ORIGINAL ARTICLE

Sequential therapy with once-weekly teriparatide injection followed by alendronate versus monotherapy with alendronate alone in patients at high risk of osteoporotic fracture: final results of the Japanese Osteoporosis Intervention Trial-05

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Abstract

Summary In this randomized, controlled trial, sequential therapy with once-weekly subcutaneous injection of teriparatide for 72 weeks, followed by alendronate for 48 weeks resulted in a significantly lower incidence of morphometric vertebral fracture than monotherapy with alendronate for 120 weeks in women with osteoporosis at high risk of fracture.

Purpose To determine whether the anti-fracture efficacy of sequential therapy with teriparatide, followed by alendronate is superior to that of monotherapy with alendronate, a prospective, randomized, open-label, blinded-endpoint trial was performed.

Methods Japanese women aged at least 75 years were eligible for the study, if they had primary osteoporosis and if they were at high risk of fracture. Patients were randomly assigned (1:1) to receive the sequential therapy (once-weekly subcutaneous injection of teriparatide 56.5 µg for 72 weeks, followed by alendronate for 48 weeks) or monotherapy with alendronate for 120 weeks. The primary endpoint in the final analysis was the incidence of morphometric vertebral fracture during the 120-week follow-up period.

Results Between October 2014 and June 2020, 505 patients in the sequential therapy group and 506 in the monotherapy group were enrolled. Of these, 489 and 496, respectively, were included in the main analysis. The incidence of morphometric vertebral fracture during the 120-week follow-up period in the sequential therapy group (64 per 627.5 person-years, annual incidence rate 0.1020) was significantly lower than that in the monotherapy group (126 per 844.2 person-years, annual incidence rate 0.1492), with a rate ratio of 0.69 (95% confidence interval 0.54 to 0.88, $P < 0.01$). After 72 weeks, no patient had a severe adverse event that was considered related to the study drug.

Conclusion Once-weekly injection of teriparatide, followed by alendronate resulted in a significantly lower incidence of morphometric vertebral fracture than alendronate monotherapy in women with osteoporosis who were at high risk of fracture.

Trial registration number, date of registration jRCTs031180235 and UMIN000015573, March 12, 2019

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Introduction

Although the diagnosis of osteoporosis relies heavily on the presence of low bone mineral density (BMD), clinical factors such as age, sex, and prior fragility fracture also have a pivotal role in assessing the risk of fracture [1–3]. For example, in elderly women with osteoporosis, the site of an existing fracture and whether its history is recent affect the risk of subsequent fracture. Patients with so-called "severe osteoporosis" should be treated with a potent anti-osteoporosis agent. However, there is no consensus about the long-term treatment strategy for severe osteoporosis.

Current treatment guidelines recommend once-daily subcutaneous injection of teriparatide for patients at high risk of fracture [3, 4]. Furthermore, once-weekly subcutaneous injection of teriparatide has been approved in Japan based on the results of a randomized, placebo-controlled trial [5]. This new regimen requires less frequent administration and may not cause deleterious changes in the cortical microarchitecture compared with the once-daily regimen [6]. These results suggest that treatment for patients with severe osteoporosis should be started with once-weekly injection of teriparatide. However, the use of teriparatide is limited to 24 months, irrespective of the regimen. As a result, teriparatide must be switched to another medication if patients have received it for the approved period because of the concern that BMD may decrease after terminating teriparatide treatment [7, 8].

In a follow-up observational study of the Japanese placebo-controlled trial mentioned above, patients who received bisphosphonate following teriparatide achieved a further increase in BMD [9]. A randomized, controlled trial also indicated that the sequential therapy with full-length parathyroid hormone, followed by alendronate significantly increased areal BMD at the lumbar spine, compared with parathyroid hormone therapy, followed by placebo or monotherapy with alendronate alone [10]. These results suggest that alendronate, one of the most commonly used anti-resorptive agents, is a suitable candidate drug for patients at high risk of osteoporotic fracture.

However, no randomized, controlled trial has evaluated the anti-fracture efficacy of sequential therapy. In this context, the Adequate Treatment of Osteoporosis (A-TOP) research group conducted the Japanese Osteoporosis Intervention Trial-05 (JOINT-05) to compare the efficacy and safety of the sequential therapy (once-weekly injection of teriparatide for 72 weeks, followed by alendronate for 48 weeks) and monotherapy (alendronate for 120 weeks) in women at high risk of fracture. In the first part of the study up to 72 weeks, it was found that teriparatide was superior to alendronate in reducing the incidence of morphometric vertebral fracture [11]. In the second part from 72 to 120 weeks, teriparatide was switched to alendronate in the sequential therapy group, and the hypothesis that the anti-fracture efficacy of sequential therapy throughout 120 weeks is superior to that of monotherapy was tested. In this paper, the final results are reported.

Methods

Study design

JOINT-05 was a prospective, randomized, open-label, blinded-endpoint trial conducted between October 2014 and June 2020 at 113 institutions in Japan. The protocol was approved by the certified review board of Toranomon Hospital and the central ethics committee of the A-TOP research group. The study was conducted in accordance with the Declaration of Helsinki and the Clinical Trials Act of the Japanese Ministry of Health, Labour, and Welfare. All patients provided written, informed consent. The study is registered with the Japan Registry of Clinical Trials (number, jRCTs031180235) and the University Hospital Medical Information Network-Clinical Trials Registry (number, UMIN000015573).

Study population

The design of the JOINT-05 has been reported previously [11, 12]. In brief, Japanese women aged at least 75 years were eligible for the study, if they had primary osteoporosis and if they were at high risk of fracture. Primary osteoporosis was diagnosed, according to the revised Diagnostic Criteria for Primary Osteoporosis of the Japanese Society for Bone and Mineral Research [13]. Specifically, primary osteoporosis was diagnosed in women who had no disease that causes low bone mineral density other than osteoporosis, who had no secondary osteoporosis and have a fragility fracture or a BMD of < 70% of the young adult mean. Patients at high risk of fracture were defined as those who had any of the following: BMD less than 60% of young adult mean (at the lumbar spine, proximal femur, radius, and second metacarpal bone) or less than − 3.3 standard deviations (SDs); at least 2 vertebral fractures in the area from the fourth thoracic vertebra (Th4) to the fourth lumbar vertebra (L4); a grade 3 prevalent fracture; or past hip fracture.

Eligibility criteria

Patients were eligible for the study, if they were:

1. diagnosed with primary osteoporosis, according to the revised 2012 Diagnostic Criteria for Primary Osteo-

porosis of the Japanese Society for Bone and Mineral Research [13];
2. women at least 75 years of age when giving informed consent;
3. could walk by themselves (walk alone, with a cane, or with a walker); and
4. at high risk of fracture (i.e., BMD less than 60% of young adult mean or less than -3.3 SDs, at least 2 vertebral fractures in the area from Th4 to L4, or a grade 3 prevalent fracture or past fracture).

Patients were excluded from the study, if they had:

1. secondary osteoporosis;
2. diagnosis of a disease other than osteoporosis that causes bone loss;
3. diagnosis of a disease that affects the strength of the vertebral bodies;
4. history of hypersensitivity such as bronchial asthma or rash;
5. contraindication to any of the study drugs used;
6. serious renal, hepatic, or cardiac disease;
7. been hospitalized; or
8. history of treatment with teriparatide.

Study treatments

Patients were randomly assigned in a 1:1 ratio to receive the sequential therapy (teriparatide 56.5 µg for 72 weeks, followed by alendronate for 48 weeks) or monotherapy with alendronate for 120 weeks. Teriparatide was administered subcutaneously once weekly. Alendronate was administered using the following formulations: 5 mg tablet (orally administered once daily), 35 mg tablet or jelly (orally administered once weekly), or 900 µg infusion bag (administered intravenously once every 4 weeks). In the sequential therapy group, 0% received the 5 mg tablet, 54.4% received the 35 mg tablet, 14.5% received the 35 mg oral jelly, and 31.1% received the 900 µg infusion bag. In the monotherapy group, 0.6% received the 5 mg tablet, 45.9% received the 35 mg tablet, 16.4% received the 35 mg oral jelly, and 37.1% received the 900 µg infusion bag. Medication compliance was monitored by recording the dates teriparatide prescriptions were issued and verifying alendronate compliance by the physician in charge approximately every 12 weeks.

To ensure balanced treatment groups at enrollment, subjects were randomly allocated by a web-based computerized system with the modified minimization method [14] adjusted for the following factors which could affect the assessment of treatment efficacy: age (75–79 vs. ≥ 80 years), BMD ($< 60\%$ vs. $\geq 60\%$ of young adult mean), number of prevalent vertebral fractures (0–1 vs. ≥ 2), presence or absence of prevalent vertebral fracture of grade 3, presence or absence

of history of hip fracture, and study institution. The algorithm for random allocation was concealed from the study personnel.

Outcome measures

The thoracic and lumbar vertebrae were imaged in two directions at 0 (baseline), 24, 48, 72, and 120 weeks. For the assessment of prevalent vertebral fracture, anteroposterior and lateral radiographs of the thoracic and lumbar spine were examined by the investigators. The grade of vertebral fracture from Th4 to L4 was assessed using the semiquantitative (SQ) technique to classify fractures as mild (grade 1: 20% to 25% reduction in vertebral height/10% to 20% reduction in vertebral area), moderate (grade 2: 25% to 40% reduction in vertebral height/20% to 40% reduction in vertebral area), or severe (grade 3: $\geq 40\%$ decrease in vertebral height/$\geq 40\%$ reduction in vertebral area) [15]. Fractures were considered to have progressed if the SQ grade changed from grade 1 to grade 2 or from grade 2 to grade 3. These assessments were reviewed centrally by one evaluator from the fracture assessment committee blinded to the assigned treatment. The committee member also adjudicated the presence or absence of a new vertebral fracture by comparing radiographs of Th4 to L4 between baseline and post-treatment. After the X-ray films were collected, two evaluators blinded to the assigned treatment reviewed the films independently, according to the SQ technique mentioned above. If inconsistencies arose between the evaluators, three evaluators reviewed the films simultaneously. The presence or absence of other fractures, such as non-vertebral fractures (fractures at any sites other than the vertebrae) and clinical fractures, was assessed by the investigators. Thereafter, three evaluators from the fracture assessment committee reviewed the assessment made by the investigators using the collected X-ray films.

BMD at the lumbar spine, proximal femur, radius, and second metacarpal bone was measured in each institution at 0, 24, 48, 72, and 120 weeks by dual-energy X-ray absorptiometry. No cross-calibration of machines was performed across institutions. Blood samples were obtained at 0, 12, 24, 48, 72, and 120 weeks to measure the serum levels of osteocalcin, procollagen type I amino-terminal propeptide (P1NP), and tartrate-resistant acid phosphatase 5b (TRACP-5b). The inter-assay coefficients of variation were 4.48–8.64% for osteocalcin, 1.09–1.74% for P1NP, and 2.5–4.4% for TRACP-5b. LSI Medience Corporation (Tokyo, Japan) analyzed the levels of osteocalcin and P1NP using a fluorometric enzyme immunoassay and an electrochemiluminescence immunoassay, respectively. SB Bioscience Co., Ltd. (Tokyo, Japan) analyzed TRACP-5b levels using an enzyme immunoassay.

The primary endpoint in the second part of the study was the incidence of morphometric vertebral fracture from

0 to 120 weeks. The accumulation of person-years at risk started at the randomization of each patient and ended at the date of the last visit, lost to follow-up, or death. One of the secondary endpoints in the second part was the incidence of morphometric vertebral fracture from 72 to 120 weeks. Other secondary endpoints included the following from 0 to 120 weeks: incidence of any fracture, clinical vertebral fracture, non-vertebral fracture, and fracture at specific skeletal sites; and progression of vertebral fracture.

Statistical considerations

Prior to the start of the study, it was assumed that the annualized incidence of vertebral fracture in the alendronate group would be 0.112 and that the hazard ratio of teriparatide relative to alendronate over 72 weeks would be 0.5 [12]. We assumed the annualized incidence of non-vertebral fracture would be 0.016 and the non-inferiority margin was set at a hazard ratio of 1.96 based on effect retention as calculated by comparing the hazard ratio of alendronate with placebo. Based on these assumptions, a sample size of 500 patients for each group was calculated to be required in order to detect the difference in the incidence of morphometric vertebral fracture in the first part (from 0 to 72 weeks) between the treatment groups with a power of 0.80 and a significance level of 0.05 [11, 12]. In the final analysis of vertebral fracture at 120 weeks, the power was estimated to be 0.99 given that the analysis population consisted of 778 patients, and the follow-up periods were longer than those in the primary analysis.

Efficacy outcomes were analyzed in the full analysis set, which consisted of randomly assigned patients who received at least one dose of the study medication and had at least one evaluable radiograph after randomization. In the analyses of the fractures, a multivariable Poisson regression model was fit to calculate the rate ratios of sequential therapy to monotherapy and their 95% confidence intervals (*CI*s). This regression model included the minimization factors for random allocation as covariates. Missing data on radiographs of Th4 to L4 were not imputed. For the incidences of morphometric vertebral fracture, any fracture, and clinical vertebral fracture, as well as the progression of vertebral fracture, the hypothesis that the efficacy of sequential therapy is superior to that of monotherapy was tested. For the incidence of non-vertebral fractures, the hypothesis that the efficacy of sequential therapy is not inferior to that of monotherapy, defined as the upper limit of the 95% *CI* for the rate ratio less than 1.96, was tested.

Safety outcomes were analyzed descriptively by treatment group in the safety analysis set, which consisted of all patients who entered the second 48-week treatment period.

Because the proportion of patients who had any adverse event up to 72 weeks in the first part was analyzed [11], the focus in this report was on the adverse events that occurred after 72 weeks. Adverse events were coded, according to the system organ class of the Medical Dictionary for Regulatory Activities.

All data were analyzed with the use of SAS® software version 9.4 (SAS Institute, Cary, NC). All reported *P* values are 2-tailed without adjustment for multiplicity.

Results

A total of 1011 patients (505 in the sequential therapy group and 506 in the monotherapy group) were enrolled in the study (Fig. 1). Of these, 489 and 496 patients in the sequential therapy and monotherapy groups, respectively, were included in the full analysis set (Online Resource 1). At 72 weeks, 251 and 357 patients, respectively, remained in the study. These patients were included in the safety analysis set. As shown in Fig. 1, 205 out of the 251 patients in the sequential therapy group switch to alendronate, and 348 out of 357 patients in the monotherapy group continued alendronate beyond 80 weeks. In addition, 265 and 184 patients, respectively, discontinued the follow-up from 72 to 120 weeks. The main reasons for discontinuation were the patient's wish and safety reasons.

Baseline characteristics were well balanced between the two groups (Table 1). The mean (SD) age was 81.4 (4.5) years in the sequential therapy group and 81.5 (4.7) years in the monotherapy group. Two-thirds of the patients in each group had prevalent vertebral fractures, and approximately 40% of the patients in each group had at least 2 prevalent vertebral fractures and at least 1 grade 3 prevalent vertebral fracture.

In the analysis of fracture risk (Table 2), the incidence of morphometric vertebral fracture from 0 to 120 weeks was significantly lower in the sequential therapy group (64 per 627.5 person-years, annual incidence rate 0.1020) than in the monotherapy group (126 per 844.2 person-years, annual incidence rate 0.1492), with a rate ratio of 0.69 (95% *CI* 0.54 to 0.88, *P* < 0.01). The incidence of morphometric vertebral fracture from 72 to 120 weeks was also significantly lower in the sequential therapy group (annual incidence rate 0.0376) than in the monotherapy group (annual incidence rate 0.1008), with a rate ratio of 0.41 (95% *CI* 0.24 to 0.71, *P* < 0.01).

The incidence of non-vertebral fracture during 120 weeks in the sequential therapy group was 23 per 678.3 person-years (annual incidence rate 0.0339), whereas that in the
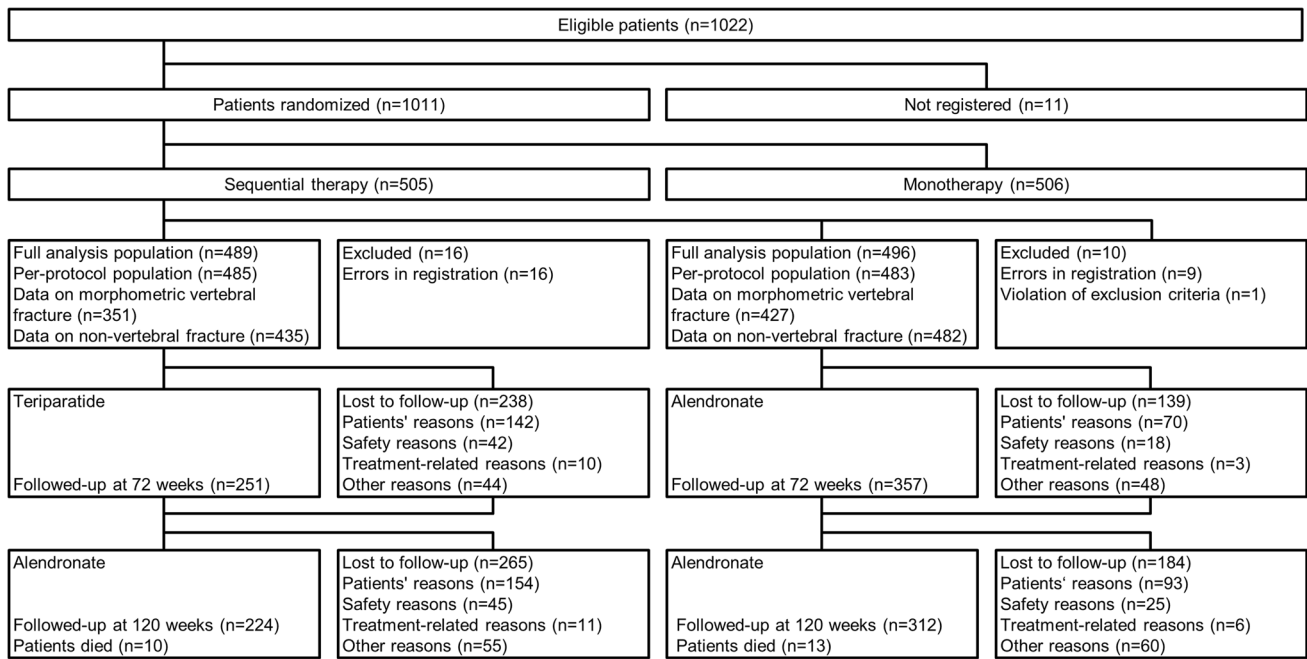
Fig. 1 Flowchart of the patients enrolled in the Japanese Osteoporosis Intervention Trial-05

monotherapy group was 25 per 891.3 person-years (annual incidence rate 0.0280), with a rate ratio of 1.27 (95% *CI* 0.84 to 1.93, *P* = 0.04 for non-inferiority). Analyses of the other endpoints did not show significant treatment effects.

Similar elevations in mean BMD (T-score) at the lumbar spine from 0 to 72 weeks were seen in the two groups (Fig. 2). However, the increase in BMD after 72 weeks was numerically greater in the sequential therapy group, although the difference between the groups at 120 weeks was not significant (*P* = 0.09). Serum levels of osteocalcin, P1NP, and TRACP-5b decreased in the sequential therapy group after 72 weeks, whereas they remained approximately constant in the monotherapy group. As a result, their serum levels at 120 weeks were similar in the two groups.

The treatment effects of sequential therapy on the incidence of morphometric vertebral fracture were generally consistent across various subgroups (Fig. 3). However, sequential therapy showed a good effect in patients with grade 3 fracture, whereas monotherapy showed it in those with grade 1–2 fracture (*P* = 0.05 for interaction).

In both groups, adverse events were most frequently reported in the following system organ classes after 72 weeks: infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders, and general disorders and administration site conditions (Table 3). The proportion of patients who had adverse events classified into these system organ classes was numerically lower in the sequential therapy group than in the monotherapy group. After 72 weeks, no patient had a severe adverse event that was considered related to the study drug by the investigator.

Discussion

In the final analysis of JOINT-05, the incidence of morphometric vertebral fracture from 0 to 120 weeks was significantly lower in the sequential therapy group than in the monotherapy group. Furthermore, the effect of sequential therapy on the reduction in non-vertebral fractures was not inferior to that of monotherapy. Although a previous randomized, controlled trial showed the superiority of sequential therapy with parathyroid hormone, followed by alendronate over monotherapy with alendronate in increasing BMD [10], it did not assess their effects on the rate of fracture. To the best of our knowledge, the present trial is the first head-to-head comparison of the anti-fracture efficacy of sequential therapy.

Alendronate was used as an anti-resorptive agent following teriparatide, but several studies suggested that denosumab might be another candidate [16–19]. Of these,

Table 1 Baseline characteristics of postmenopausal women with severe osteoporosis included in the full analysis set

	Sequential therapy ($N=489$)		Monotherapy ($N=496$)	
	Mean	SD	Mean	SD
Age (y)	81.4	4.5	81.5	4.7
Age at menopause (y)	49.6	4.4	49.2	4.4
Years from menopause (y)	31.8	6.5	32.3	6.4
No. of prevalent vertebral fractures	1.7	1.9	1.8	2.0
0	32.3%		32.1%	
1	27.0%		27.2%	
2	16.8%		15.1%	
3	10.6%		9.5%	
4	4.9%		6.0%	
5 or more	8.4%		10.1%	
Maximum grade of prevalent vertebral fractures*, %				
Grade 1	9.2%		9.5%	
Grade 2	15.7%		17.7%	
Grade 3	42.7%		40.7%	
History of proximal femoral fractures	14.1%		13.5%	
Prior treatment	53.8%		54.4%	
Prior bisphosphonates	29.7%		30.2%	
Comorbidities, %				
Hypertension	37.8%		37.5%	
Diabetes mellitus	8.2%		9.1%	
Dyslipidemia	15.7%		15.3%	
Rheumatoid arthritis	0.4%		1.2%	
Osteoarthritis	0.0%		0.2%	
Others	27.0%		28.0%	
Height (cm)	146.7	6.5	146.2	6.2
Weight (kg)	47.7	9.0	47.3	8.1
BMI (kg/m^2)	22.2	3.8	22.1	3.5
Timed up and go test (seconds)	13.1	8.1	13.7	11.1
One leg standing (seconds)	15.1	23.9	14.6	22.6
25OHVD (ng/mL)	17.6	5.9	17.5	5.6
Corrected pentosidine (pmol/mg Cr)	45.7	25.8	44.1	19.1
HbA1C (%)	5.9	0.5	5.9	0.7
Total cholesterol (mg/dL)	203.3	36.9	200.4	36.0
HDL cholesterol (mg/dL)	63.1	16.9	60.5	16.5
LDL cholesterol (mg/dL)	114.8	31.6	113.2	30.4
Triglyceride (mg/dL)	115.1	58.3	120.5	66.2
eGFR (mL/min/1.73 m^2)	63.6	17.5	62.8	16.7
Creatinine (mg/dL)	0.7	0.2	0.7	0.2
Urine creatinine (mg/dL)	77.5	58.2	73.0	50.6
Albumin (g/dL)	4.1	0.4	4.1	0.4
Ca (mg/dL)	9.5	0.5	9.5	0.4
Urine Ca (mg/dL)	11.4	8.7	11.3	8.1

Data are summarized as means with standard deviation unless otherwise specified

SD standard deviation, BMI body mass index, HbA1c hemoglobin A1c, BMD bone mineral density, L2 second lumbar vertebra, L4 fourth lumbar vertebra, 25OHVD 25-hydroxy vitamin D,

HDL high-density lipoprotein, LDL low-density lipoprotein, eGFR estimated glomerular filtration rate

*A semiquantitative method was used to classify fractures as mild (grade 1: 20% to 25% reduction in vertebral height/10% to 20% reduction in vertebral area), moderate (grade 2: 25% to 40% reduction in vertebral height/20% to 40% reduction in vertebral area), or severe (grade 3: ≥40% decrease in vertebral height/≥40% reduction in vertebral area)

two studies indicated that the increase in BMD at the lumbar spine was significantly greater in the teriparatide-to-denosumab group than in the teriparatide-to-bisphosphonate group [17, 18]. However, denosumab has to be subcutaneously injected. In contrast, alendronate can be administered orally, which is a more convenient route of administration for long-term use. In addition, the reductions in fracture risk were similar between denosumab and bisphosphonates, although their effects on BMD seemed to be different [20]. Thus, alendronate is considered to be a suitable sequential therapy, following teriparatide for patients at high risk of osteoporotic fracture.

In the second part of JOINT-05, all patients received alendronate, but the incidence of morphometric vertebral fracture from 72 to 120 weeks was significantly lower in the sequential therapy group. Furthermore, the increase in lumbar BMD after 72 weeks was numerically greater in the sequential therapy group. These results are consistent with those obtained from the previous studies that assessed the effects of anti-resorptive treatment following teriparatide on BMD [10, 16, 21]. Of these, two studies showed rapid reduction in bone resorption marker levels after switching to anti-resorptive treatment accompanied by relatively slower reduction in bone formation marker levels [16, 22]. These results may explain the mechanism underlying the favorable effects of sequential therapy.

Subgroup analyses have suggested the possible superiority of sequential therapy in patients with grade 3 prevalent vertebral fracture. These results are consistent with those obtained from the analysis of the first part [11]. Currently, teriparatide is strongly recommended for patients at very high risk of fracture [4, 22]. However, its use is limited to 24 months, and there is no consensus about the long-term treatment strategy for these patients. The present results suggest that teriparatide, followed by alendronate may be especially effective in these patients.

In the safety assessments, common adverse events reported in the second part were similar to those reported in the first part [11]. No adverse event indicating a new safety concern was observed. Although the proportion of patients who had any adverse event was lower in the second part than in the first part regardless of the assigned treatment, it may be due to the difference in treatment period between the first (72 weeks) and second (48 weeks) parts.

The overall safety profile of bisphosphonates is good [3]. Gastrointestinal disorders were frequently reported in the present study. These disorders are known to be associated with oral bisphosphonates, and proper instructions, such as remaining in the upright position for at least 30 min after intake, can reduce their frequency [23]. Musculoskeletal and connective tissue disorders were also frequently reported.

Table 2 Incidences of the primary and secondary endpoints in each treatment group and their rate ratios between the treatment groups

	Sequential therapy				Monotherapy				Rate ratio*	95% CI		P
	Count	Person	Person-years	Annual incidence rate	Count	Person	Person-years	Annual incidence rate				
Primary endpoint‡												
Morphometric vertebral fracture												
0 to 120 weeks	64	48	627.5	0.1020	126	90	844.2	0.1492	0.69	0.54	0.88	<0.01
72 to 120 weeks	8	7	213.0	0.0376	30	28	297.6	0.1008	0.41	0.24	0.71	<0.01
Secondary endpoints (0 to 120 weeks)‡												
Any fracture	87	61	678.3	0.1283	151	115	891.3	0.1694	0.80	0.58	1.10	0.17
Clinical vertebral fracture	6	5	627.5	0.0096	12	8	844.2	0.0142	0.24	2.11	0.54	0.52
Progression of vertebral fracture	30	28	627.5	0.0478	44	40	844.2	0.0521	0.98	0.63	1.52	0.93
Non-vertebral fracture	23	17	678.3	0.0339	25	25	891.3	0.0280	1.27	0.84	1.93	0.04†
Secondary endpoints (Fracture at specific skeletal sites 0 to 120 weeks)												
Forearm	4	4	678.3	0.0059	3	3	891.3	0.0034				
Humerus	1	1	678.3	0.0015	0	0	891.3	0.0000				
Femur	3	3	678.3	0.0044	7	7	891.3	0.0079				
Lower leg	1	1	678.3	0.0015	0	0	891.3	0.0000				
Clavicle	1	1	678.3	0.0015	0	0	891.3	0.0000				
Pelvis	2	2	678.3	0.0029	2	2	891.3	0.0022				
Rib	5	3	678.3	0.0074	6	6	891.3	0.0067				
Other	6	5	678.3	0.0088	7	7	891.3	0.0079				

CI confidence interval

*Generalized estimating equation-Poisson regression adjusted for age, counts, and maximum grade of prevalent vertebral fractures, history of hip fractures, and bone mineral density as covariates and individual and institute as cluster

†Non-inferiority *P*-value with a pre-specified non-inferiority margin of 1.96

‡A semiquantitative method was used to classify fractures as mild (grade 1: 20% to 25% reduction in vertebral height/10% to 20% reduction in vertebral area), moderate (grade 2: 25% to 40% reduction in vertebral height/20% to 40% reduction in vertebral area), or severe (grade 3: $\geq$40% decrease in vertebral height/$\geq$40% reduction in vertebral area)
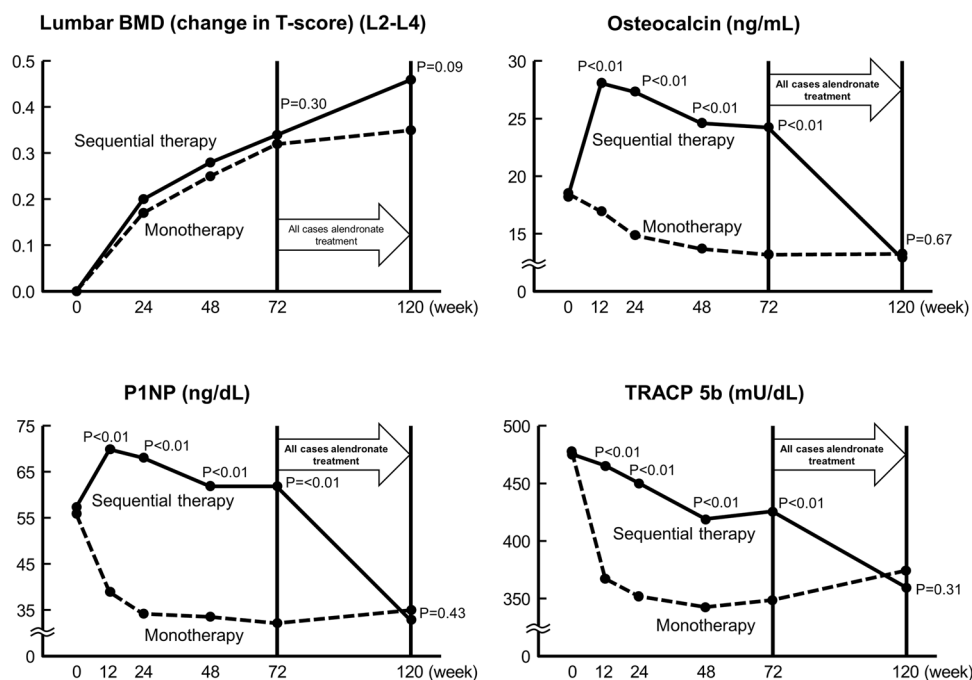
Fig. 2 Changes in bone mineral density at the lumbar spine and bone turnover markers over 120 weeks by treatment group. Percent changes in bone mineral density were 9.0% ($n=192$), 12.3% ($n=165$), 15.0% ($n=151$), and 20.2% ($n=129$) at each time point in the sequential group and 7.2% ($n=228$), 10.7% ($n=220$), 13.5% ($n=208$), and 14.8% ($n=177$) at each time point in the monotherapy group. Percent changes in osteocalcin were 54.2% ($n=364$), 50.1% ($n=338$), 35.2% ($n=288$), 33.1% ($n=263$), and -28.9% ($n=221$) at each time point in the sequential group and -8.5% ($n=424$), -19.6% ($n=416$), -25.9% ($n=392$), -28.7% ($n=362$), and -28.3% ($n=308$) at each time point in the monotherapy group. Percent changes in P1NP were 21.9% ($n=364$), 18.7% ($n=338$), 7.9% ($n=288$), 7.9% ($n=263$), and -42.5% ($n=221$) at each time point in the sequen-

tial group and -30.3% ($n=424$), -38.7% ($n=416$), -39.9% ($n=392$), -42.4% ($n=362$), and -37.3% ($n=308$) at each time point in the monotherapy group. Percent changes in TRACP-5b were -2.1% ($n=363$), -5.3% ($n=338$), $--11.8\%$ ($n=288$), -10.4% ($n=263$), and -24.3% ($n=221$) at each time point in the sequential group and -23.1% ($n=425$), -26.3% ($n=416$), -28.3% ($n=392$), -27.0% ($n=362$), and -21.6% ($n=308$) at each time point in the monotherapy group. Abbreviations: BMD, bone mineral density; P1NP, procollagen type I amino-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b. The term "teriparatide to alendronate" means the sequential therapy group, whereas "alendronate to alendronate" means the monotherapy group

Of these, myalgia, arthralgia, and bone pain are considered acute-phase reactions and generally transient [23].

Some limitations should be mentioned. First, the optimal treatment duration of alendronate following teriparatide could not be assessed because the treatment period of the second part was 48 weeks. However, the Task Force of the American Society for Bone and Mineral Research recommends 10-year treatment with oral bisphosphonate or 6-year treatment with intravenous bisphosphonate accompanied by periodic evaluation of fracture risk for women at high risk of fracture [24]. Therefore, the optimal duration may be longer than 6 or 10 years and should be assessed in future observational studies. Second, due to the large number of patients lost to follow-up, the final sample size was not large enough to detect differences between the treatment groups in the incidences of any fracture, the incidence of clinical vertebral fracture, and the progression of vertebral fracture. A larger portion of subjects discontinued

the study drugs in the sequential group than in the monotherapy group. This is most likely due to higher drug prices and the greater time and effort required attending hospital visits. Although it can be speculated that pharmacological effects also resulted in the large portion of subjects discontinuing the study drugs, no patient had a severe adverse event that was considered related to the study drug after 72 weeks.

Third, BMD was measured in each institution without specifying the analytical method. Thus, the changes in BMD should be interpreted cautiously.

In conclusion, sequential therapy with once-weekly subcutaneous injection of teriparatide, followed by alendronate was associated with a significantly greater reduction in the incidence of morphometric vertebral fracture than monotherapy with alendronate in women with primary osteoporosis who were at high risk of fracture. We consider that alendronate is a suitable successor to teriparatide.

Fig. 3 Rate ratios for the incidence of morphometric vertebral fracture stratified by baseline characteristics. Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; SQ, semiquantitative; BMD, bone mineral density
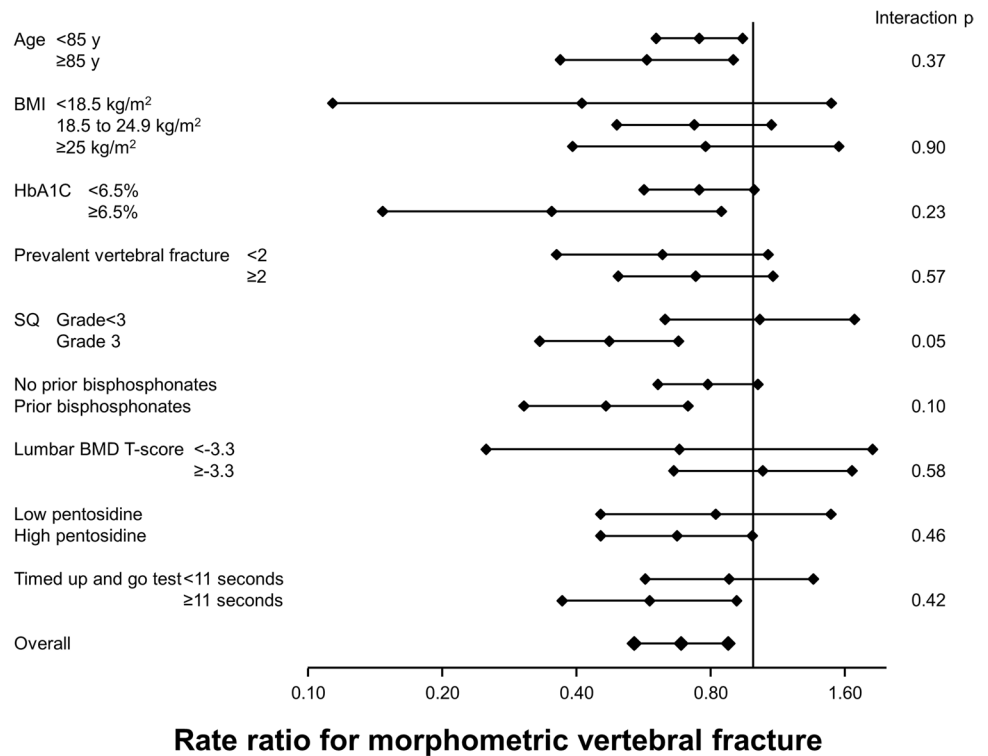

Rate ratio for morphometric vertebral fracture

Table 3 Incidence of adverse events after the initial 72 weeks

System organ class*	Sequential therapy (N=2 51)		Monotherapy (N=357)	
	n	%	n	%
Infections and infestations	7	2.8%	61	17.1%
Immune system disorders	0	0.0%	4	1.1%
Nervous system disorders	0	0.0%	14	3.9%
Eye disorders	0	0.0%	4	1.1%
Ear and labyrinth disorders	0	0.0%	5	1.4%
Cardiac disorders	4	1.6%	12	3.4%
Vascular disorders	0	0.0%	13	3.6%
Gastrointestinal disorders	6	2.4%	20	5.6%
Hepatobiliary disorders	0	0.0%	0	0.0%
Skin and subcutaneous tissue disorders	2	0.8%	31	8.7%
Musculoskeletal and connective tissue disorders†	12	4.8%	59	16.5%
Renal and urinary disorders	3	1.2%	10	2.8%
General disorders and administration site conditions	6	2.4%	21	5.9%
Blood and lymphatic system disorders	1	0.4%	1	0.3%
Respiratory, thoracic, and mediastinal disorders	0	0.0%	14	3.9%
Injury, poisoning, and procedural complications	0	0.0%	6	1.7%
Psychiatric disorders	0	0.0%	1	0.3%
Metabolism and nutrition disorders	1	0.4%	7	2.0%
Neoplasms benign, malignant, and unspecified	0	0.0%	4	1.1%
Investigations	0	0.0%	5	1.4%
Others	0	0.0%	1	0.3%

*Adverse events were coded according to the system organ class of the Medical Dictionary for Regulatory Activities

†Fractures were excluded

Declarations

Ethics approval All the procedures performed in this study were in accordance with the Clinical Trials Act of the Japanese Ministry of Health, Labor and Welfare and with the 1964 Helsinki declaration and its later amendments. The protocol was approved by the certified review board of Toranomon Hospital and the central ethics committee of the Adequate Treatment of Osteoporosis research group.

Informed consent Informed consent was obtained from all the individual participants included in the study.

Competing interests H. Hagino has received lecture fees or grants outside the submitted work from Amgen Inc., Asahi Kasei Pharma Corp., Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan Co., Ltd., Mitsubishi Tanabe Pharma Corp., Mochida Pharma Corp., Ono Pharmaceutical Co., Ltd., Pfizer Inc., Taisho Pharmaceutical Co., Ltd., Teijin Pharma Co., Ltd., and UCB Japan.

T. Sugimoto has received research grants from Asahi Kasei Pharma Corp., Astellas Pharma, Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Pfizer, and Teijin Pharma Ltd., as well as consulting fees from Kissei Pharmaceutical Co., Ltd., Shimadzu Corp., and Takeda Pharmaceutical Co., Ltd.
S. Tanaka has received lecture fees from Bayer Yakuhin, Amgen Astellas BioPharma K.K., and Research Institute of Healthcare Data Science. He has received consultation fees and outsourcing fees from Daiichi Sankyo Company, Limited, Boehringer Ingelheim, Satt, and the Public Health Research Foundation. He has received research grants from the Japan Agency for Medical Research and Development, the Japanese Ministry of Health Labor and Welfare, the Japanese Ministry of Education, Science, and Technology, and Novo Nordisk. He engaged in a research project of the Japan Agency for Medical Research and Development.
T. Sone has received research grants from Astellas Pharma, Eisai, Daiichi-Sankyo, Chugai Pharmaceutical, and Eli Lilly Japan, as well as consulting and/or lecture fees from Asahi Kasei Pharma, MSD, and Daiichi-Sankyo.
T. Nakamura has received personal fees and other from Asahi Pharma, Teijin Pharma, Daiichi-Sankyo Pharma, UCB Pharma, Amgen Inc., Astellas Pharma, and Chugai Pharma, as well as personal fees and others from MERCK.
S. Soen has received consulting fees, speaking fees, and/or honoraria from Asahi Kasei Pharma, Amgen, Astellas Pharma, Daiichi Sankyo, Eli Lilly Japan, Teijin Pharma, and UCB Japan.
S. Mori, Y. Mitomo, and K. Takahashi have nothing to disclose.

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