Osteoporos Int (2012) 23:503–512
DOI 10.1007/s00198-011-1563-8

ORIGINAL ARTICLE

Treatment with acetaminophen/paracetamol or ibuprofen alleviates post-dose symptoms related to intravenous infusion with zoledronic acid 5 mg

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Received: 25 August 2010 / Accepted: 14 January 2011 / Published online: 19 February 2011
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Abstract
Summary Patients treated with intravenous zoledronic acid 5 mg for osteoporosis may experience post-dose influenza-like symptoms. Oral acetaminophen/paracetamol or ibuprofen administered 4 h post-infusion reduced the proportion of patients with increased oral temperature and worsening post-infusion symptom scores vs. placebo, thus providing an effective strategy for the treatment of such symptoms.
Introduction Once-yearly intravenous zoledronic acid 5 mg is a safe and effective treatment for postmenopausal osteoporosis. This study assessed whether transient influenza-like post-dose symptoms associated with intravenous infusion of zoledronic acid can be reduced by post-dose administration of acetaminophen/paracetamol or ibuprofen.
Methods In an international, multicenter, randomized, double-blind, double-dummy parallel-group study, bisphosphonate-naïve postmenopausal women with osteopenia (n=481) were randomized to receive zoledronic acid 5 mg+acetaminophen/paracetamol (n=135), ibuprofen (n=137) or placebo (n=137), or placebo+placebo (n=72). Acetaminophen/paracetamol and ibuprofen were administered every 6 h for 3 days beginning 4 h post-infusion.
Results The proportion of patients with increased oral temperature (≥1°C above 37.5°C) and with worsening post-infusion symptom scores over 3 days was significantly lower in patients receiving ibuprofen (36.8% and 48.5%) or acetaminophen/paracetamol (37.3% and 46.3%) vs. those receiving placebo (63.5% and 75.9%, respectively; all p<0.0001) compared with background rates of 11.1% and 16.7%, respectively, in the absence of any active treatment. Overall incidence of adverse events was comparable for patients receiving acetaminophen/paracetamol or ibuprofen.
Conclusion Oral acetaminophen/paracetamol or ibuprofen effectively managed the transient influenza-like symptoms associated with zoledronic acid 5 mg.

Keywords Acetaminophen · Ibuprofen · Paracetamol · Zoledronic acid

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Introduction

Zoledronic acid is a potent bisphosphonate approved for the treatment of osteoporosis, Paget's disease, and hypercalcemia of malignancy. It can be administered intravenously once

yearly in the treatment of osteoporosis. In the HORIZON Pivotal Fracture Trial in which 7,765 postmenopausal women were randomized across diverse ethnic groups and geographic regions, zoledronic acid demonstrated significant fracture reduction at hip, vertebral, and non-vertebral sites over 3 years [1]. Moreover, in the HORIZON Recurrent Fracture Trial, an annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a significant reduction in the rate of new clinical fractures and with improved survival [2].

As with other bisphosphonates, intravenous infusion with zoledronic acid may result in transient post-infusion symptoms similar to those associated with mild-to-moderate influenza-like symptoms, including fever, myalgia, headache, and nausea [3]. These symptoms usually occur within 72 h after the infusion and are mild to moderate in severity, generally resolve within 1–4 days, and are much less likely to occur after later doses than after the first infusion. The mechanism underlying these symptoms is believed to be a result of the inhibition of farnesyl pyrophosphate, an enzyme in the mevalonate pathway which is responsible for the bone resorption action of aminobisphosphonates. When this enzyme is blocked, intermediates in this pathway, isopentenyl diphosphate and dimethylallyl diphosphate, accumulate in monocyctes, leading to the activation of γδ T cells and the release of interferon-γ and TNF-α [4].

We present the results of a randomized, placebo-controlled trial that tested whether two common oral analgesics/antipyretics, acetaminophen/paracetamol and ibuprofen, are effective at reducing the incidence and severity of post-infusion symptoms following a single IV infusion of zoledronic acid 5 mg in bisphosphonate-naïve postmenopausal women.

Methods

Study design

This was a randomized, multicenter, double-blind parallel-group study involving bisphosphonate-naïve postmenopausal women with osteopenia. The study comprised a 4-week screening period followed by a 3-day treatment period and a 7-day observation period. Patients were randomized to the following four treatment groups in the ratio 2:2:2:1, respectively:

- Zoledronic acid 5 mg IV + two acetaminophen/paracetamol 500 mg capsules every 6 h for 3 days
- Zoledronic acid 5 mg IV + two ibuprofen 200-mg capsules every 6 h for 3 days
- Zoledronic acid 5 mg IV + two placebo capsules every 6 h for 3 days
- Placebo IV + two placebo capsules every 6 h for 3 days

Oral study medication was started 4 h after the infusion, and rescue medication was provided for all groups as needed (every 6 h, up to a maximum of eight capsules in a 24-h period). For the zoledronic acid+acetaminophen/paracetamol group, rescue medication was ibuprofen 200 mg. For the zoledronic acid+ibuprofen group, rescue medication was acetaminophen/paracetamol 500 mg. For the zoledronic acid+placebo group, rescue medication was acetaminophen/paracetamol 500 mg. Patients also received supplementation with vitamin D (400–800 IU daily) and calcium (500–1,000 mg elemental calcium twice daily) for the duration of the study.

The primary objective of the study was to assess the effects of treatment with acetaminophen/paracetamol and ibuprofen relative to placebo in preventing clinically significant increases in oral temperature [defined as an increase of at least 1°C (1.8°F) to a value above 37.5°C (99.5°F)] following an IV infusion of zoledronic acid 5 mg. The secondary objective was to assess the effects of acetaminophen/paracetamol and ibuprofen on the change in severity of symptoms from baseline over the 3-day treatment period using a questionnaire with a four-point categorical scale (0=absent, 1=mild, 2=moderate, 3=severe) and a 0- to 100-mm visual analog scale (VAS; 0=no symptoms, 100=severe symptoms).

The study was conducted in accordance with the International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice, local regulations/guidelines, and the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

Patients

Postmenopausal women aged 45–75 years with osteopenia—defined as peripheral (heel or wrist) or central (spine or hip) bone mineral density T-score of −1.0 or less and −2.5 or more within the previous 6 months—were eligible for inclusion in the study. A woman was considered postmenopausal if she met one of the following three criteria: cessation of menses for 18 months if <50 years of age; cessation of menses for 12 months if aged ≥50 years; or documented bilateral oophorectomy at least 1 year previously.

Exclusion criteria included prior treatment with IV bisphosphonates, oral bisphosphonates, strontium, or parathyroid hormone; calculated creatinine clearance <30 mL/min at screening; urine dipstick ≥2 with protein at screening and randomization (visit 1 and/or visit 2) without evidence of contamination or bacteriuria; serum calcium ≥2.75 mmol/L or ≤2.0 mmol/L; 25-(OH) vitamin D levels <20 ng/mL (<50 mmol/L) before randomization; aspartate aminotransferase, alanine aminotransferase, or serum alkaline phosphatase >2.0×upper limit of normal; chronic use of systemic corticosteroids (oral or IV) within the last year before screening where the total dose exceeded 750 mg of oral

prednisone or equivalent; daily treatment with a statin in the month before screening; treatment with a selective estrogen receptor modulator, calcitonin, or hormone replacement therapy within the 2 months before screening; treatment with an investigational drug within the 30 days prior to screening; ongoing infection (oral temperature ≥37.5°C), chronic febrile disease or fever of unknown origin at screening or randomization; infection of the teeth or oral cavity; recent or planned dental surgery; history of iritis, uveitis, or chronic conjunctivitis; presence or history, within the 2 months before screening, of peptic ulcers, gastrointestinal bleeding, and/or melena; meeting the Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria for alcohol/substance abuse and dependence. Patients were excluded if they: were taking prescription doses of analgesics, anti-inflammatory drugs, tranquilizers, or muscle relaxants; were taking non-prescription analgesic/antipyretic medications; or required anticoagulant therapy. Patients with a known hypersensitivity to acetaminophen/paracetamol, ibuprofen, or aspirin were excluded, as were those with a history of allergic reaction or sensitivity to bisphosphonates or allergies manifested by attacks of asthma, urticaria, or acute rhinitis following treatments with aspirin or other agents with cyclooxygenase-inhibiting activity, such as nonsteroidal anti-inflammatory drugs. Further exclusion criteria included any medical or psychiatric condition which, in the opinion of the investigator, would preclude the participant from adhering to the protocol or completing the study per protocol; previous major solid organ or bone marrow transplant or being on a transplant waiting list; non-osteoporotic forms of metabolic bone disease such as Paget's disease, osteomalacia, osteogenesis imperfecta, multiple myeloma; new diagnosis or active treatment for any malignancy ≤12 months before screening; evidence/history of any metastases at or before randomization; evidence of paraneoplastic syndrome, for example, hypercalcemia during screening or by history.

Randomization and blinding

A randomization list was produced by a central location using a validated system that automated the random assignment of treatment groups to randomization numbers in the specified ratio. The randomization scheme was reviewed by a Biostatistics Quality Assurance Group at Novartis and locked by them after approval. The randomization procedure was performed in blocks for each study center. At visit 2, patients who fulfilled all the inclusion/exclusion criteria were assigned the lowest available number on the randomization list. Patients, investigator staff, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomization until the conclusion of the study.

Efficacy variables

The primary efficacy variable was the proportion of patients with a clinically significant increase in oral temperature (≥1°C to a value >37.5°C) during the first 3 days after receiving the IV study drug. Digital thermometers were provided to each patient and supplied by Fishers Laboratories, Pittsburgh, PA, USA. The investigator instructed the patient on the proper use of the thermometer orally. Two measurements of oral temperature, separated by a 10- to 15-min interval, were taken every 5–7 h (morning, afternoon, evening, and night) by the patient before taking any oral study medication. The average of the two temperature measurements at each time point was used for the analyses. A subgroup analysis was conducted by age for the primary variable to establish any treatment–age interactions. Between-treatment differences were evaluated based on Fisher's exact test. The step-up procedure of Hochberg [5] was used to ensure that the overall significance level of 5% was maintained after adjusting for the multiple comparisons. The modified intent-to-treat population was the primary analysis population which required subjects to have a baseline and at least one post-baseline temperature measurement.

Secondary efficacy variables were: mean change in oral temperature over time; clinically significant increases in oral temperature using a higher threshold (increases of ≥1°C to ≥38.5°C); the proportion of patients reporting a worsening of symptom severity (i.e., a change of ≥2 severity units) as solicited by a questionnaire; the proportion of patients reporting severe feverishness, headache, muscle or joint aches and pain, or other symptomatology according to the severity classification of the questionnaire; the proportion of patients with a 0- to 100-mm VAS score ≥75 mm over time; the proportion of patients with a VAS score >0 over time. All such variables were evaluated using Fisher's exact test. No adjustments for multiplicity of secondary efficacy variables were performed.

Safety assessments

All adverse events (AEs) and serious AEs (SAEs) were monitored (including their severity and relationship to study treatment) and recorded throughout the study. Laboratory parameters (hematology, blood chemistry, and urinalysis), vital signs, physical condition, and body weight were assessed prior to randomization and at the end of the study (day 10).

Statistical analysis

The primary efficacy objective of the study was to demonstrate superiority of acetaminophen/paracetamol and/or ibuprofen

relative to oral placebo with respect to the proportion of patients with a clinically significant increase in oral temperature over a 3-day period after receiving IV zoledronic acid. A sample size of 455 patients was planned in order to demonstrate this difference. All differences were evaluated at a significance of 0.05 based on Fisher's exact test. The step-up procedure of Hochberg [5] was used to ensure that the overall significance level, with two-sided 95% confidence intervals (CI), was maintained after adjusting for the multiple comparisons. The primary efficacy analysis was conducted on the modified intention-to-treat (MITT) population, patients who received an IV infusion and had a baseline and at least one post-baseline temperature assessment. The primary efficacy endpoint was also summarized by age group (<65, 65–69, ≥70 years); no inferential statistics were calculated for any of the subgroup measurements.

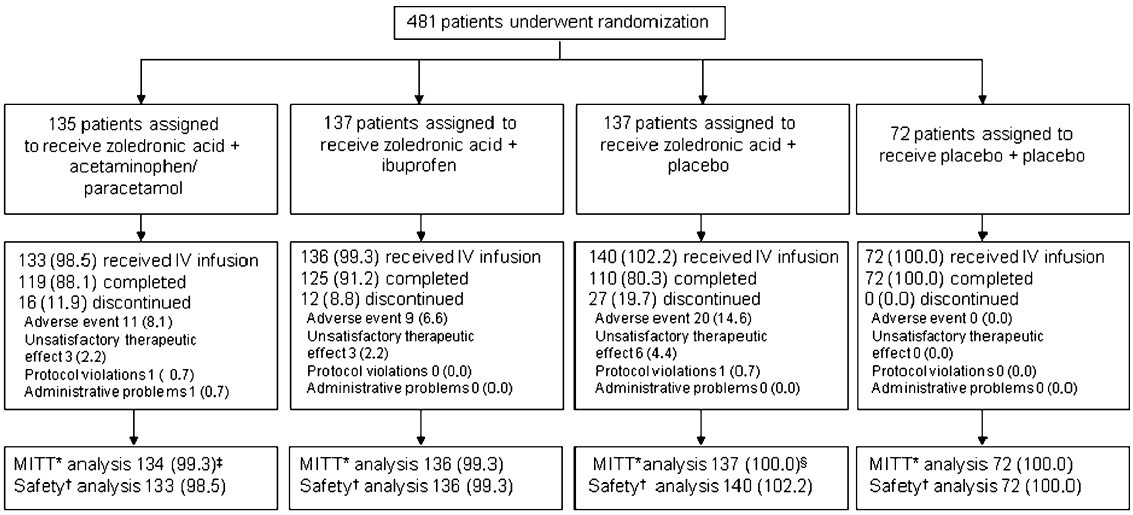
Differences in baseline characteristics between the study groups were evaluated using a chi-square test for categorical variables and a one-way analysis of variance for continuous variables. Descriptive statistics (mean, median, standard deviation, minimum, and maximum) were presented for the absolute values of the VAS score at each time point (day 1, day 2, and day 3) as well as for the corresponding change from baseline. Missing measurements were not imputed. Safety was assessed in all patients who received an IV infusion (the safety population).

Results

In total, 481 patients were randomized to treatment (ITT population). Of these, 55 (11.4%) discontinued prematurely, mainly due to AEs (Fig. 1). The median (interquartile range) duration of follow-up was 10 (2) days. Baseline demographics and disease characteristics were comparable in all treatment groups (Table 1). Almost all patients (95.0%) were white, with a mean age of 60.5 years.

Change in oral temperature

Eighty-seven percent of patients provided temperature measurements at least three times on day 1 (or at least two times on day 1 if the day 1 IV infusion was performed on or after 12 P.M.) and at least three times on days 2 and 3. The proportion of patients with increased oral temperature (≥1°C to a value >37.5°C), the primary efficacy variable, was lower in the groups that received acetaminophen/paracetamol or ibuprofen compared with those who received oral placebo following zoledronic acid infusion over the 3-day treatment period ($p<0.0001$ for both groups; Fig. 2). The incidence of increased temperature in the acetaminophen/paracetamol and ibuprofen groups was approximately half that of the group receiving oral placebo alone following zoledronic acid infusion (37.3%, 36.8% vs. 63.5%, respectively). In the placebo+placebo group, 11.1% of patients experienced a significant rise in temperature.



*The MITT population included all patients who received an IV infusion and had a baseline and at least one post-baseline temperature assessment and is based on the treatment group to which a subject was randomized to as opposed to the treatment they actually received.
†The safety population included all patients who received an IV infusion.
‡135 patients were randomized to receive zoledronic acid + acetaminophen/paracetamol, only 133 patients received this exact treatment and 1 patient received a different treatment. However, due to the criteria for MITT analysis, the total number of patients in the MITT analysis exceeds the number of patients who received zoledronic acid + acetaminophen/paracetamol.
§137 patients were randomized to receive zoledronic acid + placebo, 140 patients received this exact treatment. However, due to the criteria for MITT analysis, the total number of patients in this analysis is less than the number who received this exact treatment.

Fig. 1 Patient flow

Table 1 Baseline demographics and disease characteristics (intent-to-treat population)

	Zoledronic acid 5 mg			Placebo+placebo (n=72)	Total (n=481)
	+ acetaminophen/ paracetamol (n=135)	+ ibuprofen (n=137)	+ placebo (n=137)		
Age, years (mean±SD)	60.5±7.49	59.7±6.58	60.1±7.10	62.5±6.75	60.5±7.05
Age subgroup, *n* (%)					
<65 years	94 (69.6)	101 (73.7)	95 (69.3)	41 (56.9)	331 (68.8)
65–69 years	20 (14.8)	24 (17.5)	26 (19.0)	19 (26.4)	89 (18.5)
≥70 years	21 (15.6)	12 (8.8)	16 (11.7)	12 (16.7)	61 (12.7)
Weight, kg (mean±SD)	69.5±13.01	69.2±13.83	67.8±12.23	68.0±12.57	68.7±12.95
Oral temperature at baseline, °C (mean±SD)	36.7±0.21	36.7±0.25	36.7±0.24	36.7±0.22	36.7±0.23
Symptom VAS, mm (mean±SD)	6.0±11.84	7.8±12.70	8.1±12.93	7.7±13.66	7.4±12.67
Calculated creatinine clearance at baseline, *n* (%)					
Missing	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)
35 to <40 mL/min	1 (0.7)	0 (0)	0 (0)	0 (0)	1 (0.2)
40–50 mL/min	3 (2.2)	3 (2.2)	0 (0)	3 (4.2)	9 (1.9)
>50 mL/min	131 (97.0)	134 (97.8)	136 (99.3)	69 (95.8)	470 (97.7)
Serum calcium, mmol/L (mean±SD)	2.5±0.08	2.4±0.08	2.5±0.09	2.5±0.10	2.5±0.09
Serum 25(OH) vitamin D, nmol/L (mean±SD)	103.8±35.76	103.8±34.12	106.3±36.97	103.6±35.47	104.6±35.49
Aspirin use at baseline[a], *n* (%)	1 (0.7)	3 (2.2)	4 (2.9)	4 (5.6)	12 (2.5)

SD standard deviation, *VAS* visual analog scale (0–100 mm)

[a] Patients were required to stop taking aspirin for the duration of the trial

At 10 h post-infusion, the zoledronic acid+placebo group demonstrated a greater increase in mean oral temperature relative to the other treatment groups (Fig. 3). All groups showed an increase in mean temperature 24–48 h post infusion, with the rise most pronounced in those receiving zoledronic acid+placebo and least pronounced in those receiving placebo+placebo over time, indicated by a significant treatment and treatment-by-time interaction (p<0.0001). The rise in mean temperature was similar in the acetaminophen/paracetamol and ibuprofen groups. Mean temperature beyond 48 h post-infusion was similar for all treatment groups, except the zoledronic acid+placebo group in which oral temperature remained higher. This difference was still present 63 h post-infusion when oral temperature was 0.2°C higher in the zoledronic acid+placebo group compared with all other groups.

In a post hoc analysis, the higher threshold for increase in oral temperature (increases of ≥1°C to an oral temperature ≥38.5°C) was reached most frequently in patients treated with zoledronic acid+placebo (32.8%), with a lower incidence in the acetaminophen/paracetamol (18.7%) and ibuprofen (14.0%) groups. This threshold was not reached by any of the patients receiving placebo+placebo.

Subgroup analysis (MITT population) of the primary efficacy variable across all treatment groups showed that patients <65 years of age had a 48.4% incidence of increase in temperature of ≥1°C to an oral temperature >37.5°C compared with 23.3% for patients older than 70 years of age. As the mean age of the study population was 60.5 years, and approximately 69% of the patients were younger than 65, a post hoc analysis was performed for the

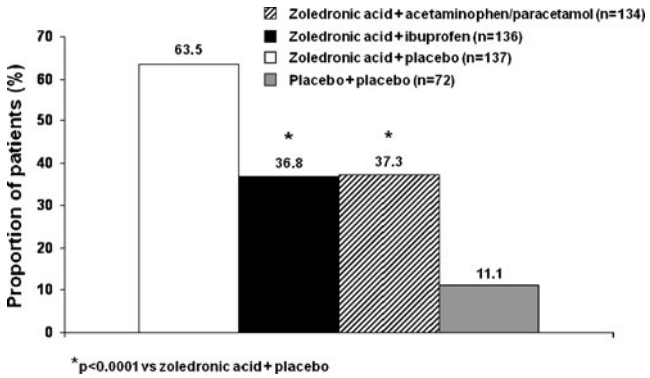


Fig. 2 Proportion of patients with a clinically significant increase in oral temperature (≥1°C to a value >37.5°C, modified intent-to-treat population)

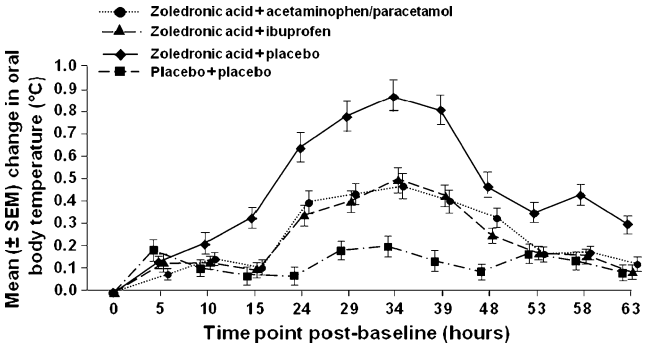


Fig. 3 Change from baseline in oral temperature over the 3-day treatment period (modified intent-to-treat population)

primary endpoint using age quartiles (<55 years; ≥55–59 years; 60–65 years; ≥66 years). An exploratory logistic regression analysis showed that overall, patients in the youngest quartile (<55 years) had approximately 1.75 times greater odds of experiencing an increase in temperature than patients in the oldest quartile (≥66 years) [odds ratio (OR)=1.75, 95% CI=0.2681–3.85, p=0.1539), although the finding was not statistically significant. Within the same sub-analysis model examining treatment differences, results indicated that the likelihood of a temperature increase for patients aged <55 years in the zoledronic acid+ placebo group was 3.21 times greater than for patients in the zoledronic acid+acetaminophen/paracetamol group (p=0.0256). For patients 55–59 years of age, the zoledronic acid + placebo group was 3.80 times more likely to experience an increase in temperature than patients in the zoledronic acid + acetaminophen/paracetamol group (p=0.0071). For patients aged 60–65 years, the zoledronic acid + placebo group was 6.13 times more likely to experience an increase in temperature than patients in the zoledronic acid + acetaminophen/paracetamol group (p=0.0034). No differences were observed for patients aged 66 years or older. A similar pattern existed for the comparison of age groups between the zoledronic acid + ibuprofen and zoledronic acid + placebo groups.

Symptom severity

The proportion of patients in the placebo + placebo group reporting symptom worsening (16.7%) provided an estimate of the background rate of response in the absence of any active treatment (Table 2). According to the responses from the categorical questionnaire, worsening in symptom severity was observed in a significantly greater proportion of patients receiving zoledronic acid + placebo than in the groups receiving either acetaminophen/paracetamol or ibuprofen (both p<0.0001). Similarly, severe symptoms (fever, headache, aches and pains, or other), as assessed by the questionnaire, were reported by 25.2% of patients receiving acetaminophen/paracetamol or ibuprofen compared with 48.9% in the zoledronic acid + placebo group (both p≤0.0002) on days 1–3 (Table 2). Again, the incidence of 6.9% reported in the placebo + placebo group provided an estimate of the background rate of severe symptom reporting in the absence of active treatment.

The most pronounced mean change from baseline in VAS score for symptom severity on day 1 was reported in the zoledronic acid + placebo group (15.4 mm), with only a slight increase observed in the placebo + placebo group (1.7 mm; Fig. 4). On day 2, scores rose by a mean of 18 mm in the acetaminophen/paracetamol group and by 15 mm in the ibuprofen group compared with 34.7 mm in the zoledronic acid + placebo group and 2.1 mm in the placebo + placebo group. The increases in VAS scores were highest on day 2 for all groups.

No patient in the placebo + placebo group reported severe symptoms as measured using a VAS score, at any time. Almost one fifth of patients in the zoledronic acid + placebo group (19.4%) reported a VAS score ≥75 mm on day 2 compared with 8.5% in the acetaminophen/paracetamol group and 5.5% of patients in the ibuprofen group. Patients with severe symptoms were less for these three groups on days 1 and 3. In the 3-day period after infusion, patients were less likely to have severe symptoms if they received acetaminophen/paracetamol (OR=0.46, 95% CI= 0.23–0.92, p=0.0284) or ibuprofen (OR=0.28, 95% CI= 0.14–0.59, p=0.0006) following zoledronic acid infusion

Table 2 Symptom severity assessed using a four-point categorical questionnaire (modified intent-to-treat population)

Outcome	Zoledronic acid 5 mg			Placebo+placebo (n=72)
	+ acetaminophen/paracetamol (n=134)	+ ibuprofen (n=136)	+ placebo (n=137)	
Patients with symptom worsening, n (%)	62 (46.3)**	66 (48.5)**	104 (75.9)	12 (16.7)
Patients reporting severe symptoms, n (%)	32 (23.9)**	36 (26.5)*	67 (48.9)	5 (6.9)

*p≤0.0002, **p<0.0001 vs. zoledronic acid+placebo

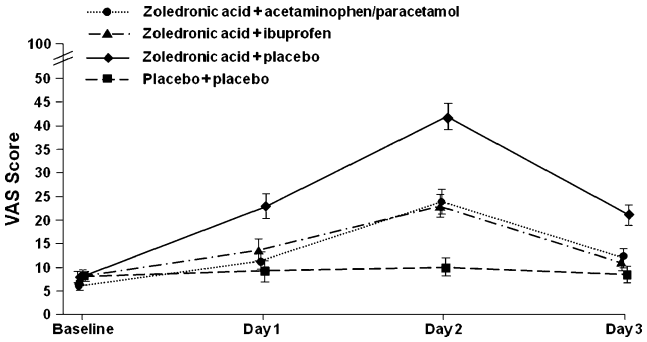


Fig. 4 Symptom worsening according to patients' responses on a 100-mm visual analog scale (modified intent-to-treat population)

compared with those who received placebo. There was no statistically significant difference between the acetaminophen/paracetamol and ibuprofen groups with respect to the likelihood of having severe symptoms.

At least half of the patients receiving placebo+placebo reported symptoms (i.e., VAS score of >0 mm) on each of the 3 days post-infusion. The proportion of patients reporting symptoms using the VAS increased from 52.4% at baseline to a maximum of 94.4% in the zoledronic acid+ placebo group, 82.7% in the ibuprofen group, and 78.0% in the acetaminophen/paracetamol group on day 2 (Fig. 5). Patients in the zoledronic acid + placebo group were more likely to have a VAS score >0 mm compared with the placebo + placebo group (OR=6.32, 95% CI=3.40–11.77, $p<0.0001$).

Use of rescue medication

Use of rescue medication during the study was highest in the zoledronic acid + placebo group (22.1%) compared with the acetaminophen/paracetamol (10.5%) and ibuprofen (9.6%) groups; no patients in the placebo + placebo group required rescue medication.

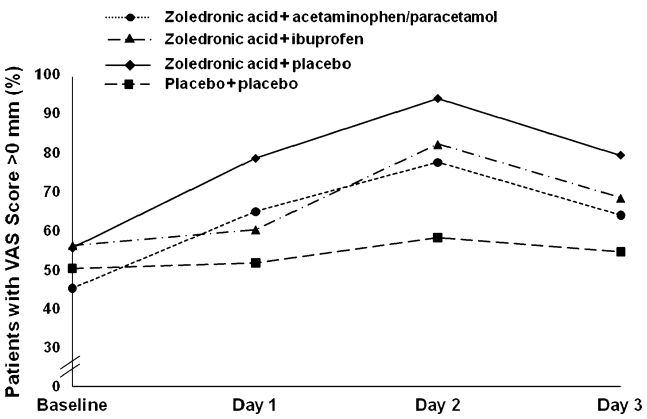


Fig. 5 Proportion of patients with visual analog scale score >0 mm at baseline and over the 3-day treatment period (modified intent-to-treat population)

Safety and tolerability

The total proportion of patients with AEs was greatest in the zoledronic acid + placebo group (60.7%), followed by the zoledronic acid + acetaminophen/paracetamol (46.6%), zoledronic acid + ibuprofen (44.1%), and placebo + placebo (25.0%) groups. The most frequent AEs reported in each treatment group during the study were headache, fever, myalgia, arthralgia, and nausea (Table 3). Most AEs were mild to moderate in severity. Only one SAE was reported in one patient receiving zoledronic acid + acetaminophen/paracetamol (non-cardiac chest pain). There were no deaths during the study.

The proportion of patients with AEs leading to discontinuation of study drug was 15.0% for patients in the zoledronic acid + placebo group, 8.3% in the acetaminophen/paracetamol group, 5.9% in the ibuprofen group, and 0% in the placebo + placebo group. The five most commonly occurring AEs (headache, pyrexia, arthralgia, myalgia, nausea) and pain were the AEs that most often led to early discontinuation. The incidence of clinically meaningful changes in laboratory parameters and vital signs was low and similar across treatment groups. No patient had an AE of atrial fibrillation, atrial flutter, or hypocalcemia. One patient, who was in the placebo + placebo group, met the criterion for a program-specified laboratory renal abnormality with a >0.5-mg/dL increase in serum creatinine at the day 10 evaluation.

Discussion

In this multicenter, randomized study of postmenopausal women with osteopenia, treatment with acetaminophen/paracetamol or ibuprofen safely and effectively alleviated symptoms following a single IV infusion of zoledronic acid 5 mg. A number of efficacy parameters were improved in patients who received acetaminophen/paracetamol or ibuprofen compared with those who received placebo after zoledronic acid infusion: Peak oral temperature was significantly lower, the onset of temperature elevation was slower, and there was a faster resolution to baseline temperature levels. In addition, fewer patients who received acetaminophen/paracetamol or ibuprofen reported symptom worsening, and the incidence of severe symptoms was reduced significantly compared with those who received oral placebo after zoledronic acid infusion. Finally, the requirement for rescue medication was reduced by over 50% among patients who received acetaminophen/paracetamol or ibuprofen compared with those who received oral placebo.

Table 3 Most frequent adverse events occurring in ≥5% of patients in any treatment group (safety population)

Adverse event, *n* (%)	Zoledronic acid 5 mg			Placebo+placebo (*n*=72)
	+ acetaminophen/paracetamol (*n*=133)	+ ibuprofen (*n*=136)	+ placebo (*n*=140)	
Headache	21 (15.8)	22 (16.2)	44 (31.4)	8 (11.1)
Pyrexia	13 (9.8)	18 (13.2)	20 (14.3)	3 (4.2)
Myalgia	12 (9.0)	10 (7.4)	17 (12.1)	2 (2.8)
Arthralgia	15 (11.3)	12 (8.8)	16 (11.4)	1 (1.4)
Nausea	12 (9.0)	7 (5.1)	12 (8.6)	3 (4.2)
Pain	0 (0.0)	9 (6.6)	11 (7.9)	0 (0.0)
Chills	4 (3.0)	6 (4.4)	7 (5.0)	0 (0.0)
Back pain	1 (0.8)	9 (6.6)	6 (4.3)	0 (0.0)
Pain in extremity	7 (5.3)	8 (5.9)	6 (4.3)	1 (1.4)
Fatigue	7 (5.3)	2 (1.5)	5 (3.6)	0 (0.0)

Notably, in this study where symptoms were elicited by categorical questionnaire and VAS, 11.1% of patients in the placebo + placebo group reported headache and 4.2% reported fever as adverse events, and half of this group of patients reported symptoms on the VAS. These observations provide an estimate of the background rate of symptom reporting in the absence of active treatment and demonstrate the high sensitivity but low specificity of these measures. It is possible that solicitation of symptoms by the above methods may have resulted in higher rates of events compared with spontaneous reporting. Moreover, the requirement for patients to take their temperature eight times daily may have increased the reporting of pyrexia.

The exploratory logistic regression analysis of treatment response by age quartiles suggested that younger patients (<65 years) are at a greater risk of body temperature increase than older patients (≥65 years). This result should be interpreted cautiously, however, taking into account the magnitude of the treatment-by-age interaction that is present. Moreover, this study was not designed to assess the effect of antipyretic treatment in subgroups. Given the large proportion of younger patients included in this study—over two thirds were aged <65 years—a greater number of symptoms associated with zoledronic acid infusion may have been reported than would be anticipated in the typical population of patients for which zoledronic acid is likely to be prescribed (postmenopausal women aged ≥65 years).

Incidence rates of the most common AEs (occurring in ≥5% of patients in any treatment group) in the zoledronic acid+placebo group from the current study were similar to those reported in the zoledronic acid arm of the HORIZON Pivotal Fracture Trial, for example pyrexia (14.3% vs. 16.1%, which occurred ≤3 days of infusion) [1]. The exception to these AEs was headache, which was reported more frequently in this study (31.4% vs. 7.1%, which occurred ≤3 days of infusion) than in the HORIZON Pivotal Fracture Trial. Headache was also more frequently reported in the zoledronic acid+acetaminophen/paracetamol group compared with a similar group in the HORIZON Recurrent Fracture Trial (in which paracetamol was administered during and for 72 h after the infusion; 15.8% vs. 7.1%) [2]. Other AEs more frequently observed in the current study compared with the HORIZON Recurrent Fracture Trial included myalgia, pyrexia, and arthralgia. The reasons for the higher incidences of headache and other symptoms in the current trial are unclear, but may relate to the different patient populations involved in the studies or to the earlier use of paracetamol in the HORIZON Recurrent Fracture Trial. The patients enrolled in our study were bisphosphonate naïve, whereas previous use of bisphosphonates was permitted in patients enrolled in the HORIZON Pivotal and Recurrent Fracture Trials [1, 2]. A reduction in the occurrence of acute phase symptoms with subsequent administration of bisphosphonates has been documented in other studies [6].

The ability to reduce the incidence and severity of acute phase symptoms using acetaminophen/paracetamol or ibuprofen is important in order to ensure that any post-treatment effects are kept to a level acceptable to patients. This is an important consideration for patient compliance as those patients who experience acute phase symptoms may be reluctant to continue with treatment despite evidence of a reduction in these symptoms with subsequent administration. Treatment compliance is a known issue in the use of oral bisphosphonates for the treatment of osteoporosis [7].

In conclusion, patients who are bisphosphonate-naïve may experience transient but predictable temperature increases after an IV infusion of zoledronic acid 5 mg. In this study, the temperature increase peaked at day 2 and lasted for about 24 h. Administration of acetaminophen/paracetamol or ibuprofen, beginning 4 h after the start of the infusion, significantly lowered the incidence of temperature

increases, prevented symptom worsening, and reduced the incidence of severe and other symptoms. These findings suggest that the administration of oral acetaminophen/paracetamol or ibuprofen could be considered 4 h post-infusion for patients receiving intravenous zoledronic acid who have not previously been treated with bisphosphonates.

Acknowledgments The authors would like to thank all the patients who participated in the study and the following study investigators—Australia: Philip Clifton-Bligh, Michael Hooper, Bronwyn Stuckey, Peter Nash, Stephen Stranks; Canada: Jeannette Janzen, Jack Kooy, Richard Kremer, Jean-Pascal Ouellet, Brian Zidel, Ben Lasko; Russia: Sergey Mazurenko, Svetlana Rodionova, Valentina Soroskaya, Lidia Benovolenskaya; South Africa: Graham Ellis, Stanley Lipschitz, SL Brown; USA: James Dreyfus, Susan Nattrass, Theodore Rooney, Suzanne Trupin, Thomas Klein

Conflicts of interest JD Wark is employed by the University of Melbourne. He has received consultancy fees, speaker's bureau, contract research, and investigator-initiated research grants from Novartis. He has received industry support from Novartis, Servier, Amgen, Sanofi-Aventis/Procter & Gamble, Eli Lilly, UCB Pharma, Government support from Australian NHMRC, Australian Research Council, and other support from the Gardiner Foundation, Arthritis Australia, Scoliosis Research Society, Cancer Council of Victoria, Curtin University of Technology.

W Bensen is a clinical professor of medicine at St. Joseph's Hospital and McMaster University. He has received consultancy fees, speaker bureau fees, contract research and advisory board fees from Amgen/Wyeth, BMS, Roche, Abbott, UCB, Schering-Plough, Pfizer, Merck, Procter & Gamble, Sanofi-Aventis, Eli Lilly, Servier and Novartis.

C Recknor is employed by United Osteoporosis Centers. He has received speaker's fees from Novartis, Zelos, Roche, GlaxoSmithKline, Amgen, NEGA Medical Center, Embryon, Liposcience, and consulting or advisory fees from Novartis, Takeda, Eli Lilly, Procter & Gamble.

O Ryabitseva is employed by the Russian State Institution of Healthcare. She has received clinical research grants and consulting fees from Novartis. She has also received clinical research grants from Schering-Plough and Roche.

J Chiodo III is an employee of Otsuka America Pharmaceuticals Inc

P Mesenbrink is an employee of Novartis Pharmaceutical Corporation who owns full ADRs, restricted ADRs and tradeable options of Novartis stock.

TJ De Villiers is self-employed in private practice. He has served on advisory boards for Novartis, Servier and Wyeth, has received speaker's honoraria from Novartis, Wyeth, Novo Nordisk and MSD, and has been an investigator in clinical trials sponsored by Novartis, Pfizer, Wyeth, MSD, Eli Lilly and Roche.

Appendix—List of study centers and institutional review board

The following institutional review boards or ethics committees reviewed and approved the study protocol:

Australia: Royal North Shore Hospital, St Leonards, New South Wales; HREC, Sir Charles Gairdner Hospital, Nedlands, Western Australia; Melbourne Health Research Directorate, Melbourne Hospital Parkville Victoria; Royal Brisbane Hospital & Royal Women's Hospital & Health Service District HREC, Herston, Queensland; Research and Ethics Committee, Repatriation General Hospital, Daws Park, South Australia.

Canada: McGill University Health Center; Institutional Review Board Services, Kells Medical Research Group; The Medical Arts Health Research Group, Penticton, British Columbia; Royal Victoria Hospital, Montreal, Quebec; Q&T Research, Sherbrooke, Quebec; Malten Medical Centre, Mississauga, Ontario; Manna Research, Toronto, Ontario.

Russia: Local ethics committee affiliated with Kazan State Medical University, Kazan; Local ethics committee affiliated with Reumatology Center at Regional Hospital #1, Ekaterinburg; Local ethics committee at Medical and Sanitary Unit #122, St. Petersburg; Local ethics committee affiliated with N.N. Priorov Central Research Institute of Traumatology and Orthopedics, Moscow; Independent ethics committee at Tula Regional hospital, Tula; Local ethics committee affiliated with Institute of Rheumatology at Russian Academy of Medical Science, Moscow; Research Center ethics committee at Medical Center of the President of Russian Federation, Moscow.

South Africa: SAMA Research Ethics Committee, Pretoria; Research Ethics Committee, University of Cape International Academic Programmes Office (IAPO), Rondebosch; University of the Witwatersrand Human Research Ethics Committee, Johannesburg;

USA: Quorum Central IRB, Seattle, WA; Mercy Medical Center—Des Moines Institutional Review Committee, Des Moines, IA.

The following is a list of study centers:

Australia: Northern Metabolic Bone Centre, St Leonards, New South Wales; Gordon Private Rooms, Gordon, New South Wales; Keogh Institute for Medical Research, Nedlands, Western Australia; Royal Melbourne Hospital, Parkville, Victoria; Sixth Avenue Specialist Centre, Cotton Tree, Queenslands; Repatriation General Hospital, Daw Park, South Australia.

Canada: Wynn Tech Inc, Hamilton, Ontario; Kells Medical Research Group, Pointe Claire, Quebec; PCT Networks Inc, Penticton, British Columbia; Royal Victoria Hospital, Montreal, Quebec; Q&T Research, Sherbrooke, Quebec; Malten Medical Centre, Mississauga, Ontario; Manna Research, Toronto, Ontario.

Russia: Regional Hospital no 1, Ekaterinburg; Centre of Osteoporosis and Skeleton Metabolic Diseases, St Petersburg; N.N. Priorov Central Research, Institute of Traumatology and Orthopedics, Moscow; Tula Regional Hospital, Tula; Institute of Rheumatology, Russian Academy of Medical Science, Moscow; Outpatient department with the Medical Center of Administration of the President of the Russian Federation, Moscow

South Africa: Medi-Clinic, Cape Town; Helderbery Osteoporosis Clinic, Cape Town; Osteoporosis Clinic, Johannesburg; Donald Gordon Medical Centre, Johannesburg.

USA: Medical Specialists Clinical Research Center, Munster, IN; Puget Sound Osteoporosis Center, Seattle, WA; United Osteoporosis Center, Gainesville, GA; Mercy Arthritic and Osteoporosis Center, Des Moines IA; Women's Health Center, Champaign, IL; Heartland Research, Whichata, KS.

References

1. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 356:1809–1822
2. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S (2007) Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 357:1799–1809
3. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM (2010) Characterization of and risk factors for the acute-phase response after zoledronic acid. J Clin Endocrinol Metab 95:4380–4387
4. Roelofs AJ, Jauhiainen M, Monkkonen H, Rogers MJ, Monkkonen J, Thompson K (2009) Peripheral blood monocytes are responsible for gammadelta T cell activation induced by zoledronic acid through accumulation of IPP/DMAPP. Br J Haematol 144:245–250
5. Hochberg Y (1988) A sharper Bonferroni procedure for multiple tests of significance. Biometrika 75:800–802
6. Strampel W, Emkey R, Civitelli R (2007) Safety considerations with bisphosphonates for the treatment of osteoporosis. Drug Saf 30:755–763
7. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, Silverman S (2006) Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 81:1013–1022