



Design of a randomized trial of teriparatide followed by alendronate: Japanese Osteoporosis Intervention Trial-05 (JOINT-05)

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Abstract

Introduction Despite advances in drug treatment, the optimal treatment strategy for severe osteoporosis remains uncertain.

Materials and methods This article reports the design and rationale for the Japanese Osteoporosis Intervention Trial-05 (JOINT-05), a randomized, controlled trial that compares the efficacy and safety of teriparatide followed by alendronate with alendronate monotherapy for severe osteoporosis.

Results Postmenopausal women aged at least 75 years were eligible for the study if they were at high risk of fracture. Patients were recruited from 113 institutions in Japan between October 2014 and December 2017. They were randomly assigned in a 1:1 ratio to the sequential therapy arm (once-weekly subcutaneous injections of teriparatide 56.5 µg for 72 weeks followed by alendronate for 48 weeks) or monotherapy arm (alendronate for 120 weeks). The regimens for alendronate are 5 mg (orally administered once daily), 35 mg (orally administered once weekly), or 900 µg (intravenously administered once every 4 weeks). The primary endpoint is the incidence of morphometric vertebral fracture at 72 weeks. The secondary endpoints include the incidence of morphometric vertebral fracture at 120 weeks; incidence of morphometric vertebral or non-vertebral fractures at 72 and 120 weeks; incidence of clinical vertebral fracture at 72 and 120 weeks; changes in bone mineral density, quality of life scores (EuroQol 5 Dimensions and the Japanese Osteoporosis Quality of Life Questionnaire short form), and a visual analog scale for back pain; and adverse events.

Conclusion We reported the design and rationale for the JOINT-05. The trial is registered with the Japan Registry of Clinical Trials (jRCTs031180235) and the University Hospital Medical Information Network-Clinical Trials Registry (UMIN000015573).

Keywords Clinical trial protocol · Vertebral fracture · Osteoporosis · Alendronate · Teriparatide

Introduction

The increased incidence of fractures worldwide, estimated to include 9.0 million osteoporotic fractures of which 1.6 million were at the hip, has led to a high need for fracture

prevention in patients with severe osteoporosis [1]. Teriparatide, an anabolic agent that increases bone mineral density (BMD) by stimulating bone formation [2], is one of the most potent treatment options for severe osteoporosis. The degree of increase in BMD with daily teriparatide injections is greater than that of alendronate [3]. Recently, once-weekly injection of teriparatide has been approved in Japan based on a placebo-controlled phase III trial, in which the incidence of morphometric vertebral fractures during the treatment period of 72 weeks was significantly decreased [4]. However, teriparatide must be switched to another treatment once patients have received it for the maximum approved period and, without switching to an adequate treatment, BMD may decrease rapidly after termination of teriparatide [5, 6]. A 1-year follow-up observational study of the Teriparatide Once-Weekly Efficacy Research (TOWER) trial showed that patients who received bisphosphonate after teriparatide

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achieved a further gain in BMD above that achieved at the end of teriparatide treatment [7]. This result suggests that bisphosphonate may be a promising treatment option for patients who have completed receiving teriparatide. Other studies revealed that raloxifene and denosumab also maintain BMD [5, 6, 8, 9]. However, the optimal treatment strategy for severe osteoporosis remains uncertain due to the limited evidence for fracture prevention.

The efficacy of osteoporosis medications is primarily demonstrated in placebo-controlled trials; however, head-to-head comparisons are rare. Some researchers have conducted network meta-analyses of published randomized clinical trials to assess the comparative efficacy of active drugs, but their findings were not consistent. One study conducted indirect comparisons and reported that teriparatide is more effective than alendronate for reducing vertebral fracture significantly [10], but a smaller difference was observed in two previous studies [11, 12]. We, therefore, planned the Japanese Osteoporosis Intervention Trial-05 (JOINT-05), which has two objectives. The primary objective is to determine whether a once-weekly injection of teriparatide for 72 months is superior to alendronate monotherapy in reducing morphometric vertebral fractures in postmenopausal women with severe osteoporosis. The secondary objective is to determine whether sequential treatment with teriparatide followed by alendronate for 120 months is superior to monotherapy in terms of vertebral or non-vertebral fractures, changes in BMD, quality of life scores, visual analog scale (VAS) scores for back pain, and adverse events. This article reports the design and rationale of the JOINT-05.

Materials and methods

Study design and ethics

The JOINT-05 is a multi-center, open-label, randomized, controlled trial conducted in Japan according to the Declaration of Helsinki and the Clinical Trials Act of the Japanese Ministry of Health, Labour, and Welfare. The protocol was approved by the certified ethics committee and the central ethics committee for the JOINT. Patients were recruited from 113 medical facilities throughout Japan between October 2014 and December 2017. Written informed consent was obtained from all individual participants included in the study. The trial is registered with the Japan Registry of Clinical Trials, number jRCTs031180235 and the University Hospital Medical Information Network-Clinical Trials Registry, number UMIN000015573.

Overall procedures and study oversight

Patients who met all of the eligibility criteria were randomly assigned in a 1:1 ratio to the sequential therapy arm (once-weekly injections of teriparatide for 72 weeks followed by oral or intravenous administration of alendronate for 48 weeks) or monotherapy arm (alendronate for 120 weeks). Random allocation was implemented by a web-based computerized system for the modified minimization method adjusted for the following prognostic factors: age (75–79 vs. < 80 years), BMD [$60\% \leq$ vs. $< 60\%$ of young adult mean (YAM)], number of prevalent vertebral fractures (0–1 vs. ≥ 2), presence/absence of prevalent vertebral fractures of grade 3 [13], presence/absence of history of femoral neck fracture, and the study institution. The algorithm for random allocation is concealed from the investigators and other study personnel. Planned follow-up duration is 72 weeks for the primary analysis and 120 weeks for the final analysis. The Joint Center for Researchers, Associates, and Clinicians (JCRAC) Data Center uses the electronic data capture system to enroll patients, collect and manage the data, prepare documents for monitoring purposes, and provide datasets for statistical analysis. The JCRAC Data Center prompts study personnel to submit the required data and scrutinizes the data. It also issues queries about the submitted data if necessary and corrects the data according to the replies to the queries.

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 Osteoporosis of the Japanese Society for Bone and Mineral Research [14];
2. Japanese 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);
4. at high risk of fracture (i.e., BMD less than 60% of YAM 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), or a grade 3 prevalent fracture or past fracture of the proximal femur).

Patients were excluded from the study if they had

1. secondary osteoporosis due to the following conditions: hyperparathyroidism, hyperthyroidism, gonadal

dysfunction, Cushing's syndrome, nutritional deficiency state such as vitamin D deficiency, drug-induced conditions induced by drugs such as steroids, immobility, osteogenesis imperfecta, Marfan's syndrome, rheumatoid arthritis, diabetes mellitus, chronic kidney disease, hepatic disease, and alcohol dependence; the diagnosis of secondary osteoporosis was made based on the judgement of the investigators at each medical facility;

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 disease (serum creatinine ≥ 2 mg/dL), hepatic disease (AST or ALT ≥ 2.5 times the upper limit of the reference level/100 IU/L or more), or cardiac disease (\geq grade 2 or more according to the severity classification of side effects by MHLW);
7. been hospitalized; or
8. history of treatment with teriparatide.

Treatments

Patients in the sequential therapy arm receive once-weekly subcutaneous injections of teriparatide 56.5 μ g for 72 weeks and alendronate for 48 weeks, whereas those in the monotherapy arm receive alendronate for 120 weeks. Alendronate is provided as a 5 mg tablet (orally administered once daily), 35 mg tablet or jelly (orally administered once weekly), or 900 μ g infusion bag (intravenously administered once every 4 weeks).

Concomitant use of the following drugs is prohibited: (1) drugs approved for the treatment of osteoporosis, (2) corticosteroids, (3) aromatase inhibitors, (4) gonadotropin-releasing hormone agonists, and (5) other study drugs. Skeletal internal or external radiation therapy and surgery of the lumbar spine, thoracic spine, or pelvis are also prohibited.

Assessments

Vertebral fractures

The assessment schedule is summarized in Table 1. The thoracic and lumbar vertebrae are to be imaged in two directions at 0 (baseline), 24, 48, 72, and 120 weeks. For the assessment of prevalent vertebral fractures, anteroposterior and lateral radiographs of the thoracic and lumbar spine obtained

Table 1 Schedule of assessments and data collection

	Time point (weeks)						
	0	4	12	24	48	72	120
Plain X-ray							
New (or worsened) vertebral fracture	○			○	○	○	○
Clinical fracture (vertebral or non-vertebral)	As required. Note: administer QOL/ADL questionnaires within 2 weeks of the day on which a clinical fracture occurs						
BMD (dual-energy X-ray absorptiometry or radioabsorptiometry)	○			○	○	○	○
QOL/ADL questionnaires (EQ-5D, JOQOL short form, VAS)	○	○	○	○	○	○	○
Cognitive assessment (MMSE)	○					○	○
Physical functional assessment (TUG, standing on one leg)	○					○	○
Laboratory tests (blood)							
TRACP-5b, PINP, osteocalcin	○		○	○	○	○	○
25(OH)VD	○						
Total cholesterol, HDL-C, LDL-C, triglycerides, HbA1c	○					○	○
Ca, albumin, creatinine	○		○			○	○
Laboratory tests (urine)							
Ca, albumin, creatinine	○			○		○	○
General laboratory tests (blood and urine)	○			Once within this period			○
Food frequency questionnaires	○						
Interview about oral conditions	○					○	○
Assessment of adverse events	As required						

QOL quality of life, ADL activities of daily living, BMD bone mineral density, JOQOL Japanese Osteoporosis Quality of Life, VAS visual analog scale, MMSE Mini-Mental State Examination, TUG timed up and go test

within 3 months before starting the study were examined by the investigators. They assessed the grade of vertebral fractures from Th4 to L4 according to the semiquantitative technique [13]. These assessments were centrally reviewed by one evaluator of the fracture assessment committee who was blinded to the assigned treatment. When a diagnosis of prevalent vertebral fracture differed between the investigator and the committee member, the diagnosis made by the committee member was adopted.

The committee also adjudicates the presence or absence of a new vertebral fracture by comparing radiographs of Th4–L4 between baseline and post-treatment (24, 48, 72, and 120 weeks). After X-ray films are collected, two independent evaluators, an orthopedist and a radiologist, blinded to the assigned treatment review the films simultaneously according to the semiquantitative technique mentioned above. When a vertebral body that was normal at baseline has deformed and exhibits a morphometric fracture after starting the treatment, it is defined as the occurrence of a new vertebral fracture. If inconsistencies arise between the evaluators, they are to discuss them with each other to reach consensus.

Non-vertebral fractures

During the study, all fractures identified through monitoring clinical symptoms and confirmed with radiography by the investigators are considered possible clinical fractures. These fractures are centrally reviewed by the fracture assessment committee as follows.

To assess prevalent non-vertebral fractures, the records of all non-vertebral fractures (excluding vertebral, facial, and skull fractures) that occurred after the age of 50 years are collected. In addition, all incident non-vertebral fractures are assessed by using the radiographs at the time of the onset of fractures, except for vertebral, facial, and skull fractures. Information such as the date, site, and the circumstance of the fracture onset are also recorded simultaneously. After X-ray films taken at each institution are collected, they are reviewed by two independent evaluators of the committee. In cases of inconsistencies between the evaluators, discussions are carried out to reach consensus.

Clinical data

Other clinical data are shown in Table 1. BMD of the lumbar vertebrae, proximal femur, forearm, and second metacarpal are measured at 0 (baseline), 24, 48, 72, and 120 weeks. The sites analyzed at baseline are to be kept the same during the study. Hip structure is analyzed when the proximal femur is analyzed with a GE or Hologic QDR-4500 model or later. The investigators collect blood and urine samples at 0, 12, 24, 48, 72, and 120 weeks. They submit the samples

to the central laboratory facility for blood and urine marker analyses. Other evaluations include a VAS for back pain, quality of life scores [EuroQol 5 Dimensions (EQ-5D) and the Japanese Osteoporosis Quality of Life Questionnaire (JOQOL) short form], cognitive evaluation (Mini-Mental State Examination), physical functional assessment [Timed Up and Go test (TUG), standing on one leg with eyes open], questionnaires on oral health, determinations of height and weight, and adverse events.

Statistical considerations

Endpoints

The primary endpoint is the incidence of morphometric vertebral fracture at 72 weeks. The accumulation of person-years at risk begins at the randomization of each patient and ends at the date of the last visit (or date of last radiographs for analysis of vertebral fractures), date of lost to follow-up, or date of death. The secondary endpoints are the incidence of morphometric vertebral fracture at 120 weeks, incidence of morphometric vertebral or non-vertebral fractures at 72 and 120 weeks, incidence of non-vertebral fracture at 72 and 120 weeks, incidence of clinical vertebral fracture at 72 and 120 weeks, progression of vertebral fracture at 72 and 120 weeks, changes in BMD, EQ-5D, JOQOL, and VAS for back pain between baseline and 24, 48, 72, and 120 weeks (and at 4 and 12 weeks for EQ-5D, JOQOL, and VAS for back pain), and adverse events.

Sample size determination

The primary hypothesis of the study is that the incidence of vertebral fractures at 72 weeks in the sequential therapy arm will be lower than that in the monotherapy arm. The planned sample size of the study, 500 per arm, was calculated on the basis of the primary hypothesis and the following results of previous studies.

In the TOWER trial, the hazard ratio for morphometric vertebral fractures was 0.2, and the hazard ratio for clinical fragility fractures was 0.39 [4]. In a randomized, placebo-controlled trial of daily teriparatide conducted outside Japan, the hazard ratio for vertebral fractures was 0.35 at 20 µg/day and 0.31 at 40 µg/day, and the hazard ratio for non-vertebral fractures was 0.47 at 20 µg/day and 0.46 at 40 µg/day [15]. Estimates calculated in a meta-analysis resulted in an alendronate-to-placebo hazard ratio of 0.52 for vertebral fractures and 0.51 for non-vertebral fractures [16]. In a population limited to the 326 patients on risedronate monotherapy in the Japanese Osteoporosis Intervention Trial-03 [17] who were at least 75 years of age, had a BMD of less than -3.3 SD of the YAM, and had at least 2 prevalent vertebral fractures or a grade 3 fracture, the annualized incidence

of all fractures was 0.124, the annualized incidence of vertebral fractures was 0.112, and the annualized incidence of non-vertebral fractures was 0.016.

Assuming a 3-year enrollment period and a 72-week follow-up period, the annualized incidence of vertebral fractures associated with alendronate treatment was set at 0.112, and for the alternative hypothesis, the hazard ratio between the two arms over 72 weeks was set at 0.5. Using a two-sided log-rank test with a 5% significance level, a sample size of 407 per arm was found to be necessary to achieve a power of 80%. A planned sample size of 500 per arm was then calculated assuming a dropout rate of 20%.

Statistical analysis plan

For the primary analysis, a multivariate Poisson regression model that includes the minimization factors for random allocation as covariates to the incidence of morphometric vertebral fractures will be fitted to estimate the hazard ratio between the two treatment arms with its 95% confidence interval and p value. The same Poisson regression models will also be fitted to the incidence of the secondary outcome fractures. BMD, EQ-5D, JOQOL, and VAS for back pain at 0, 24, 48, 72, and 120 weeks (and at 4 and 12 weeks for EQ-5D, JOQOL, and VAS for back pain) will be analyzed descriptively, and their results will be expressed as means \pm standard errors at each visit by treatment arm. Their changes from baseline will also be analyzed descriptively in the same manner. Furthermore, differences in their changes from baseline between the two treatment arms will be compared by the t test.

Subgroup analyses stratified by the following factors that accompanied the interaction tests are also planned: age, body mass index, HbA1c, estimated glomerular filtration rate, prevalent vertebral fracture, grade of prevalent vertebral fracture, history of bisphosphonates, BMD, pentosidine, and TUG.

All efficacy analyses will use the full analysis set, that is, use all patients randomized except for those without any post-treatment efficacy data, those who do not meet the eligibility criteria, and those who do not receive the allocated treatment at all. All p values are two-tailed without multiplicity adjustment, and a p value of less than 0.05 indicates that the difference is significant. Academic statisticians will conduct all analyses using SAS® software version 9.4 (SAS Institute, Cary, NC).

Discussion

The JOINT-05 is the first head-to-head trial of sequential teriparatide followed by alendronate or alendronate monotherapy for severe osteoporosis. The limitations of the study

include the potential for differential compliance and attrition rates due to the substantial differences in the cost and routes of administration of teriparatide and alendronate. Another concern is statistical power. As the primary endpoint is the incidence of morphometric vertebral fractures, the JOINT-05 is not adequately powered to detect differences in the incidence of non-vertebral fractures.

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Author contributions TS, SM, and HH conceived of the hypothesis and design of this study. ST is the trial statistician and drafted the manuscript. All authors contributed to the final manuscript.

Compliance with ethical standards

Conflict of interest ST has received lecture fees from Astra-Zeneca, Taiho, and Ono. He has received consultation fees from DeNA Life Science and CanBus. He has received outsourcing fees from Satt and Asahi Kasei Pharma. HH has received lecture and consultancy fees from Asahi Kasei Pharma Corp., Astellas Pharma Inc., MSD Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., Pfizer Co., Ltd., Mitsubishi Tanabe Pharma Corp., Mochida Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Pfizer Inc., Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd. TS 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. SM has no conflicts of interest to disclose.

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