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Design of a Multicenter, Randomized, Open Label, Parallel Group Study to Evaluate the Efficacy of Loxoprofen on Acute-Phase Reactions in Japanese Primary Osteoporosis Patients Treated with Zoledronic Acid

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Abstract

Treatment of osteoporosis with once-yearly zoledronic acid was approved in September 2016 in Japan. Like other bisphosphonates, zoledronic acid causes acute-phase responses (APRs), which are more severe in Asian populations than in multinational populations. The aim of this multicenter, randomized, open label, parallel group study is to investigate the incidence of APRs in Japanese patients with primary osteoporosis in real clinical settings, and to test the hypotheses that APRs are suppressed by administering one of the most commonly used non-steroidal anti-inflammatory drugs in Japan, loxoprofen, immediately after the treatment with zoledronic acid, and the incidence of APRs in patients with prior history of treatment with bisphosphonate is lower than that in naïve patients. A total of 400 patients aged 60 or older were randomly allocated to a zoledronic acid plus loxoprofen group or zoledronic acid group on a 1:1 basis. After the treatment, patients were observed for 7 days, during which patients will record APRs for the first 3 days, and body temperature and drugs taken for 7 days. Primary endpoints are incidence of APRs and increase in body temperature, and secondary endpoints are relationship between prior treatment for osteoporosis in the past 3 years versus incidence of APRs, and that versus a change in body temperature. Results supporting the hypotheses will indicate that APRs are manageable with loxoprofen, which patients likely already have, and the APRs will develop less frequently and be less severe in the following years, despite the high risk of APRs in Japanese patients.

Keywords: Acute-phase reaction; Bisphosphonate; Loxoprofen; Osteoporosis; Zoledronic acid

Introduction

The bisphosphonate zoledronic acid significantly increases bone mineral density and suppresses the incidence of fractures [1]. In Japan, zoledronic acid (intravenous 5 mg once-yearly) was approved for the treatment of osteoporosis in September 2016. Compared to other bisphosphonates, such as alendronate, risedronate, and ibandronate, which are administered to patients once-daily, weekly, or monthly, once-yearly treatment with zoledronic acid is expected to achieve high compliance with significant efficacy in the treatment of osteoporosis in Japan. However, also like these other nitrogen-containing bisphosphonates (alendronate, risedronate, and ibandronate) zoledronic acid is associated with a high incidence of acute-phase reactions (APRs), including pyrexia and myalgia, for 3 days after the administration [1,2].

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT) and subsequent sub-analyses have shown a higher incidence of APRs in the Asian populations compared to those in the multinational populations included in the studies [1,3,4]. A sub-analysis of the HORIZON-PFT showed that the incidences of pyrexia and arthralgia in the Chinese population were higher than those in the multinational population, of which 14.2% were Asians (pyrexia, 28.2 *vs.* 16.1%; arthralgia, 21.5 *vs.* 6.3%) [1,4]. The highest risk of developing APRs was reported in the non-Japanese Asians and Pacific Islanders (odds ratio: 2.20 and 3.39) [3].

A very recent 2-year phase III study (ZOledroNate treatment in Efficacy to osteoporosis; ZONE study) carried out in Japan has shown that the incidence rate of drug-related adverse events (AEs) within 3 days after administration of zoledronic acid was 57.4% and that of placebo was 11.7% [2,5]. The authors stated that such difference was seen in APRs within 3 days of administration (pyrexia, 39.3% in the zoledronic acid group *vs.* 2.7% in the placebo group; arthralgia, 10.8 *vs.* 0.3%; myalgia, 8.1 *vs.* 0%; malaise, 7.8 *vs.* 1.8%; influenza-like illness, 6.9 *vs.* 0%; and headache, 6.0 *vs.* 0.9%), whereas APRs were reported in 31.6% of patients treated with zoledronic acid in the multinational HORIZON-PFT study [1]. These results indicate that the incidence of

APRs is higher in the Asian populations, including Japanese, compared to non-Asian populations.

It should be noted that, unlike approved doses of other bisphosphonates in Japan, which are usually half of those approved in other countries (e.g., alendronate 5 mg daily or 35 mg weekly in Japan *vs.* 10 mg or 70 mg in US.; risedronate 2.5 mg daily or 17.5 mg weekly or 75 mg monthly in Japan *vs.* 5 mg or 35 mg or 150 mg in US.), that of zoledronic acid is the same as in other countries (5 mg once-yearly). Because of the relatively high approved dose for zoledronic acid, further investigations on the APRs in real clinical settings may help our understanding of the incidence of APRs in Japanese patients.

Although the incidence of APRs appears to be higher in Japanese patients, the patients should not be discouraged to use zoledronic acid, because of the fact that APRs are manageable. Previous studies have shown that APRs can be managed by treating patients with antipyretic and anti-inflammatory drugs such as acetaminophen and ibuprofen [1,6,7].

The non-steroidal anti-inflammatory drug (NSAID) loxoprofen sodium, a pro-drug, is one of the most commonly used NSAIDs in Japan. Compared to other NSAIDs, such as indomethacin and celecoxib, loxoprofen showed less membrane permeability and low direct cytotoxicity, and therefore lower incidence of NSAIDs-induced gastroenteropathy [8]. Loxoprofen is also the NSAID most often prescribed by orthopedists in Japan [9]. Therefore, this study was designed to examine the efficacy of loxoprofen in decreasing the incidence and severity of the zoledronic acid-associated APRs.

Furthermore, accumulating evidence indicates that the incidence rate of APRs is lower in patients with prior history of treatment with bisphosphonates than in naïve patients [1,10]. If this is applicable to Japanese patients, it will be further evidence by which Japanese patients can be encouraged to be treated with the once-yearly zoledronic acid in subsequent years.

This study was designed to investigate the incidence rate of APRs in Japanese patients with primary osteoporosis, and to test the hypotheses that the incidence and severity of APRs are decreased by administering loxoprofen immediately after the treatment with once-yearly zoledronic acid, and the incidence of APRs in patients with prior history of treatment with bisphosphonate is lower than that in naïve patients.

Materials and Methods

The aim of this multicenter, randomized, open label, parallel group study is to evaluate the efficacy of loxoprofen in decreasing the incidence of APRs and severity of pyrexia, and to examine whether the incidence of APRs is affected by the prior history of treatment with bisphosphonates in Japanese primary osteoporosis patients.

Study design

Patients with primary osteoporosis were recruited from March 2017 to October 2017, and those who meet all the inclusion criteria were randomly allocated to either a zoledronic acid and loxoprofen (ZOL +LOX) group or a zoledronic acid (ZOL) group (Figures 1 and 2). Patients were treated with zoledronic acid on day 1, observed for 7 days during which patients record any APRs for the first 3 days after the zoledronic acid treatment, and body temperature and drugs taken by patients for 7 days, and evaluated by investigators on day 8 at the end of the observation period or within one month after the completion of the study.

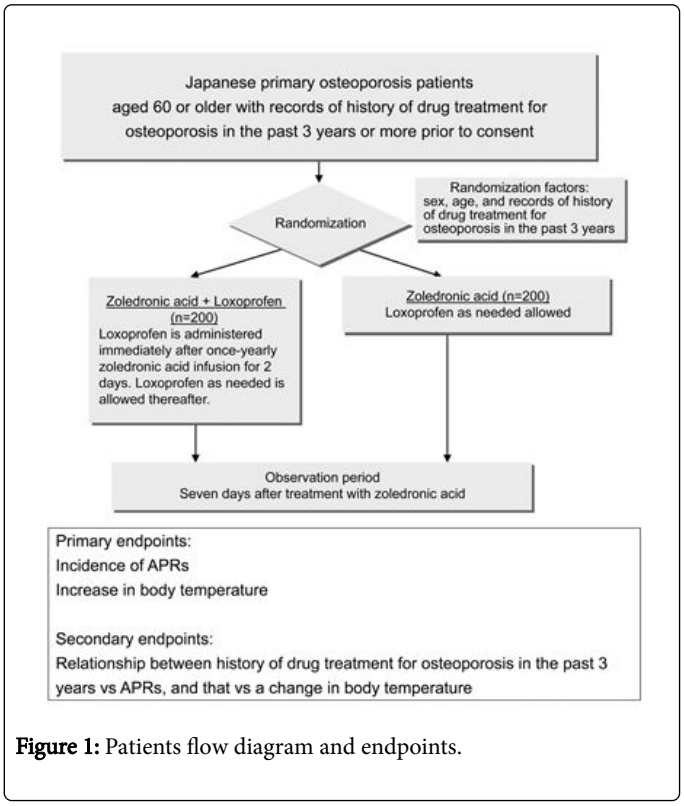

Figure 1: Patients flow diagram and endpoints.

Investigators could terminate a patient's treatment with study drugs and participation in the study for any one of the following 3 reasons, and observe, examine, and assess patients as far as possible at the time of discontinuation: an investigator determines that the continuation of the study was difficult due to AEs; a patient requested the discontinuation of the study or treatment, or requested withdrawal of the consent; or an investigator determines that it was difficult to continue the study for other reasons.

The study is planned to be completed by March 2018.

The study protocol was reviewed and approved by the Internal Review Board at each study site in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants to be included in the study. This study is registered at UMIN-CTR (UMIN000026507).

Patient eligibility

Patients' inclusion and exclusion criteria are summarized in Table 1. In brief, Japanese primary osteoporosis patients aged 60 or older with records of history of drug treatment for osteoporosis in the past 3 years or more before consent were included in the study. Patients who met any one of the following criteria were excluded from the study: secondary osteoporosis; severe kidney, liver, or heart disease; malignant tumor; hypersensitivity to zoledronic acid, other bisphosphonates, or loxoprofen; hypocalcemia; participation in other clinical studies; and patients for whom an investigator determines that the study participation was inappropriate.

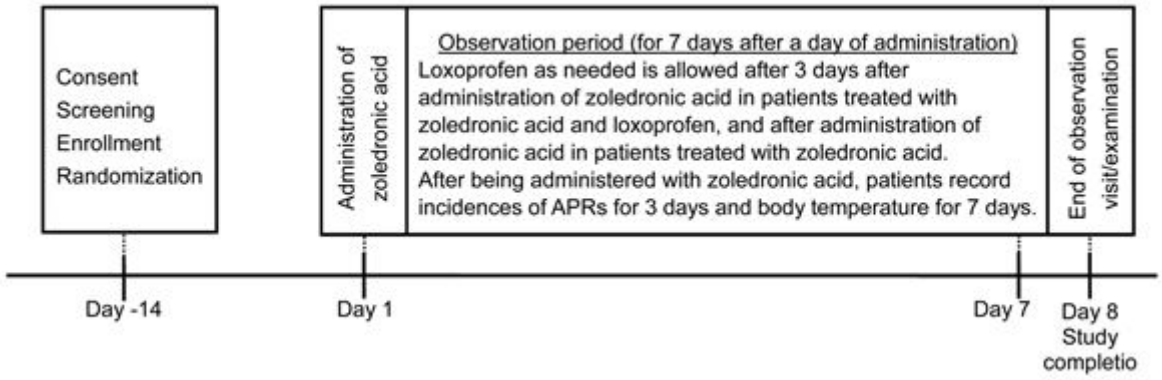

Figure 2: Study design.

Inclusion criteria	Exclusion criteria
-Primary osteoporosis	-Secondary osteoporosis
-Japanese patients aged 60 or older at consent	-Severe kidney (creatinine clearance <35 mL/min), liver, or heart disease
-Records of history of drug treatment for osteoporosis in the past 3 years or more before consent	-Current malignant tumor or history within past 5 years
	-Hypersensitivity to zoledronic acid, other bisphosphonates, or loxoprofen
	-Hypocalcemia
	-Participation in other clinical studies within 24 weeks before obtaining consent for this study
	-Patients for whom an investigator determines that the study participation is inappropriate.

Table 1: Inclusion and exclusion criteria.

Randomization

Eligible patients were randomized 1:1 to the ZOL+LOX group or ZOL group, based on their sex, age (≥ 75 years or <75 years), and prior bisphosphonate use in the past 3 years, using a centralized patient registration system.

Intervention

Patients received either a single dose of 5 mg zoledronic acid through a 15-min intravenous infusion alone (ZOL group) in the morning, or that immediately followed by 60 mg oral loxoprofen (ZOL +LOX group). Patients in the ZOL+LOX group received loxoprofen immediately and 6 h after the zoledronic acid infusion on the day of zoledronic acid administration, and in the morning (8:00), during the day (14:00), and in the evening (20:00) on the following day.

Previous studies have shown that patients start to experience pyrexia 24 to 48 h after administering zoledronic acid [2,6]. Therefore, patients in the ZOL+LOX group were to follow the scheduled medication regimen to evaluate the efficacy of loxoprofen. However, patients were allowed to take oral 60–120 mg loxoprofen as needed after 3 days of the treatment with zoledronic acid in the ZOL+LOX group, and after treatment with zoledronic acid in the ZOL group, if an investigator determined it was necessary based on evaluation and examinations, for ethical considerations.

Endpoints

Primary endpoints of this study are incidence of APRs and an increase in body temperature, and the secondary endpoints are a relationship between prior treatment for osteoporosis in the past 3 years versus the incidence of APRs, and that versus a change in body temperature.

Clinical data

Baseline: Investigators assessed the following items to determine patient eligibility at Visit 1, at least 14 days before registration (use of data obtained within 8 weeks before the administration of zoledronic acid was allowed): sex and birthdate, height and body weight, medical history, complications, history of drug use for the treatment of osteoporosis, FRAX® fracture risk assessment (to be calculated by the end of observation visit), number of past vertebral fractures (judged by the investigators based on X-ray images), bone density measurement by dual-energy X-ray absorptiometry, bone metabolism markers (tartrate-resistant acid phosphatase 5b and N-terminal propeptide of type I collagen), 25-hydroxycholecalciferol, and clinical laboratory tests (creatinine, creatinine clearance, urea nitrogen, serum protein, serum albumin, and serum calcium concentration).

On the day of treatment with zoledronic acid, body temperature was measured twice before zoledronic acid administration, at the time of examination and just before administration of zoledronic acid, followed by 3 more measurement time points, at 14:00, 17:00, and 20:00, a total of 5 measurements.

Observation period

During the 7-day observation period (patients who discontinued the study were to record the following items until study discontinuation), patients recorded the following incidences in a patient diary, and provided the diary to the investigator at the end of the observation visit: APRs up to 3 days after zoledronic acid

administration; body temperature up to 7 days after the administration according to the schedule; and drugs taken, including NSAIDs, and the status of their usage.

APRs in this study are defined as AEs of "pyrexia, myalgia, or arthralgia, headache, malaise, and others" that develop within 3 days after a day of zoledronic acid administration and those determined by the investigators. An increase in body temperature is defined as body temperature ≥ 37.5°C and ≥ 1°C temperature increase from average body temperature measured just before zoledronic acid administration on day 1.

Body temperature was measured at 8:00, 11:00, 14:00, 17:00, and 20:00 on days 2 to 3, and at 11:00 and 17:00 on days 4 to 7. In addition to the pre-determined time points, body temperature was measured when patients take loxoprofen as needed and an APR develops.

As for the drugs that patients were to record in the patient diary, investigators recorded usages of the following drugs on a survey form from the time of eligibility screening to the end of the observation period or until the time of discontinuation: lipid-lowering agents, analgesic drugs such as NSAIDs (excluding those for external application and suppositories), corticosteroids (excluding external application), vitamin D, vitamin K, calcium, and calcitonin.

AEs were monitored from the day of zoledronic acid administration until the end of the observation period. The investigators recorded day of onset, body temperature at the time of onset, APR or not, name of AE, severity, seriousness, actions taken for loxoprofen (continued, dose reduced, or discontinued), any other actions taken, causal relationship with study drugs, outcome, and date the outcome is confirmed.

Sample size

The estimated sample size in this study was to be 400 patients, from approximately 30 study sites (14 patients per study site). The results of the additional analysis of the ZONE study have shown that the incidence rate of AEs within 3 days after zoledronic acid administration in bisphosphonate-naïve patients is 55.6% [5]. Since this rate includes all AEs, not only APRs, the incidence of APRs in the ZOL group in this study is estimated to be about 50%. Since no data were available for an estimation of the APR incidence rate in patients treated with zoledronic acid and loxoprofen, we referred to the results of a previous study in which it was shown that 60.7% of patients in the ZOL+placebo group experienced an increase in body temperature or used rescue medication, compared to 39.8% in the ZOL +acetaminophen group [6]. Accordingly, the ratio of patients in the ZOL+LOX to ZOL groups was hypothesized to be 3:2, and therefore the APR incidence in the ZOL+LOX group was estimated to be 35%.

Based on the above assumptions, the number of patients required for a two-sided significance level of 5%, detection power of 80%, and applicability of Fisher's exact test was 183 in each group (a total of 366). Considering that about 10% of patients might discontinue, withdraw, and be excluded from the analyses, the total number of patients is determined to be 400 to obtain statistical significance between the groups.

Statistical analysis

In this study, the full analysis set (FAS) was defined as a group of patients who were treated with zoledronic acid, and had at least 1 record of APR assessment or body temperature measurement after the treatment. Of patients in the FAS, those who had no protocol violations and were in compliance with the protocol will be included in the per protocol set (PPS).

As for the primary endpoint, the incidence of APRs and an increase in body temperature in the ZOL+LOX group will be compared with those in the ZOL group. All parameters related to efficacy will be analyzed in both the FAS and PPS. Two-tailed p values will be calculated, with $p<0.05$ indicating statistical significance. Safety will be evaluated in the safety analysis set, in which all patients who receive at least 1 treatment with zoledronic acid will be included. The incidence rate for each AE will be obtained in each treatment group.

Since the incidence of APRs in Japanese is likely higher than that in other non-Asian populations [2], interim analysis is planned to be carried out once the sample size reaches one third of the planned sample size (n=135). Upon analyses of safety based on the development of APRs and AEs, an independent data monitoring committee will determine whether the study should be continued or terminated.

Results

This study was designed to investigate the incidence of APRs in Japanese patients, and to test the efficacy of loxoprofen in decreasing the incidence and severity of APRs as previously shown with other NSAIDs in overseas studies [6,7]. A previous controlled study has shown a significantly higher incidence rate of developing APRs in a Japanese population [2]. Considering the relatively high approved dose for zoledronic acid in Japan, it is critically important to investigate the actual incidence and severity of APRs that develop in Japanese patients in actual clinical settings.

Based on the previous studies [6,7], the Japan Osteoporosis Society and the Japanese Society for Bone and Mineral Research (JSBMER) jointly released a notice on April 4, 2017, recommending the use of acetaminophen and ibuprofen as a treatment measure for the zoledronic acid-induced APRs [11]. In Japan, osteoporosis is usually treated by medical practitioners of orthopaedic surgery. Many patients visit them for pain as a primary physical complaint, and therefore are very often prescribed with antipyretic analgesics, especially loxoprofen, which is the most frequently prescribed drug in Japan [8,9]. If this study proves that loxoprofen reduces the incidence and severity of APRs, like ibuprofen, the majority of patients will not need an additional prescription for loxoprofen, because the likelihood is high that their orthopaedic surgeons have already prescribed loxoprofen at the initial visit. Furthermore, patients would not need to risk the use of a new antipyretic analgesic they have never used before. Even if patients are not prescribed loxoprofen at the doctor's visit, the chance of having loxoprofen at home is very high, because loxoprofen is also available over the counter, and many Japanese have it for emergency use at home.

Another advantage of showing a significant efficacy of loxoprofen in decreasing APRs is that patients tend to show preferences for certain antipyretic analgesics. If loxoprofen is included in addition to acetaminophen and ibuprofen, patients will have more selections to choose from. We also expect to show that APRs become less severe with the subsequent treatments in Japanese patients, so that patients can be encouraged to receive the treatment with zoledronic acid in the following years.

In the notice released by the Japan Osteoporosis Society and the JSBMER in April 2017, we are reminded that NSAIDs are nephrotoxic

drugs, and zoledronic acid should be used with caution when patients are treated with concomitant nephrotoxic medications [11]. The majority of osteoporosis patients are elderly, and it is agreed that long-term treatment with NSAIDs should be avoided in those patients. However, since patients require treatment with NSAIDs for only two to three days to prevent or treat APRs, the use of loxoprofen is likely to pose low risk to the kidney functions of patients.

Discussion

This protocol was developed to investigate the incidence of APRs in Japanese patients with primary osteoporosis in actual clinical settings, and to assess the efficacy of the most frequently prescribed NSAID, loxoprofen, in suppressing the development and severity of APRs. Upon completion of the study, we expect to show a significant efficacy of loxoprofen in decreasing onset and severity of APRs and pyrexia, as well as a lower incidence rate of APRs in patients with prior treatment with bisphosphonates compared to naïve patients, suggesting that zoledronic acid-induced APRs are manageable with loxoprofen even in Japanese patients, who have a high risk of developing APRs.

Conflict of Interest

This study is supported by Comprehensive Support Project for Life related Disease (CSP-LD) of Public Health Research Foundation. The research fund was provided to CSP-LD by Asahi Kasei Pharma Corp. Asahi Kasei Pharma Corp and CSP-LD take no part in this study other than providing information relevant to proper use of the study drug. All decisions concerning the planning, implementation of this study are made by the executive committee of this study.

NO received consulting fees from Asahi Kasei Pharma Corp, payment for lectures including service on speakers bureaus from Asahi Kasei Pharma Corp, Astellas Pharma Inc., Chugai Pharmaceutical Co., Daiichi-Sankyo Co., Ltd., Eisai Co., Ltd., Mitsubishi-Tanabe Pharma Corp., Ono Pharmaceutical Co., Pfizer Japan Inc., Shionogi & Co., Ltd., Takeda Pharmaceutical Co. and Teijin Pharma Ltd.

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SI received payment for lectures including service on speaker's bureaus from Chugai Pharmaceutical Co.

SF received a consulting fee from Amgen Astellas Biopharma K.K during the conduct of the study and received a consulting fee from EliLilly K.K., and has served as a speaker bureau of Alere Medical Co., Ltd. Pfizer Inc. and Asahi Kasei Pharma Corp.

HM, KM, TY, TK and TI have declared no conflict of interest.

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