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ORIGINAL ARTICLE

Zoledronic acid efficacy and safety over five years in postmenopausal osteoporosis

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Abstract
Summary In a 5-year study involving 119 postmenopausal women, zoledronic acid 4 mg given once-yearly for 2, 3 or 5 years was well tolerated with no evidence of excessive bone turnover reduction or any safety signals. BMD increased significantly. Bone turnover markers decreased from baseline and were maintained within premenopausal reference ranges.
Introduction After completion of the core study, two consecutive, 2-year, open-label extensions investigated the efficacy and safety of zoledronic acid 4 mg over 5 years in postmenopausal osteoporosis.
Methods In the core study, patients received 1 to 4 mg zoledronic acid or placebo. In the first extension, most patients received 4 mg per year and then patients entered the second extension and received 4 mg per year or calcium only. Patients were divided into three subgroups according to years of active treatment received (2, 3 or 5 years). Changes in BMD and bone turnover markers (bone ALP and CTX-I) were assessed.

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Results All subgroups showed substantial increases in BMD and decreases in bone markers. By the end of the core study, 37.5% of patients revealed a suboptimal reduction (< 30%) of bone ALP levels. After subsequent study drug administration during the extensions, there was no evidence of progressive reduction of bone turnover markers. Furthermore, increased marker levels after treatment discontinuation demonstrates preservation of bone remodelling capacity.

Conclusions This study showed that zoledronic acid 4 mg once-yearly was well tolerated and effective in reducing biomarkers over 5 years. Detailed analysis of bone marker changes, however, suggests that this drug regimen causes insufficient reduction of remodelling activity in one third of patients.

Keywords Bone mineral density · Bone turnover · Osteopenia · Osteoporosis · Zoledronic acid

Introduction

Prolonged treatment with bisphosphonates has been associated with a theoretical risk of excessive reduction of bone turnover, which could potentially cause increased fracture propensity over time. However, 7-year data with risedronate [1] and 10-year data with alendronate [2] have not revealed any increase in fracture risk over time.

Zoledronic acid is a nitrogen-containing bisphosphonate that is currently undergoing clinical trials in patients with osteoporosis and osteopenia. In a recent 1-year, placebo-controlled trial in postmenopausal women with osteoporosis/osteopenia (defined as a low bone mineral density (BMD)), a variety of different zoledronic acid dosing regimens significantly reduced bone resorption markers and increased lumbar spine and femoral neck BMD by 4.3–5.1% and 3.1–3.5%, respectively at 12 months ($P<0.001$ for both) [3]. This study demonstrated that a once-yearly dose of zoledronic acid (4 mg given as a 15 min i.v. infusion) was effective in increasing BMD and reducing bone turnover.

Patients who participated in this 1-year trial had the opportunity to enter two consecutive, 2-year extension studies. The objective of these extension studies was to assess the long-term efficacy and safety of prolonged use of zoledronic acid for a further 4 years.

Methods

Study design

This 5-year trial comprised an initial 1-year, randomized, double-blind, placebo-controlled trial that was followed by two consecutive, open-label, 2-year extension studies. Major inclusion and exclusion criteria for patients who entered the initial 1-year study have been published previously [3]. Only patients who had completed the prior phase of the study were eligible to enter the next phase. All patients provided written informed consent. At all study sites, the protocol was approved by a properly constituted Institutional Review Board/Independent Ethics Committee prior to commencement of the study.

The trial design for the core and two extension phases is shown in Fig. 1. In the 1-year core study, postmenopausal women with osteoporosis/osteopenia (defined as a low BMD at baseline [T-score <−2 at the lumbar spine]) were randomized to receive placebo (saline infusion, n=19) or one of five active treatment regimens involving a total annual dose of 1 mg, 2 mg or 4 mg i.v. zoledronic acid (1-

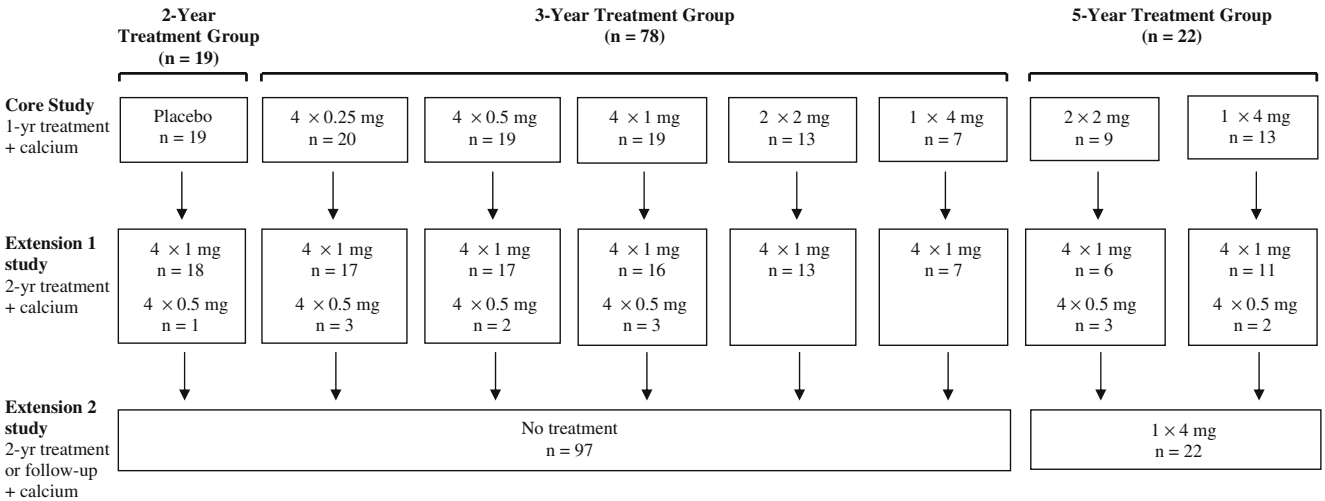

Fig. 1 Design of the core, extension 1, and extension 2 studies. Data represent annual treatment frequency × dose. The patient numbers shown in the figure represent only those patients in the core and extension 1 studies who subsequently entered the extension 2 study

hydroxy-2-imidazol-1-yl-phosphonoethyl bisphosphonic acid, Novartis Pharma AG; 4×0.25 mg [n=20], 4×0.5 mg [n=19], 4×1 mg [n=19], 2×2 mg [n=22], 1×4 mg [n=20]). Blinding was maintained during the core study as infusions were prepared in a central pharmacy. The majority of the patients who entered the first 2-year extension phase (extension 1 study) received 1 mg zoledronic acid every 3 months (total annual dose, 4 mg; n=105). Some patients entering the extension 1 study received 0.5 mg zoledronic acid every 3 months (total annual dose, 2 mg; n=14). This protocol amendment was made in response to an Ethics Committee recommendation at one centre. In the second 2-year extension phase (extension 2 study), patients received a single annual 4 mg dose of zoledronic acid (n=22) or calcium only (n=97). All patients who entered the active treatment arm of the extension 2 study had previously received 4 mg zoledronic acid per year (2×2 mg, 1×4 mg, or 4×1 mg) during the core and extension 1 studies. The design of the 5-year trial resulted in patients receiving active treatment for a total of 2 (n=19), 3 (n=78) or 5 (n=22) years. All patients received 1 g calcium/day *per os* for the duration of the 5-year study. Vitamin D insufficiency was prevented through supplementation, but this was restricted to 1,000 IU daily or less (including vitamin D metabolites).

Efficacy assessments

Efficacy was determined by assessment of BMD using DXA at the lumbar spine, proximal femur, distal radius, and total body. Bone turnover markers (serum bone-specific alkaline phosphatase (bone ALP) and serum type I collagen C-telopeptide (CTX-I)) were assessed as well as patient height. All samples for bone marker analysis were obtained under fasting conditions and samples were drawn prior to the subsequent infusion.

Serum CTX-I assays were performed in batches by Medinet Europe and measured using a serum CrossLaps® One Step ELISA kit (Nordic Bioscience Diagnostics, Herlev, Denmark). Initial bone ALP analyses were performed by Medinet Europe using the Tandem®-MP Ostase® enzyme immunoassay (Hybritech, San Diego, CA, USA). However, this assay became unavailable during the trial, and subsequent assays were performed by Synarc using the Access Ostase assay (Beckman Coulter Inc., Fullerton, CA, USA). Both of these assays use the same monoclonal antibody directed against human bone ALP and so are highly correlated and give comparable results.

DXA measurements were performed using Hologic QDR or Lunar instruments. All scans were performed within ±2 weeks of scheduled visits. Duplicate LS DXA scans with repositioning of the patient between the two scans was performed at the final visit (month 60). A central laboratory (Synarc) was responsible for quality control and quality assurance supervision of the DXA measurements.

Bone ALP and CTX-I were compared with premenopausal normative data from the OFELY study (bone ALP: 6.2–12.8 ng/ml [5–95% percentiles]; serum CTX-I: 0.92–4.33 nmol/L [5–95% percentiles]) [4]. Reductions in fracture risk are discussed in relation to biomarker data from other trials [5, 6] which concluded that a bone ALP reduction by 30% or more may be required for non-vertebral fracture risk reduction.

Safety assessments

Safety assessments included physical examination, regular measurement of vital signs, routine hematology, blood chemistry, and urine assessments, radiographic assessment of the thoracic and lumbar spine, and recording of all adverse events. Hematology, blood chemistry, and urine analyses were performed every 6 months at a central laboratory. Serum creatinine (S_{Cr}) measurements were taken every 6 months and used to calculate creatinine clearance (C_{Cr}) using the female version of the Cockcroft and Gault equation [7].

All radiographs were analyzed using a digitized fracture algorithm and both qualitative and morphometric (quantitative) assessments contributed to the final radiographic analysis.

Statistical analyses

Safety and efficacy data were summarized using the safety population i.e., all patients who entered the extension 2 study and from whom at least one extension 2 study safety or efficacy measurement was obtained. Patients were divided into three follow-up groups according to the number of years of active treatment they had received (2, 3 or 5 years). Only descriptive analyses were performed using observed data because of the limited numbers of patients.

The assessment of safety after 5 years was mainly based on the number and percentage of patients who reported: i) adverse events due to study drug administration (defined as events that occurred within 3 days of drug infusion and that involved pyrexia, myalgia, arthralgia, bone pain, or influenza-like illness); ii) adverse events affecting renal function; iii) renal abnormalities defined as having creatinine clearance < 30 mL/min, increase in serum creatinine from baseline > 44.2 μmol/L [0.5 mg/dL] or urinary protein level > 2+ [dipstick] or ≥250 mg/L; iv) fractures (vertebral and non-vertebral) as assessed by DXA or reported as adverse events.

Descriptive statistics were generated for all efficacy endpoints, i.e., percentage change from core study baseline in BMD and patient height, and absolute and percentage change from core study baseline in bone turnover markers.

Table 1 Patient disposition and baseline demographics

	Years of zoledronic acid treatment[a]			Total n (%)
	2 years n (%)	3 years n (%)	5 years n (%)	
Number of patients				
Entered extension 2 study	19	78	22	119
Completed extension 2 study	18 (94.7)	73 (93.6)	22 (100.0)	113 (95.0)
Discontinued extension 2 study	1 (5.3)	5 (6.4)	0	6 (5.0)
Reason for discontinuation				
Protocol violation	1 (5.3)	1 (1.3)	0	2 (1.7)
Subject withdrew consent	0	2 (2.6)	0	2 (1.7)
Lost to follow-up	0	2 (2.6)	0	2 (1.7)
Baseline demographics[b]				
Age (mean [SD])	65.4 (6.4)	64.3 (6.5)	62.7 (6.7)	64.2 (6.5)
Race				
Caucasian	18 (94.7)	78 (100.0)	22 (100.0)	118 (99.2)
Oriental	1 (5.3)	0	0	1 (0.8)

[a] Total number of years of zoledronic acid treatment during the core, extension 1, and extension 2 studies.
[b] Demographics, at core study baseline, of the safety population in the extension 2 study.

Results

Study population and execution

This 5-year study was completed by 119 postmenopausal women. Six patients (5%) from the 2- and 3-year follow-up groups discontinued prematurely (two protocol violators, two withdrew their consent and two were lost to follow-up). There were no discontinuations for safety reasons. In a deviation from the stated protocol, four of the 22 patients in the 5-year follow-up group received only one infusion during the extension 2 study. Patient disposition for the extension 2 study and demographic data at core study baseline are shown in Table 1.

Efficacy

Bone mineral density

Table 2 shows the mean percentage changes from core study baseline in BMD at the end of the core, extension 1 and extension 2 studies (months 12, 36 and 60 of the trial). All three follow-up groups showed substantial gains in BMD at month 60. These increases were consistent in all

Table 2 Percentage change in bone mineral density in zoledronic acid-treated patients

Bone mineral density	Years of zoledronic acid treatment[a]		
	2 years (n=19)	3 years (n=78)	5 years (n=22)
Lumbar spine			
Baseline-g/cm^2	0.71 (0.05)	0.72 (0.06)	0.71 (0.08)
Month 12-% change from baseline	0.84 (3.09)	5.76 (2.88)	4.60 (3.71)
Month 36[b]-% change from baseline	8.17 (4.46)	9.68 (4.25)	8.66 (3.03)
Month 60[c]-% change from baseline	8.52 (5.80)	9.01 (4.97)	6.40 (6.60)
Proximal femur			
Baseline-g/cm^2	0.71 (0.06)	0.72 (0.09)	0.70 (0.13)
Month 12-% change from baseline	−0.51 (1.79)	2.88 (1.74)	3.57 (3.73)
Month 36[b]-% change from baseline	4.69 (2.81)	4.99 (2.62)	5.81 (5.15)
Month 60[c]-% change from baseline	5.50 (3.70)	4.92 (4.04)	5.16 (4.53)
Distal radius			
Baseline-g/cm^2	0.40 (0.05)	0.42 (0.06)	0.43 (0.06)
Month 12-% change from baseline	−0.65 (2.87)	0.66 (3.08)	0.05 (2.28)
Month 36[b]-% change from baseline	1.45 (2.72)	2.62 (2.80)	1.93 (2.59)
Month 60[c]-% change from baseline	2.99 (3.57)	2.60 (3.90)	2.15 (3.16)
Total body			
Baseline-g/cm^2	0.85 (0.08)	0.89 (0.09)	0.86 (0.07)
Month 12-% change from baseline	1.75 (6.95)	1.87 (4.12)	2.97 (3.21)
Month 36[b]-% change from baseline	3.83 (8.01)	3.11 (5.66)	3.77 (4.13)
Month 60[c]-% change from baseline	5.05 (8.35)	3.59 (5.43)	4.89 (4.47)

[a] Total number of years of zoledronic acid treatment during the core, extension 1, and extension 2 studies.
[b] End of extension 1 study
[c] End of extension 2 study
Figures are mean (SD)

groups and at all anatomical regions (range of mean percentage increases from core study baseline at month 60 for lumbar spine: 6.4% to 9.0%; proximal femur: 4.9% to 5.5%; distal radius: 2.2% to 3.0%; total body: 3.6% to 5.0%). The BMD increase was of similar magnitude at 36 and 60 months. Thus, the gains achieved at month 36 were well maintained for a further 2 years in all patients. As a result of the small patient numbers, it is not possible to infer any clinically relevant differences in BMD gains between groups.

Bone resorption

Serum CTX-I levels decreased substantially after active treatment in all three follow-up groups (Table 3). Patients in the 2- and 3-year follow-up groups showed median CTX-I changes from core study baseline of −78.0% and −77.5%, respectively, at the end of the active treatment period (month 36). After 2 years without treatment (i.e., by month 60), CTX-I levels showed an upward trend in these two groups (Fig. 2). By the end of the extension 2 study, the 2- and 3-year follow-up groups showed median CTX-I values, which were still −44.8% and −50.3%, respectively, below core study baseline.

In the 5-year follow-up group, CTX-I levels showed median changes from core study baseline of −38.4% to −90.5%. This follow-up group also showed a tendency for mean CTX-I levels to rise, in spite of continued treatment, from month 24 (median value, 0.8 nmol/L; median change from core study baseline, −81.6%) to month 60 (median value, 2.4 nmol/L; median change from core study baseline, −48.5%; Table 3).

In the 4 mg group, the mean CTX-I immediately dropped after the 1st infusion in the core study as reported by Reid et al. [3], and this reduction was maintained by about 50% before the 2nd infusion at 24 months.

Over time, mean CTX-I levels remained within the premenopausal reference range in the 3- and 5-year follow-up groups, and after 12 months in the 2-year follow-up group (Fig. 2). Individual CTX-I levels below the lower limit of the premenopausal reference range were recorded occasionally, but subsequent measurements in these patients were always within the reference range. CTX-I levels that remained below the lower limit of the premenopausal reference range for the duration of the study were not found in any patient.

Table 3 Change from core study baseline in bone turnover marker levels

Years of zoledronic acid treatment[a]	2 years (n=19)			3 years (n=78)			5 years (n=22)		
	Baseline	Absolute change	Percentage change	Baseline	Absolute change	Percentage change	Baseline	Absolute change	Percentage change
CTX-I (nmol/L)	4.6 (3.8, 6.5)			4.8 (3.5, 6.5)			6.0 (3.9, 7.0)		
Month 12[b]		−0.8 (−1.7, −0.1)	−16.2 (−39.5, −2.9)		−2.7 (−4.4, −1.1)	−61.0 (−71.6, −38.9)		−3.8 (−5.4, −2.4)	−64.4 (−72.0, −51.9)
Month 36[c]		−3.5 (−5.3, −2.8)	−78.0 (−87.3, −68.6)		−3.6 (−5.6, −2.5)	−77.5 (−87.6, −64.5)		−3.9 (−5.7, −2.5)	−71.4 (−80.0, −57.1)
Month 60[d]		−2.1 (−3.6, −1.7)	−44.8 (−53.4, −39.2)		−2.5 (−3.6, −1.0)	−50.3 (−61.7, −31.1)		−2.4 (−4.9, −1.9)	−48.5 (−63.2, −32.7)
Bone ALP (μg/L)	13.6 (10.3, 16.8)			15.7 (10.7, 19.3)			15.6 (12.0, 18.4)		
Month 12[b]		0.9 (−1.7, 2.1)	5.4 (−12.6, 20.4)		−7.0 (−10.5, −4.6)	−46.5 (−56.7, −35.8)		−6.3 (−8.4, −3.4)	−37.3 (−46.6, −30.8)
Month 36[c]		−7.2 (−10.0, −5.0)	−48.3 (−59.2, −37.5)		−7.2 (−11.3, −4.3)	−47.3 (−59.3, −36.0)		−7.0 (−9.8, −4.6)	−46.7 (−54.7 −42.7)
Month 60[d]		−5.4 (−7.5, −3.2)	−33.5 (−45.6, −28.0)		−5.0 (−7.9, −2.2)	−32.5 (−44.8, −19.0)		−4.7 (−7.3, −3.4)	−36.6 (−42.7, −27.0)

[a] Total number of years of zoledronic acid treatment during the core, extension 1, and extension 2 studies.
[b] End of core study
[c] End of extension 1 study
[d] End of extension 2 study
Figures are median (interquartile range)

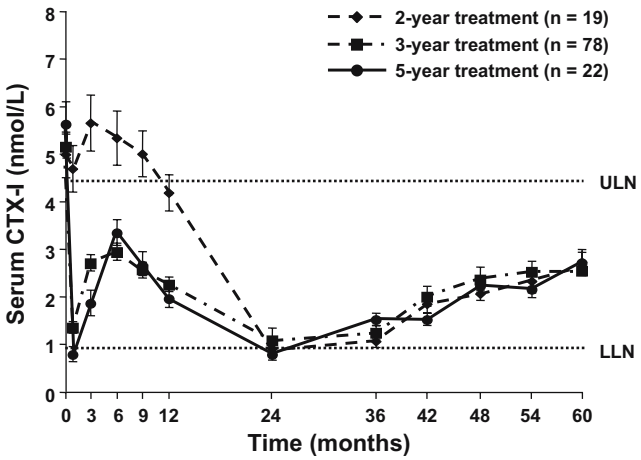

Fig. 2 Mean serum levels of CTX-I from core study baseline to month 60. LLN, lower limit of normal premenopausal reference range (5–95% percentiles); ULN, upper limit of normal premenopausal reference range (5–95% percentiles) [4]

Bone formation

Bone ALP levels decreased substantially after active treatment in all three follow-up groups (Table 3), but levels remained within the premenopausal reference range in the majority of women (Fig. 3). Patients in the 2- and 3-year follow-up groups showed median bone ALP changes from core study baseline of −48.3% and −47.3%, respectively, at the end of their active treatment period (month 36) and the decrease was maximal at 57.7% (at month 24). After two years without treatment (i.e., by month 60), the degree of bone formation reduction had become less marked (median changes from core study baseline of −33.5% and −32.5%, respectively).

In the core study, analysis of bone ALP reduction in the 1×4 mg treatment group showed a nadir at 6 months and then an upward trend was observed between 6 and 12 months (Fig. 3). The analysis of individual values revealed that 37.5% of patients failed to reach the threshold of 30% suppression of bone ALP at month 12. In the 5-year follow-up of this treatment group, bone ALP showed median changes between −37.3% and −57.7% from core study baseline. This group also showed a tendency for mean bone ALP levels to rise (Fig. 3), in spite of continued treatment, from month 24 to month 60 (median change from −57.7% to −36.6%) (Table 3).

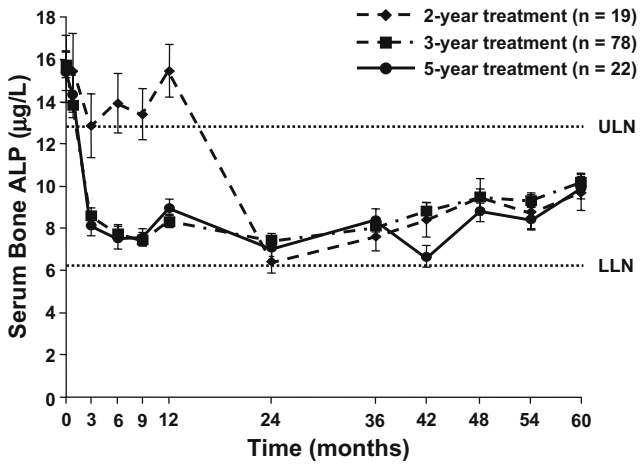

Fig. 3 Mean serum levels of bone ALP from core study baseline to month 60. LLN, lower limit of normal premenopausal reference range (5–95% percentiles); ULN, upper limit of normal premenopausal reference range (5–95% percentiles) [4]

Patient height

Mean patient height decreased slightly in all three follow-up groups at month 60. The mean height loss from core study baseline was 0.37 cm in the 5-year follow-up group, 0.25 cm in the 3-year follow-up group and 0.48 cm in the 2-year follow-up group.

Fractures

Although this study did not aim to assess fracture incidence, fracture events were captured. A total of six patients (5.0%) experienced fractures during the extension 2 study (one vertebral in the 3-year follow-up group; five non-vertebral [three in the 3-year follow-up group and two in the 5-year follow-up group]). Of the non-vertebral fractures, three were located on the foot, one in the ankle, and one in the radius. No fracture event, vertebral or non-vertebral, was reported for the 2-year follow-up group.

Safety

Clinical adverse events which occurred in 5% or more of patients reported during the extension 2 study are listed in Table 4. The most frequent events were arthralgia,

Table 4 Most frequent (≥5%) clinical adverse events occurring in the extension 2 study (safety population)

Adverse event	Years of zoledronic acid treatment[a]		
	2 years (n=19)	3 years (n=78)	5 years (n=22)
Arthralgia	0	6 (7.7)	4 (18.2)
Hypertension NOS	1 (5.3)	8 (10.3)	3 (13.6)
Back pain	4 (21.1)	4 (5.1)	3 (13.6)
Nasopharyngitis	1 (5.3)	4 (5.1)	3 (13.6)
Osteoarthritis NOS	2 (10.5)	6 (7.7)	2 (9.1)
Fall	1 (5.3)	4 (5.1)	2 (9.1)
Bronchitis NOS	0	6 (7.7)	1 (4.5)
Pain in extremity	1 (5.3)	4 (5.1)	1 (4.5)

[a] Total number of years of zoledronic acid treatment during the core, extension 1, and extension 2 studies.

NOS, not otherwise specified

Figures represent n (%)

hypertension, back pain, nasopharyngitis, osteoarthritis, falls, bronchitis and pain in an extremity. A total of eight patients (6.7%) experienced serious adverse events. Of the 15 events reported by those patients, the most frequent were cardiovascular (7 events), two were back injuries, and there was one incidence of osteoarthritis; however, none of these events were considered to be related to the study drug.

Six patients (5.0%) experienced protocol-defined renal abnormalities and four patients (3.4%) experienced a renal adverse event. Six patients (5.0%) suffered a fracture, no cases of osteonecrosis of the jaw were reported and no adverse event led to discontinuation of the study medication.

An adverse event due to study drug administration was reported in one patient (hip arthralgia in a patient in the 5-year follow-up group). This adverse event was of mild severity; it started on the day of the first study drug infusion in the extension 2 study and lasted for approximately 13 months. Although this event occurred within 3 days of drug administration the investigator did not consider this event to be related to the study medication.

Renal function

Adverse events associated with deterioration of renal function were experienced by four (3.4%) patients, three events were renal impairment (reported from the same site) and one was hyperuricaemia. Only one of these patients' investigators suspected that the adverse event was related to the study medication. Two patients were from the 5-year follow-up group and included the patient with hyperuricemia and there was one patient from each of the 2 and 3-year follow-up groups.

A total of six patients (5.0%) experienced protocol-defined renal abnormalities during the extension 2 study. One patient at month 42 experienced an increase in S_{CR} that corresponded to a decrease in C_{CR}; however, these values were not consistent when retested. The remaining five patients reported urinary protein levels ≥ 250 mg/L. In two patients, both in the 5-year follow-up group, proteinuria was present at baseline and intermittently throughout the 5-year study. The other cases were not considered clinically significant by the study investigator.

Discussion

This study shows that i.v. zoledronic acid, when used in a variety of dosing regimens, increases BMD and reduces bone turnover in women with postmenopausal osteoporosis and osteopenia. The long duration of this study allows trends to be identified and inferences made regarding the degree of reduction in bone remodelling achieved by zoledronic acid, the suitability of 4 mg as a total annual dose in this patient population and the long-term safety of zoledronic acid.

Zoledronic acid treatment allowed the majority of the study population to achieve bone turnover marker levels that were in the lower half of the reference range for healthy premenopausal women [4]. Although transient decreases in resorption marker below the normal premenopausal range were recorded in a few patients, no patient showed sustained reduction. Secondly, even among the patients who received 5 years of active treatment, zoledronic acid did not cause a cumulative reduction of bone turnover with each new dose. In fact, there was a progressive increase in serum bone ALP and CTX-I levels during the extension 2 study in all follow-up groups, including the 5-year follow-up group. This slight upward trend in bone turnover marker levels in the 5-year follow-up group suggests that the bone retained remodeling capacity, even during continuous treatment.

Furthermore, the reductions in bone ALP elicited by 5 years of treatment with zoledronic acid in the current study (4 mg annual dose) are smaller than those reported after 10 years of treatment with alendronate (10 mg/day) [2]. Patients who received 10 years of continuous treatment with alendronate showed a nadir at year 4 (mean reduction > 60%) compared to year 2 in this study. After 10 years of alendronate treatment, bone ALP was reduced by an average of approximately 50% (absolute median value, 10.1 μg/mL) [2], compared to a reduction of 36.6% after a 5-year treatment with zoledronic acid in this study.

In patients who received a single 4 mg dose of zoledronic acid in the core study, mean bone ALP levels increased towards the end of the 12-month study, from a nadir at 6 months [3].

Harris et al. [5] reported that risedronate patients with a 33% reduction in bone ALP achieved a 39% reduction of new non-vertebral fractures over 3 years. On the other hand, by analyzing the relationship between bone marker changes and fracture reduction, Bauer et al. [6] suggested that a reduction in bone ALP by at least 30% was necessary to lower the risk of non-spine fractures in alendronate-treated women. In the core study, about 37% of patients treated with zoledronic acid 4 mg did not achieve a 30% reduction in bone ALP after 1 year. Moreover, in the present study, mean bone ALP and CTX-I levels increased progressively from month 24 onwards in patients treated for up to 5 years.

All the three treatment subgroups displayed increasing trends in CTX-I after the 24-month timepoint with the 5-year subgroup showed a lesser upward trend than the 2 and 3 year treatment groups. Due to the small group size, however, the differences were not significant. This is further corroborated by the large error bars around the data points. In previous trials using bisphosphonates, which

were underdosed resulting in lack of antifracture efficacy (e.g., early ibandronate study, tiludronate study), an upward trend in biomarkers was noticeable, suggesting insufficient reduction of bone turnover to keep stable reduction of remodeling activity [8, 9]. This same mechanism could also play a role in this trial. Future analyses of our results obtained with the higher 5 mg dose in the ongoing 3-year extension to our pivotal study may substantiate or negate this notion.

The adverse event data collected during this study show that zoledronic acid is well tolerated in long-term use. None of the serious adverse events reported were attributed to the study drug and of the non-serious adverse events reported, only one was attributed to the study drug and this was mild in severity. None of the events led to discontinuation of the study medication or discontinuation of the study.

In particular, no renal safety signals were detected. Adverse events associated with deterioration of renal function were reported in 3.4% of patients and there were a total of 5.0% of patients with a renal abnormality. However, in one of these patients, repetition of the test by a local laboratory yielded a normal result. Moreover, there was no apparent temporal relationship between the last infusion of zoledronic acid and the timing of the abnormal test result. For example, in the seven patients in whom the recorded renal adverse event did not appear to be associated with an ongoing problem at baseline, a period of 10–15 months elapsed between the recording of the renal adverse event and the patient's last infusion. Since serum creatinine levels were measured every 6 months in the extension 2 study, earlier identification of the abnormalities would have been expected if the abnormal renal test results obtained in these patients had been associated with zoledronic acid administration.

This study has several limitations. The design of this trial (small treatment groups, multiple treatment regimens, open-label design, and lack of randomization in extension 1 and 2 studies) limits the strength of the conclusions that can be drawn.

In conclusion, this study shows that when administered at intervals of 3 to 12 months, zoledronic acid causes sustained BMD increases and reduces bone turnover in postmenopausal women with low BMD. There was no evidence of sustained reduction in bone turnover below the lower limit for premenopausal women. However, changes in bone markers in this study suggest that an annual dose of 4 mg zoledronic acid may be suboptimal in a significant fraction of patients.

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