CLINICAL ARTICLE

Intravenous Zoledronic Acid 5 mg on Bone Turnover Markers and Bone Mineral Density in East China Subjects with Newly Diagnosed Osteoporosis: A 24-month Clinical Study

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Objective: This randomized, double-blind, placebo-controlled study assessed the necessity of early intervention, safety and efficacy of intravenous zoledronic acid 5 mg/year in East China women with newly diagnosed osteoporosis at high risk of fracture during a 24-month treatment period.

Methods: Subjects (57 [52–62] years old) were randomized 3:2 to zoledronic acid versus placebo (randomized at baseline, zoledronic acid [175 cases], placebo-zoledronic acid [110 cases]). The bone mineral density of the lumbar spine and total hip was measured every 6 months with the use of dual-energy X-ray absorptiometry. Serum procollagen I N-terminal pro-peptide (PINP) and serum C-telopeptide of type I collagen (CTX) levels were measured every 6 months. The primary end point was the rate of change in the bone mineral density at the posteroanterior spine.

Results: For subjects with measurements at 24 months, zoledronic acid significantly increased bone mineral density (BMD) at the lumbar spine (mean percent change ± SD, zoledronic acid 5.390% ± 0.854% versus placebo-zoledronic acid −1.038% ± 0.599%), the total hip (zoledronic acid 1.900% ± 0.262% versus placebo–zoledronic acid −1.631% ± 0.649%). Serum procollagen I N-terminal pro-peptide (PINP) and CTX decreased rapidly with zoledronic acid 5 mg treatment ($P < 0.001$ versus placebo at 6 month and 24 months) and changed from baseline in the zoledronic acid 5 mg and placebo–zoledronic acid 5 mg at 6 months by a mean of −66.348% and −75.375%, respectively ($P < 0.001$), and at 24 months by −49.950% and −52.325%, respectively ($P < 0.001$). No cases of serious adverse events were observed in two groups. Headache, pyrexia and myalgia occurred more commonly within the first 3 days after infusion with zoledronic acid 5 mg than with placebo (13.7% versus 2.1%, $P = 0.0018$; 28.0% versus 3.2%, $P < 0.001$; 21.7% versus 4.2%, $P < 0.001$, respectively).

Conclusions: These data show that early application of zoledronic acid 5 mg/year was well stimulated and tolerated for bone mass in newly diagnosed east china subjects with osteoporosis in a 24-month treatment.

Key words: Bone mineral density; Bone turnover markers; Early intervention; Placebo-controlled study; Zoledronic acid

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Introduction

Osteoporosis is a skeletal system disease characterized by degradation of bone strength and a consequent increase in fracture risk[1]. Currently, China has the largest number of osteoporosis patients worldwide. According to one survey in China, the incidence of osteoporosis was two times higher in women than in men, with approximately 112 million female patients[2]. With its rapidly increasing aging population, osteoporosis and osteoporotic fractures are a serious threat to public health in China, and are associated with large medical costs and severe burden for society and families[3,4]. Therefore, osteoporosis and osteoporotic fractures have become a serious public health concern, which require further attention in China[5]. Osteoporotic fractures, the most serious complications of osteoporosis, are responsible for more days of disability than most types of cancer[6].

Recent studies on osteoporosis medications have let to big improvements in treatment options. Currently, strategies for treating osteoporosis are based on pharmaceutical intervention. The drugs preventing and curing this extremely complex and challenging disease mostly include bone absorption-inhibitor drugs and bone formation-acceleration drugs. Many studies report that bone formation-acceleration drugs such as teriparatide can induce drug toxicity, are associated with a risk of inducing tumors, and increase the incidence of cardiovascular disease and stroke[7].

Oral bisphosphonates, once a week, are used to treat osteoporosis in clinical practice. However, the compliance of oral bisphosphonate therapy is poor, such that more than half of patients stop taking treatment within 1 year of initiation[8,9]. Low compliance is associated with more fragility fracture outcomes[7]. Zoledronic acid (Aclasta, Novartis Pharma), a bisphosphonate administered intravenously which reduces fracture risk, is, therefore, likely to benefit the health of the population and impact favorably on public health expenditure and the burden of society and family[10]. At a dose of 5 mg once a year, it has anti-fracture efficacy in postmenopausal women with osteoporosis and positive effects on bone mineral density in men. The intravenous bisphosphonate, zoledronate, reduces fracture risk when administered annually[11,12]. Therefore, zoledronate has good efficacy and treatment compliance.

High bone turnover level is a typical characteristic in most postmenopausal women; bone mass decreases dramatically in this phase[13]. Then, as menopause progresses, bone mass loss can become increasingly serious. Therefore, we believe that if we can prevent and treat osteoporosis in the early period, it will be beneficial to the maintenance of bone mass. Greater bone mass will significantly reduce the risk of fracture in postmenopausal women. Bone turnover markers combined with bone mineral density (BMD) are important in monitoring the curative effect of osteoporosis and predicting risk of fracture. Markers such as procollagen I N-terminal pro-peptide (PINP) and serum C-terminal peptide of type I collagen (S-CTX) can be used as a clinical tool to identify postmenopausal women with high levels of bone turnover.

Thus, we assume that early intervention with intravenous zoledronic acid 5 mg/year will be beneficial by improving BMD and bone turnover markers, and reducing the risk of fractures in postmenopausal women. To test this hypothesis, we conducted a 24-month randomized, double-blind, placebo-controlled trial of intravenous zoledronic acid 5 mg/year in women in East China with newly diagnosed osteoporosis at high risk of fracture, thereby assessing the necessity of early intervention, and the safety and efficacy of intravenous zoledronic acid 5 mg/year. This report also presents the first 2-year clinical study of intravenous zoledronic acid 5 mg/year treatment in subjects in East China.

Materials and Methods

Subjects

The primary purpose of this study was to assess the response to 24 months of 5 mg/year intravenous zoledronic acid compared with placebo in subjects in east China with newly diagnosed osteoporosis and at high risk of fracture. The primary efficacy variable was the percent change in lumbar spine BMD from baseline to last measurement through 24 months. Other efficacy analyses included changes from baseline to 6, 12, and 18 months in lumbar spine BMD, and changes from baseline to 6, 12, 18, and 24 months in total hip BMD and bone turnover markers. The study was conducted at Xinhua Hospital in Zhejiang.

Chinese postmenopausal women (with newly diagnosed osteoporosis) were eligible to participate if they were 50–65 years of age, at high risk of fracture, and met the following diagnostic and exclusion criteria.

The diagnosis of osteoporosis was based on the following recommended criteria of the World Health Organization (WHO)[14]: Survey the lumbar vertebra normal position bone density by using dual energy X-ray absorptiometry, T score −2.5 to −3.3 could be diagnosed as osteoporosis [T = the standard deviation of (measured value-peak bone mass)/(normal adult bone density)].

Patients were excluded from the study based on the following criteria: (i) those that also had diseases that severely affect the metabolism of bone or calcium, such as diabetes, Cushing's syndrome, changes in function of the thyroid or parathyroid, osteomalacia, rheumatoid arthritis, multiple myeloma, bone tumor, osteoarthrosis, Paget's disease, and osteogenesis imperfecta; (ii) those that also had severe primary cardiac diseases, or diseases of the cerebral vessels or hematopoietic system; (iii) those that also had severe liver function or renal insufficiencies; (iv) those taking drugs within the past 6 months that affect bone metabolism, such as estrogen, steroid hormones, calcitonin, parathyroid hormones, bisphosphonates, fluoride, vitamin D, anticonvulsant drugs, and diuretics; (v) those who had a medical history of mental illness; and (vi) patients with Alzheimer's disease.

We screened 800 postmenopausal women in the Zhejiang area. Of these, 600 women were interested and were

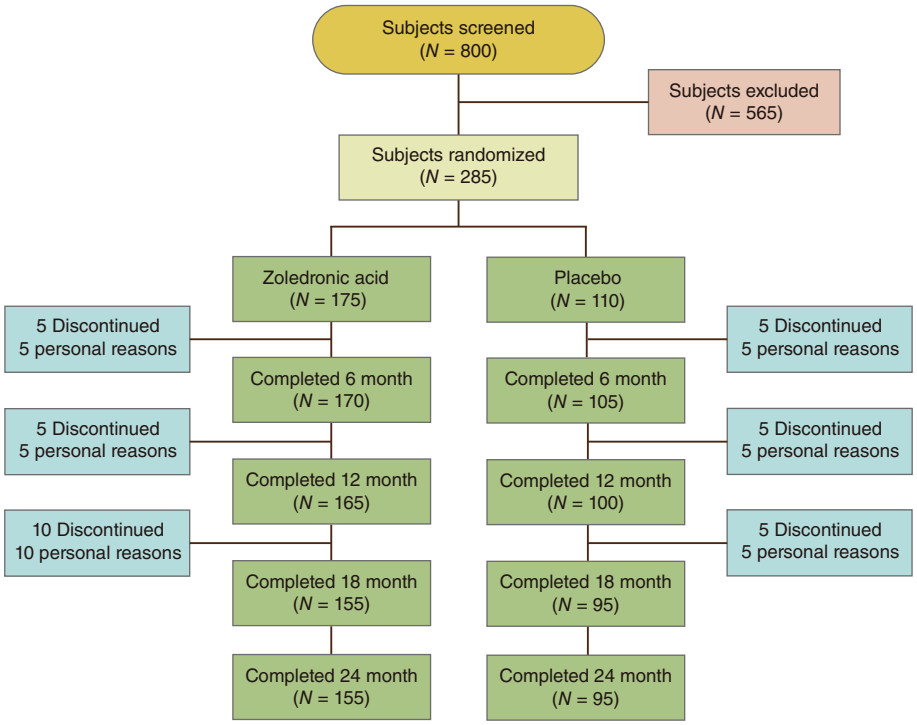

Fig. 1 Flow of participants through the study.

eligible for further screening. Of these women, 315 were deemed ineligible because their bone density was too high or low, and on the basis of screening blood tests, leaving 285 women who were eligible for the study. Thus, the final cohort consisted of 285 women.

The flow of trial participants is shown in Fig. 1.

This study (ClinicalTrials.gov identifier ChiCTR-POC-16008026) was conducted in compliance with the ethical principles stated in the Declaration of Helsinki, and was approved by the local Ethics Committee of The Second Affiliated Hospital of Zhejiang Chinese Medicine University. All subjects provided written informed consent for their participation before they enrolled in this study.

Study Design

As part of the standard therapy for subjects with osteoporosis and to provide protection for subjects receiving placebo, all subjects received daily calcium and vitamin D supplementation (1 tab Caltrate-D per day) from the start of the screening phase and throughout the study.

The 285 subjects (57 [52–62] years old) were randomized 3:2 to zoledronic acid versus placebo (randomized at baseline, zoledronic acid [175 cases] and placebo-zoledronic acid [110 cases]).

Blood was collected at baseline and at 6, 12, 18, and 24 months for routine chemical and bone turnover markers analysis.

Bone mineral density was measured with using dual-energy X-ray absorptiometry at baseline and every 6 months thereafter. BMD and T-score were measured on the PA lumbar spine (L_1–L_4) and total hip at baseline and at 6, 12, 18, and 24 months using dual-energy X-ray absorptiometry on an Osteocore II Bone Densitometer (Osteocore II Osteodensitometer, Medilink, France). BMD of other regions was not measured.

A standardized questionnaire was administered at each visit to assess side effects. Adverse events were recorded and coded with the use of the Medical Dictionary for Regulatory Activities system. Events meeting criteria for a maxillofacial adverse event or for cardiac arrhythmia classified as a serious adverse event were adjudicated by a committee of independent external experts who were unaware of the group assignments.

This 24-month, randomized, double-blind, placebo-controlled study was conducted in east China from November 2010 to December 2014.

Between January 2011 and November 2012, participants were randomly assigned to receive zoledronic acid at a dose of 5 mg or placebo, administered as a 15-min to 30-min intravenous infusion at baseline and month 12. All study participants and researchers were unaware of the study-drug assignments throughout the trial.

Measurements of Bone Mineral Density and Bone Turnover Markers

To minimize the assay variability within and between the patients, all samples were shipped in batches from Xinhua Hospital laboratory for analysis at the end of the study. Samples from the same patient were analyzed in the same batch.

The markers of bone turnover, β-C-terminal telopeptide of type I collagen (β-CTX) and procollagen type I N-terminal propeptide (P1NP), were measured at baseline and thereafter every 6 months. Blood was collected after overnight fasting at 8.00–8.30 hours, prior to administration of Zoledronic acid, and serum was stored at −70 °C prior to shipping on dry ice. Measurements were performed at an internationally accredited local laboratory using the automated Roche Cobas e601 immunoassay analyzer (DIAN Diagnostics, Hangzhou, China). BMD was measured at baseline and thereafter every 6 months at lumbar spine (L_1–L_4) and left total hip, using dual-energy X-ray absorptiometry on an Osteocore II Bone Densitometer (Osteocore II Osteodensitometer; Medilink, France). An independent investigator of BMD was responsible for the supervision of quality control for these measurements and notified the investigators of this study if any patient had a decrease in bone density of more than 5% from the baseline values.

Statistical Analysis

The primary end point was percent change from baseline at month 24 in lumbar spine BMD. The secondary end points were relative change from baseline at months 6 and 24 in the two markers of bone turnover. All primary randomized or completed baseline characteristic analyses were based on both intention to treat and protocol, such that data from all 285 participants randomized at the inception of the trial or 250 subjects completed the trial were included. All other analyses were performed according to the per-protocol principle with the use of all comparable and reliable data from all patients who completed the study. The per-protocol population included all subjects who completed the study; this population was defined as the completed analysis set (CAS). Efficacy and safety analyses were conducted on the CAS. All analyses were performed on raw data, but BMD and bone turnover marker (BTM) data are presented as percent change from baseline, for ease of interpretation. The two independent-samples *t*-test or *t′*-test (if data were found not to be normally distributed) were used to compare baseline measurements between two groups. Changes in BMD (expressed as percentage changes from baseline) between groups were compared using a *t*-test or *t′*-test, adjusting for baseline BMD. Baseline subject characteristics were compared between the treatment groups using a two-sample *t*-test for continuous variables and Fisher's exact test for categorical variables. Comparison between the completed treatment groups for percent change in BMD and BTM at the last measurement point during the placebo-controlled phase (24 months) was assessed using a two-sample *t*-test or *t′*-test. The frequency of adverse events (AE) was compared between randomized treatment groups using Fisher's exact test[15]. Descriptive statistics for percent change from baseline were presented as mean ± standard deviation for BMD and markers of bone turnover. All analyses were performed with the SPSS 22.0 software package. For all tests, a *P* value ≤0.05 was considered to indicate statistical significance. All Statistical testing was performed at a two-sided significance level of 0.05 unless otherwise noted.

Results

Subjects

Of the 800 patients who were screened for the study, 285 were randomized to double-blind treatment. Thirty-five (12.5%) discontinued from the study: 20 who received zoledronic acid 5 mg and 15 who received placebo, most commonly for personal reasons (Fig. 1). Thus, 250 women completed the study. In all the women, naturally menopause had occurred at least 5 years previously. Baseline characteristics were comparable between treatment groups at Randomized or completed period of the study (Table 1).

Bone Mineral Density

Only small increases from baseline occurred in the BMD values of both treatment groups (Table 2). For the CAS population, the percent change from baseline to month 24 was 5.390% ± 0.854% in the zoledronic acid 5 mg group and −1.038% ± 0.599% in the placebo group ($P < 0.001$).

The primary efficacy endpoint was percent change in BMD at the lumbar spine (L_1–L_4) at last observation through 24 months; the mean percent change (±SD) was 5.39% ± 0.854% in the zoledronic acid group versus −1.038% ± 0.599% in the placebo group ($P < 0.001$, Table 2). The results are shown in Fig. 2A. The mean percent change in BMD at the total hip at last observation through 24 months was 1.900% ± 0.262% in the zoledronic acid group versus −1.631% ± 0.649% in the placebo group ($P < 0.001$, Table 2). The results are shown in Fig. 2B.

The BMD at the posteroanterior spine increased continuously in subjects treated with zoledronic acid, while decreased in those treated with the placebo. As shown in Fig. 2A, the BMD at the total hip also increased continuously in the zoledronic acid group from baseline to month 12, while decreased continuously in the placebo group. The BMD at the total hip basically keep steady in the zoledronic acid group from month 12 to month 24, while it decreased continuously in the placebo group (Fig. 2B).

P-values for the two-way comparisons were calculated by analysis of *t′*-test.

Markers of Bone Turnover

Overall, zoledronic acid treatment was associated with a rapid decrease in mean percent change of PINP (Fig. 2C) and CTX (Fig. 2D). Within the zoledronic acid treatment group, mean percent change of PINP decreased significantly by 6 months of treatment (mean 66.348%, $P < 0.001$) and elevated slowly throughout the 6-month and 12-month treatment periods, then basically remained steady in the zoledronic acid group from month 12 to month 24. Within the placebo treatment group, the mean percent change of PINP slowly decreased throughout the placebo treatment period.

TABLE 1 Randomized or completed baseline characteristics of postmenopausal women with osteoporosis treated with Intravenous zoledronic acid 5 mg or placebo

Characteristic		ZOL group	Placebo group	*P*-value
Age (years)	Randomized	57.22 ± 2.81	57.48 ± 3.18	0.482
	Completed	57.11 ± 2.75	57.12 ± 3.16	0.987
Height (cm)	Randomized	159.91 ± 5.99	159.70 ± 5.55	0.771
	Completed	164.01 ± 5.91	160.05 ± 5.71	0.957
Weight (kg)	Randomized	59.31 ± 2.64	58.77 ± 2.56	0.087
	Completed	59.27 ± 2.61	58.95 ± 2.58	0.344
Body-mass index (kg/m^2)	Randomized	22.65 ± 1.90	23.07 ± 2.17	0.840
	Completed	21.82 ± 1.08	21.58 ± 0.96	0.077
Years since natural menopause (years)	Randomized	9.73 ± 1.43	10.07 ± 1.52	0.090
	Completed	9.78 ± 1.45	9.98 ± 1.55	0.304
Alcohol consumption [Yes, cases (%)]	Randomized	35(22.6)	45(47.4)	0.053
	Completed	40(22.8)	45(40.9)	0.14
Serum t-P1NP level (ng/mL)	Randomized	58.171 ± 8.367	59.459 ± 7.601	0.191
	Completed	58.489 ± 8.574	58.542 ± 7.781	0.961
Serum β-CTX level (ng/mL)	Randomized	0.551 ± 0.095	0.545 ± 0.089	0.605
	Completed	0.534 ± 0.088	0.530 ± 0.078	0.668
Total hip BMD (g/cm^2)	Randomized	0.759 ± 0.043	0.751 ± 0.042	0.085
	Completed	0.754 ± 0.042	0.748 ± 0.043	0.324
Posteroanterior spine BMD (g/cm^2)	Randomized	0.636 ± 0.043	0.634 ± 0.044	0.759
	Completed	0.631 ± 0.041	0.628 ± 0.043	0.564

Subjects randomized: Zoledronic acid group, *n* = 175; placebo group, *n* = 110. Subjects completed: Zoledronic acid group, *n* = 155, placebo group, *n* = 95.; The data shown are for the postmenopausal women in the randomized and completed population. *P*-values are for the two-way comparisons and were determined by analysis of *t*-test. The body-mass index is the weight in kilograms divided by the square of the height in meters. Values are mean ± standard deviation or *n* (%). A two-sample *t*-test for continuous variables and Fisher exact test for categorical variables.; β-CTX, C-telopeptide of type I collagen; PINP, N-terminal propeptide of type I collagen; ZOL, zoledronic acid.

TABLE 2 Mean percent changes in bone mineral density at month 24 and rates of change among women treated with zoledronic acid or placebo (g/cm^2)

Bone site	Zoledronic acid group (*n* = 155)	Placebo group (*n* = 95)	*P*-value
Posteroanterior spine	5.390 ± 0.854	−1.038 ± 0.599	<0.001
Total hip	1.900 ± 0.262	−1.631 ± 0.649	<0.001

Values are means ± standard deviation. *P*-values for the two-way comparisons were calculated by analysis of *t*'-test.

The mean percent change in PINP at month 6 and month 24 was −66.348% ± 2.825% and −49.950% ± 7.168%, respectively, in the zoledronic acid group versus −6.800% ± 2.131% and −13.725% ± 1.745%, respectively, in the Placebo group ($P < 0.001$, Table 3, Fig. 2C). The mean percent change in CTX at month 6 and month 24 was −75.375% ± 3.203% and −52.325% ± 4.151%, respectively, in the zoledronic acid group versus −3.600% ± 1.039% and −7.791% ± 3.006%, respectively, in the placebo group ($P < 0.001$, Table 3, Fig. 2D).

Adverse Events or Safety

Safety was assessed through the collection of AE at all visits. No cases of serious AE, such as osteonecrosis of the jaw, atrial fibrillation, ocular inflammation, symptomatic hypocalcemia, or fragility fractures, were observed in the zoledronate group or the placebo group. AE that occurred in >5.0% of patients within 3 days of initial dosing were shown in Table 3. The subjects who received zoledronic acid reported more common adverse events of pyrexia, myalgia, or headache (Table 4). There were no significant differences between the groups in the incidence of arthralgia or back pain (Table 4). Both treatments were well-tolerated, albeit with a higher incidence of influenza-like illness and pyrexia events occurring within 3 days post-infusion with zoledronic acid. The most common post-dose symptom AE were generally mild to moderate in intensity and were of short duration (the majority lasting 3 days or less).

Discussion

We found that the administration of intravenous zoledronic acid could increase the bone mineral density at the spine and the femoral neck. Zoledronic acid also reduced the P1NP and CTX levels, which reflect the stimulation of osteoclast activity.

This finding demonstrates that early application of zoledronic acid 5 mg/year was well stimulated and tolerated for bone mass in newly diagnosed subjects in east China with osteoporosis in a 24-month treatment.

The results of this study were similar to the results for past research in other countries and regions[10,16,17]. Because the early treatment of osteoporosis is very important[18,19], the

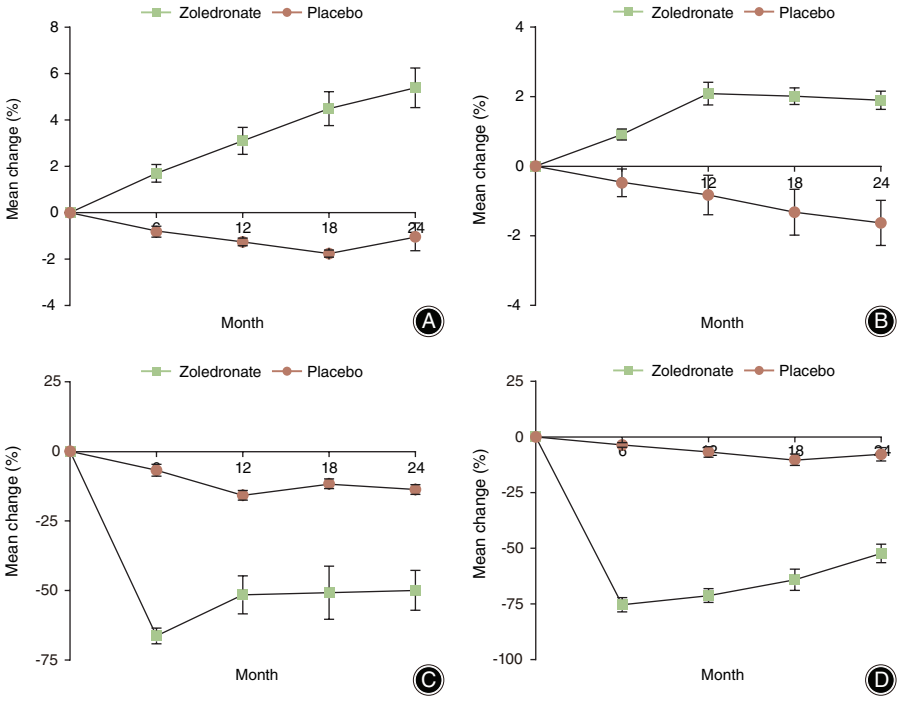

Fig. 2 Mean percent changes in the bone mineral density of the posteroanterior spine (A) and total hip (B) as determined with dual-energy X-ray absorptiometry and in serum P1NP (C) and β-CTX (D) level (ng/mL). I bars represent the standard deviation (error bars that are not seen are contained within the data-point symbols).

TABLE 3 Mean percent changes in serum β-CTX level and serum t-P1NP level at 6 or 24 months

	Zoledronic acid group (n = 155)		Placebo group (n = 95)	
BTMs	Month 6	Month 24	Month 6	Month 24
Serum t-P1NP level	−66.348 ± 2.825	−49.950 ± 7.168	−6.800 ± 2.131*	−13.725 ± 1.745*
Serum β-CTX level	−75.375 ± 3.203	−52.325 ± 4.151	−3.600 ± 1.039#	−7.791 ± 3.006#

BTM, bone turnover markers. Values are means ± standard deviation. Comparisons of serum t-P1NP level at the same month between the zoledronic acid group and the placebo group, *P < 0.001. Comparisons of serum β-CTX level at the same month between the zoledronic acid group and the placebo group, #P < 0.001.

TABLE 4 Percentage of visits at which subjects reported side effects [n (%)]

Side effect	ZOL group (n = 155)	Placebo group (n = 95)	P-value
Headache (influenza-like illness)	21 (13.5)	2 (2.1)	0.003
Pyrexia	43 (27.7)	3 (3.2)	<0.001
Myalgia	34 (21.9)	4 (4.2)	<0.001
Arthralgia	29 (18.7)	11 (11.6)	0.157
Back pain	24 (15.4)	14 (14.7)	1

Adverse events (AE) that occurred in >5.0% of patients within 3 days of initial dosing. Five most common adverse events in zoledronic acid group. P-values were calculated with the use of Fisher's exact test. The output data of 2-Tail P-values were collected as the last P-values. The two-tail P-value is calculated. Patients with more than one AE may appear in both occurrence categories. A participant with multiple occurrences of an adverse event within a preferred term (according to codes used in the Medical Dictionary for Regulatory Activities) was counted only once.

changes in BMD and bone turnover observed during the early period of osteoporosis are likely to be more important than those observed during later period of osteoporosis.

Taken together, these data suggest that administration of zoledronate may prevent fragility fractures in patients with osteoporosis. The current data have potentially important implications for patient care and for future research in fracture prevention. If very early zoledronate administration reduces fracture risk, it would facilitate greater availability of an effective treatment without increasing drug costs and health-care costs[20,21].

No cases of serious adverse events, such as osteonecrosis of the jaw, atrial fibrillation, ocular inflammation, symptomatic hypocalcemia, or fragility fractures, were observed in this early use of zoledronate group[22–25]. Our findings also suggest that early treatment with zoledronate might be an effective strategy for osteoporosis prevention.

In addition, the long-term administration of zoledronate as well as estrogen, calcium supplements, with or without vitamin D, and alendronate may lead to atypical

fractures[26–28]. The administration of anti-osteoporosis also may lead to a higher risk of cardiovascular events in the older subjects[29].

Finally, the strategy of early treatment with zoledronate may be effective, safe, inexpensive, and well tolerated.

Oral bisphosphonates prevent bone loss in early postmenopausal women, but their utility for fracture prevention over extended periods is questionable because of high rates of treatment discontinuation[30]. However, patients showed good adherence in this study.

Our study has particular strengths, such as being double-blind, randomized, and placebo-controlled, but it also has limitations. The sample size is small. To address the possibility that missing data influenced the results of the primary analysis, we conducted additional analyses using the intention-to-treat (ITT) analysis, which produced similar results to those for per-protocol analysis. The consistency of these results suggests that the withdrawal of the 35 participants did not influence the outcome. Although the number of participants was small, the confidence intervals around the changes in bone turnover and BMD are compact, providing reassurance that the findings are valid.

In further research, we will evaluate the long-term efficacy of zoledronate in China.

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