8.4	0.770	5.8 ± 10.3	0.032	6.9 ± 12.0	0.162	-4.7 ± 6.0	0.100	4.2 ± 11.0	0.459																		
	%Δ18 M	13.0 ± 9.5	0.003	-4.1 ± 5.7	0.076	-1.9 ± 5.7	0.291	9.0 ± 10.5	0.002	0.3 ± 8.4	0.972	4.4 ± 8.8	0.046	17.2 ± 8.0	0.001	-2.6 ± 10.0	0.585	0.9 ± 9.0	0.907																		

Values are presented as mean ± standard deviation.

TTT, treatment with once-weekly teriparatide (W-TPTD) for 18 months (18 M); TBT, sequential treatment of W-TPTD/bisphosphonates/W-TPTD, each for 6 months (6 M); TET, sequential treatment with W-TPTD for 6 months and EL for 6 months, followed by treatment with W-TPTD again for 6 months; NN, narrow neck of the femur; IT, intertrochanteric region; FS, femoral shaft; CBT, cortical bone thickness; CSA, cross-sectional area; SM, section modules; BR, buckling ratio; 0 M, 0 month; 12 M, 12 months.

**Table 3**  
Adverse drug reactions.

Adverse drug reactions	Number of cases
Feeling bad	5
Vomiting	1
Malaise	1
Chills	1
Back pain	1
Decreased appetite	1
Diarrhea	1
Rash	1
Discomfort in mouth	1
Hepatic impairment	1

after 6 months, although BMD in the lumbar spine increased. Moreover, Black et al. [5] reported that alendronate therapy after parathyroid hormone therapy led to significant increases in bone mineral density over 2 years. However, in our study, group TBT did not show any significant difference in total hip BMD during 6–12 months even after switching the regimen from W-TPTD to BP. This difference may be partly because of the different mechanisms of action between W-TPTD and once-daily teriparatide. Once-daily teriparatide has been reported to directly stimulate bone formation by bone remodeling and to increase spaces for remodeling [11]. In contrast, W-TPTD did not promote porosity and enhance bone formation on the inner surface, but maintained the normal formation of cortical bone [12,13]. These findings suggest the possible reasons why total hip BMD did not decrease even with sequential treatment using BP in our study.

No significant change in TBS was observed in all treatment groups (Supplementary Table 2). This is probably because changes in TBS are not easily observed within a short period. Moreover, evaluation sensitivity to TBS is lower than that to BMD because the data are based on DXA. Senn et al. [14] reported that TBS increased 2 years after administration of daily teriparatide. Based on the above findings, it can be suggested that longer treatment duration is necessary to confirm significant improvements, because our study was completed at 18 months.

In our study, no change was observed in total hip BMD. In HSA, the intensity index significantly improved in the intertrochanteric region in group TBT (Table 2); however, the index decreased in narrow neck. Khoo et al. [15] reported that the coefficient of variation at the neck was larger than that at the intertrochanteric region, which provided better data with less variability. The improvement in intensity index for intertrochanteric region in group TBT suggested the effectiveness of BP used in the sequential treatment to improve the index for hip joint.

The changes in bone turnover markers decreased in group TBT from 6 to 12 months when the drug was switched to BP. Nevertheless, resuming the administration of W-TPTD increased the value of bone turnover marker. This finding supported the change in lumbar spine BMD. Because the measurement of markers in our study was at 6 months after switching the drug, the duration required to affect BMD could not be determined from the change in marker.

Although lumbar spine BMD in group TBT increased over time in our study, group TET showed a tendency to decrease during 6–12 months after switching to EL and again increased at 18 months when W-TPTD was resumed. Eastell et al. [16] showed that during the second year of treatment, lumbar spine BMD continued to increase significantly in the teriparatide group, did not change significantly in the raloxifene group. Patients receiving raloxifene in year 2 had no further change in spine BMD (change from baseline, 7.9%) from year 1 of teriparatide (change from baseline, 8.3%). Based on the results in group TET and the above reports, BP was

considered a useful drug for sequential treatment with teriparatide.

The incidence of ADRs in our study was 13.5% (14 of 104 subjects), but no serious ADRs were observed. Fujita et al. [17] reported that the incidence of ADRs with W-TPTD (28.2 µg/dose) was 24.1%. Although the doses and observation periods were different, the incidence of ADRs in our study did not exceed that in any of the existing reports.

There are certain limitations to this study. First, because this was a retrospective study evaluating efficacy in subjects who continued treatment for more than 6 months, the efficacy in subjects discontinuing the treatment within a short period was not discussed. Second, as the number of subjects in group TTT was small, we could not measure the markers and compare them. It was not large enough to assess the effects of treatment on the rate of fracture and our conclusions are based on changes in BMD. It is difficult to apply our results to other types of BPs, because minodronic acid was approved for use in Japan only for the treatment of osteoporosis.

## 5. Conclusions

For subjects having difficulty in continuing treatment with W-TPTD due to frequent visits, drug costs, or ADRs, and for those willing to effectually receive W-TPTD providing a limited treatment duration in their entire lives, sequential treatment with W-TPTD and bone antiresorptive drug is potentially a useful option for treating osteoporosis.

## Conflicts of interest

Genichiro Katahira has received a research grant from Asahi Kasei Pharma Corporation, Japan. This study was conducted with financial support from the Asahi Kasei Pharma Corporation. However, the Asahi Kasei Pharma Corporation only provided funding and academic advice, and it was not involved in the management or analysis of our data.

## CRedit authorship contribution statement

**Genichiro Katahira:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Kotaro Akiba:** Formal analysis, Writing - review & editing. **Junichi Takada:** Formal analysis, Writing - review & editing. **Kousuke Iba:** Writing - review & editing. **Toshihiko Yamashita:** Writing - review & editing.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.afos.2020.01.001>.

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