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ORIGINAL ARTICLE

Study design of multi-center, open-label randomized controlled, head-to-head trial comparing minodronic acid and raloxifene: Japanese Osteoporosis Intervention Trial (JOINT)-04

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Abstract

We planned to conduct multi-center, open-labeled, blinded-endpoints, head-to-head randomized trial of minodronate and raloxifene to compare incidences of vertebral and non-vertebral fractures. The study is the Japanese Osteoporosis Intervention Trial protocol number 4 (JOINT-4). Here, we present the pre-fixed study design. The inclusion criteria are ambulatory older women with osteoporosis, aged > 60 years, and without pre-specified risk factors for secondary osteoporosis and dementia. The subjects who meet selection criteria will be randomly allocated to the raloxifene (60 mg/day) or minodronate (1 mg/day or 50 mg/4 weeks) groups using the central registry. The co-primary endpoints are osteoporotic (vertebral, humeral, femoral, and radial), vertebral, and major osteoporotic (clinical vertebral, humeral, femoral, and radial) fractures. Furthermore, we plan to use the Hochberg procedure to preserve an overall type 1 error rate. In addition, changes in bone mineral density (BMD), hip-structure analysis (HSA) variables, height, bone turnover markers, serum cholesterol and triglyceride concentrations, dental health questionnaire, fall frequency, fall risk index, nursing care level, physical function, quality of life (QOL), and safety profiles were assessed as secondary endpoints. To detect 24% reduction of major osteoporotic fractures with 80% power and a two-sided significance level of 5% with a 2-year observation period, 1734 patients/treatment arm would be required. Subgroup analysis stratified to the following factors age, body mass index, BMD, 25-hydroxyvitamin D concentration, estimated glomerular filtration rate (eGFR), prevalent vertebral fracture number, hypertension status, and diabetes mellitus is pre-specified. The protocol is registered in the trial registry system, and the trial identification number is UMIN000005433.

Keywords Head-to-head randomized trial · Minodronate · Raloxifene · Osteoporotic · Fractures

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Introduction

Osteoporosis, which is characterized by compromised bone strength and increased susceptibility to fractures that deteriorates the quality of life (QOL) and increases mortality, constitutes a national burden on an aging society [1–3]. Previous clinical trials have shown the effectiveness of several pharmaceutical therapies in the prevention of incident fractures. Amino-containing bisphosphonates (alendronate, minodronate, risedronate, ibandronate, and zoledronate) have potent antiresorptive properties that increase the bone mineral density (BMD) [4]. Among the bisphosphonates, minodronate has shown potent anti-resorption in both in vitro and in vivo studies [5]. A randomized, double-blind placebo-controlled trial of minodronate was conducted in Japan [6], and daily oral administration of 1-mg minodronate for 24 months reduced the risk of vertebral fractures by 59% [relative risk (RR): 0.41, 95% confidence interval (CI): 0.27–0.63], compared to the placebo. Recently, a monthly oral preparation of minodronate was made available in clinical practice, because the equivalency of the effects of daily and monthly preparations has been shown in BMD changes [7]. There are no available data showing the effect of minodronate on non-vertebral fracture occurrence.

Raloxifene, a member of the class of selective estrogen receptor modulators (SERM), also demonstrated efficacy in fracture prevention. The large Multiple Outcomes of Raloxifene Evaluation (MORE) study [8], a randomized, double-blind placebo-controlled trial, showed that raloxifene reduced the incidence of new vertebral fractures by 30% (RR 0.7, 95% CI 0.5–0.8) compared to placebo in women with pre-existing fractures, assessed at 36 months. However, no significant differences were found in the non-vertebral fracture (placebo 9.3% and raloxifene 8.5%). Moreover, there are no data of fracture risk reduction in the Japanese population.

Both minodronate and raloxifene were classified as anti-bone-resorbing agents, but there is no evidence to support the specific agent that should be adapted to different situational demands. In general, SERM may be used in relatively younger patients with osteoporosis aged < 70 years, and bisphosphonates may be followed by SERM. However, no concrete evidence has been presented to show how to distinguish patients that may benefit more from SERM or bisphosphonate.

To obtain clinical evidence to support the relative efficacy and safety of bisphosphonates and SERM as treatment options in clinical practice, and information about their adequate use, we propose to conduct a head-to-head randomized trial of minodronate and raloxifene with incidences of vertebral and non-vertebral fractures in women with osteoporosis as a primary endpoint. We have also planned to perform the secondary analysis to determine the superior drug in patients with different backgrounds. This paper presents the study design of the clinical trial designed to obtain the target clinical evidence mentioned above.

Materials and methods

The Japanese Osteoporosis Intervention Trial protocol number 4 (JOINT-04) is a multi-center, open-label, randomized controlled trial in Japan and is registered at the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) under trial identification number UMIN000005433. The protocol was approved by the Central Ethical committee for Adequate Treatment of Osteoporosis (A-TOP) group (Dr. Rikushi Morita, Chairman) and was reviewed by the institutional review board of each participating institution. The trial is to be conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained prior to patient enrollment after a thorough explanation of the trial objectives, duration, and procedures.

Study design

Patients who met all the entry criteria are randomly allocated in a 1:1 ratio to receive minodronate or raloxifene. Randomization was implemented using a web-based computerized system for the modified minimization method that adjusts for imbalances in the following six variables: age; number of pre-existing vertebral fractures; history of non-vertebral fractures of the humerus, femur, or radius; bone mineral density (BMD); number of risk factors (alcohol intake, smoking, and history of parents' femoral neck fracture); and sites, as defined by the guideline and study site. Follow-up duration is 2 years, and during the study period, patients in the raloxifene group will be administered oral doses of 60 mg/day, whereas those in the minodronate group will receive either 1 mg/day or 50 mg/4 weeks. The test drugs are commercially available drugs. All patients are to begin treatment within 30 days of randomization. Data will be collected by the investigators and site management organizations (I'ROM Co., Ltd., Tokyo, Japan, and LINICAL Co., Ltd., Osaka, Japan) using an electric data capture system. The data management and patient registration will be conducted by the Japan Clinical Research Support Unit (J-CRSU, Tokyo, Japan). All statistical analyses will be performed by academic biostatisticians. The interim analysis for safety and efficacy is planned at 1 year after enrollment of half of the planned number of patients by the ethical committee.

Eligibility criteria

The inclusion criteria are the women who meet the requirements for pharmacological therapy for osteoporosis, aged ≥ 60 years, can walk by themselves, can answer the questionnaires, and satisfy the criteria to start chemotherapy, which was defined by "the Japanese guidelines for the prevention and treatment of osteoporosis (2006 Edition)" [9]. In addition, at least one of the following risk factor for incident fracture needs to be met: aged ≥ 70 years, one or more prevalent fractures between thoracic (T) 4 and lumbar (L) 4, and BMD below –3SD of the young adult mean (YAM). Subjects will be excluded if they have contraindication to the drugs, metabolic bone diseases other than osteoporosis, severe degenerative deformation of the spine (T4–L4), abnormal heart, hepatic, and kidney function, and dysfunction in communication of intentions, take antitumor drugs that might affect bone metabolism, have taken or are taking teriparatide or eldecalcitol at any time, had taken an SERM within the previous month, or had taken bisphosphonates within the previous 6 months. All subjects will be required to provide informed consent before undergoing any examination or study procedure.

Study outcomes

The primary endpoints are osteoporotic (vertebral, humeral, femoral, and radial), vertebral, and major osteoporotic (clinical vertebral, humeral, femoral, and radial) fractures. The secondary endpoints are BMD, hip-structure analysis (HSA) variables, height, markers of bone turnover, lipid value, questionnaire survey for dental health, frequency of falls, fall risk index, nursing care level, physical function, QOL, and safety profiles.

Assessment of vertebral fractures

The vertebral fractures will fundamentally be assessed using a previously reported method [10]. Briefly, to assess prevalent vertebral fractures, anteroposterior and lateral radiographs of the thoracic and lumbar spine are first evaluated by the practitioner independent from the central committee at baseline. For assessments, the vertebral body between T4 and L4 is assessed using the semi-quantitative (SQ) method. After the first X-ray films are collected, two independent evaluators, an orthopedist (TN) and a radiologist (MF), review the films simultaneously after masking the patient's information. If the diagnosis of the prevalent vertebral fractures differs from those made by the practitioners, the diagnosis made by independent evaluators will be preferentially adopted. If inconsistencies arise between the two independent readers, the two evaluators will discuss the issue to reach a consensus. Incident vertebral fractures are assessed at 6, 12, and 24 months in the same manner as prevalent vertebral fractures. In addition, all the individuals performing the incident vertebral fracture assessments will be completely blinded to the treatment assignment.

To assess incident clinical vertebral fractures, practitioners will take X-ray films of the vertebral body between T4 and L4 whenever a subject complains of back pain. Other procedures in the assessment scheme are the same as those used in assessing vertebral fractures.

Assessment of non-vertebral fractures

To assess prevalent non-vertebral fractures, all incidences (excluding vertebral, facial, and skull) occurring after the subject turned 50 years will be recorded. All incident non-vertebral fractures will be assessed by acquiring radiographs whenever the subjects experience fractures other than vertebral, facial, and skull fractures. Information such as date, site, and circumstance of fracture will be recorded simultaneously. After collection, the X-ray films taken by the investigator will be reviewed by two independent evaluators. Inconsistencies between the two evaluators will be discussed until a consensus is reached.

Assessment of clinical data

The BMD will be measured for either hip (proximal femur), lumbar vertebrae, distal radius, second metacarpal bone, or heel bone at baseline. If the BMD is obtained from the hip (proximal femur), or lumbar vertebrae, then the follow-up BMD data will be measured at 6, 12, and 24 months. The BMD will be assessed based on either the dual-energy X-ray absorption (DXA) method at the lumbar vertebrae (L2–4), the proximal portion of the femur (total proximal femur and femoral neck), and the distal one-third of the radius or peripheral quantitative computed tomography (pQCT) method at the radius. The metacarpal bone density will be measured using the radiogrammetry as reported previously [10] [11].

The HSA-structural analysis will be carried out at the site installed QDR-400, DELPHI, or Discovery and the assessments will be performed at baseline, 6, 12, and 24 months. In addition, subjects will be interviewed using intraoral questionnaire surveys administered by the practitioners every 6 months. The fall risk index will be determined based on 21 questionnaire-based items including physical, cognitive, emotional, and social aspects of functioning and environmental factors [12], and the nursing care level and QOL will be assessed at baseline, 12 and 24 months. QOL will be analyzed using self-administered questionnaires (EQ-5D). The physical function will be evaluated at baseline and 2 years after initiating treatment. Other routine biochemical examinations will be carried out at baseline, 6 and 24 months after

initiating treatment to assess the biochemical adverse events. Biochemical data determined in advance will be collected and evaluated by the LSI Medience Corporation [formerly Mitsubishi Chemical Medience Corporation (Minato-ku, Tokyo, Japan)].

All subjects will be questioned about adverse events at every visit, and all reported adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MEDRA, version 12.1). Parameters such as the date, categorization of "known reaction" or "unknown reaction," causal relationship between adverse event and treatment, and severity will be simultaneously reported.

Statistical considerations

Sample size

We assume that the annual incidence rate of major osteoporotic fractures is 34.5/1000 persons for the minodronate arm of the study. This assumption is based on a clinical phase 3 trial for minodronate [6] and JOINT-02 study for alendronate, which both consisted of Japanese women with osteoporosis [10]. In addition, we assume that the rate of major osteoporotic fractures is 24% lower for minodronate than it is for raloxifene. We made this assumption based on the data of two studies: the phase 3 study for minodronate [2] and the MORE study implemented in the US [8], since there are currently no study data for studies of the effect of raloxifene in Japanese subjects. Using the hazard ratios obtained from the above two studies (minodronate vs placebo and raloxifene vs placebo), we calculated the hazard ratio as 0.613 for minodronate vs raloxifene. To account for the ethnic difference, we used a hazard ratio of 0.76, which is approximately 20% the conservative value of 0.694, in calculating the sample size. To determine the superiority of the above values with 80% power, a two-sided overall significance level of 5%, 3-year registration period, and follow-up of 2 years, 1567 patients/arm would be required. To allow for a loss to follow-up rate of 25%, we would need to enroll 1734 patients in each treatment arm.

Statistical analysis

We proposed the following three hypotheses according to the co-primary endpoints:

1. The incidence of osteoporotic fracture in minodronate arm is lower than that in the raloxifene arm.
2. The incidence rate of vertebral fracture in the minodronate arm is lower than that in the raloxifene arm.
3. The incidence rate of major osteoporotic fracture in the minodronate arm is lower than that in the raloxifene arm.

First, we will perform a hypothesis test for the osteoporotic fracture before testing for the vertebral and major osteoporotic fractures. Since osteoporotic fractures include both vertebral and major osteoporotic fracture, the type 1 error rate did not increase by first testing hypothesis 1), followed by the other two hypotheses. Furthermore, to account for the multiplicity of hypothesis testing for hypotheses 2 and 3, we used the Hochberg procedure to preserve an overall type 1 error rate.

The primary analysis will be carried out using the Poisson regression model. In addition, the hazard ratio between the two arms will be calculated. All the efficacy analysis will be performed using a full analysis set (FAS) with all the randomized patients excluding those without efficacy data, who do not fulfill the inclusion criteria and who do not receive treatment. Subgroup analysis stratified to the following factors are also planned: age, body mass index, BMD, 25-hydroxyvitamin D concentration, estimated glomerular filtration rate (eGFR), number of prevalent vertebral fractures, the presence of any co-morbidity, and presence of hypertension, and diabetes mellitus. In addition, the biological effect of each drug on lipid metabolism, QOL, and dental health will be compared. The per protocol set (PPS) consists of patients without any serious protocol violation and without patient loss to follow-up within 3 months.

All comparison will be two-sided and performed at a $P=0.05$ level of significance. The statistical analyses will be performed using the SAS version 9.4 (SAS Institute, Cary, NC, USA).

Discussion

The research group of adequate treatment for osteoporosis (A-TOP research group) is an organization of the Japan Osteoporosis Society that executes clinical research studies and was established to provide adaptable evidence in osteoporosis treatment to the world. Clinical evidence is especially important in developing and administering osteoporosis drugs, since patients with osteoporosis usually have numerous complications. However, these cases do not meet the strict inclusion criteria of clinical trials developing treatment agents. Furthermore, the generalizability of the results of such clinical trials to the real clinical practice may be questionable.

Other concerns in the treatment of osteoporosis have been raised, particularly on how practitioners select osteoporosis drugs. Unfortunately, no decision-making data are available for drug selection in each patient with their different requirements. For instance, there are three different drug treatment options for reducing bone resorption, SERM, bisphosphonates, and denosumab. Thus, evidence regarding the factors informing the selection of these agents is required.

We planned to conduct the JOINT-04 study to obtain clinical evidence to evaluate the relative efficacy and safety of minodronate and raloxifene in a clinical practice setting, and information about the proper use of bisphosphonates and SERM. Since neither treatment may be more effective in the total population, we preplanned a subgroup analysis to distinguish the type of patients that may benefit more from raloxifene or minodronate. In addition, based on the information obtained, the biological effects of each drug will be comparatively assessed using the numerous outcome measures defined as the secondary outcome. The present proposed study is designed as a head-to-head randomized trial of minodronate and raloxifene investigating the associated incidental vertebral and non-vertebral fractures in women with osteoporosis in a clinical setting. Furthermore, it is the first, large-scale, randomized controlled trial of these agents worldwide.

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Compliance with ethical standards

Conflict of interest YU has received a consultancy fee from Teijin Pharma. 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. His wife has been engaged in a research project of Bayer. TM and MT are employees of the Public Health Research Foundation. TS has received research grants from Asahi Kasei Pharma, Astellas Pharma, Daiichi-Sankyo, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, Pfizer and Teijin Pharma, and consulting fees from Daiichi-Sankyo and Takeda Pharmaceutical. AT received consultancy or lecture fees from Asahi Kasei, Teijin, Ono, Chugai, Takeda, and Daiichi-Sankyo pharma. SS received lecture and consultancy fees from Asahikasei Pharmaceutical Co., Astellas Pharma, Chugai Pharmaceutical Co., Daiichi Sankyo Co., Eisai Co., Eli Lilly Japan, Ono Pharmaceutical Co., Pfizer Co., Takeda Pharmaceutical Co. 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. ToS 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. MF received consulting fees from Asahi Kasei Pharma and lecture fees from Daiichi-Sankyo, MSD, and Chugai Parma. HO received fees from Phizer co.jp. MS received lecture and consultancy fees from Asahikasei Pharma and Teijin Pharma.

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