Zoledronic acid for the treatment and prevention of primary and secondary osteoporosis

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Abstract: There is increasing interest in therapies that can be administered less frequently and/or avoid gastrointestinal irritation. The efficacy of once-yearly zoledronic acid (5 mg) in the treatment and prevention of osteoporosis has been evaluated in different patient populations. In the 3-year HORIZON-Pivotal Fracture Trial in postmenopausal women with osteoporosis, zoledronic acid reduced the risk of vertebral and hip fracture by 70% and 41%, respectively, *versus* placebo. The efficacy of zoledronic acid in preventing subsequent fracture in patients with a hip fracture was evaluated in the HORIZON-Recurrent Fracture Trial. New vertebral and nonvertebral fractures were significantly reduced by treatment initiated within 90 days of incident hip fracture, without evidence of delayed fracture healing. Data from a 1-year study show that a single zoledronic acid 5-mg infusion is superior to oral risedronate 5 mg/day for treatment and prevention of glucocorticoid-induced osteoporosis. Increases in bone mineral density and decreases in bone turnover markers were significantly greater with zoledronic acid than with risedronate. Two different treatment regimens of zoledronic acid were found to be more effective than placebo for prevention of bone loss in postmenopausal women and reducing markers of bone turnover after 2 years.

In conclusion, zoledronic acid 5 mg once-yearly infusion has demonstrated marked efficacy in the treatment and prevention of primary and secondary osteoporosis, with a combination of fracture risk reduction and prevention of bone loss at key sites. It is the only agent shown to reduce the incidence of fracture and mortality in patients with a previous low-trauma hip fracture.

Keywords: bone mineral density, glucocorticoid-induced osteoporosis, hip fractures, osteopenia, osteoporosis, postmenopausal, zoledronic acid

Introduction

Fractures occurring as a result of primary osteoporosis are an important cause of disability among postmenopausal women [Robbins *et al.* 2007], a sector of the population that is increasing in line with the aging of populations not only in the Western world, but also in Asia and Latin America. Furthermore, the prevalence of secondary osteoporosis is increasing, with the widespread clinical use of glucocorticoids for a variety of disorders, including autoimmune, pulmonary, and gastrointestinal diseases, malignancies, and for immunosuppression in the treatment of patients receiving organ transplants. Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary

osteoporosis, and fractures have been reported in 30–50% of patients receiving chronic glucocorticoid therapy [Mazziotti *et al.* 2007].

Bisphosphonate treatment leads to inhibition of osteoclast-mediated bone resorption and subsequent reduction in vertebral and nonvertebral fracture risk. As a result, the bisphosphonates have become widely accepted as effective, well-tolerated treatments for postmenopausal osteoporosis and GIO. The available bisphosphonates fall into two groups [Suzuki *et al.* 2006]: non-nitrogen containing and nitrogen containing. The less-potent non-nitrogen-containing bisphosphonates (clodronate and etidronate) act by being incorporated into modified ATP, thereby

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blocking the energy supply to osteoclasts and triggering apoptotic cell death. The potent nitrogen-containing bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid) inactivate osteoclasts, by disrupting key cellular functions mediated by small GTPase signaling proteins. The potency of nitrogen-containing bisphosphonates is related to their ability to inhibit the enzyme farnesyl diphosphate synthase, with zoledronic acid showing the greatest potency and alendronate the lowest (zoledronic acid > risedronate > ibandronate > alendronate) [Nancollas *et al.* 2006].

As with any chronic condition, patient compliance and persistence with therapy are important factors in clinical efficacy [Silverman, 2006; Conte and Guarneri, 2004], and bisphosphonate treatment is no exception. Treatment of osteoporosis is complicated by the asymptomatic nature of this disease and the lack of options for patient self monitoring [Boonen *et al.* 2008c]. Moreover, poor compliance with oral dosing of bisphosphonates is further complicated by the need for pre- and postdose fasting, and posture requirements (patients taking oral bisphosphonates should not lie down for 30 minutes [60 minutes for ibandronate] after taking the tablet) [Boonen *et al.* 2008c]. Importantly, failure to adhere to daily oral bisphosphonate therapy has been implicated in smaller increases in bone density and higher fracture rates [Siris *et al.* 2006; Yood *et al.* 2003]. Although it might be expected that less-frequent dosing might improve compliance, the introduction of once-weekly oral dosing for alendronate and risedronate has had insufficient impact [Huybrechts *et al.* 2006; Lo *et al.* 2006; Cramer *et al.* 2005]. While medication possession ratios are improved with less-frequent dosing during the first year of therapy (69.2% *versus* 57.6% with once-weekly and once-daily dosing, respectively), compliance remains suboptimal. Even with weekly regimens, intermittent use is common, with 49.6% of women experiencing 60-day prescription gaps during the first year of therapy [Lo *et al.* 2006]. Overall, after 2 years of therapy, compliance levels appear to stabilize at around 40% with oral regimens [Siris *et al.* 2006].

Issues relating to compliance and persistence have fuelled a move to highly potent bisphosphonates that have a pharmacodynamic profile compatible with infrequent intravenous (iv) dosing, such as quarterly dosing with ibandronate and yearly dosing with zoledronic acid. In particular,

zoledronic acid achieves therapeutic activity at micromolar concentrations [Conte and Guarneri, 2004]. Compared with other bisphosphonates, it has the highest kinetic binding affinity, with rapid uptake, lower desorption, higher reattachment after release from bone and lower diffusion within bone [Boonen *et al.* 2008c]. After dosing, a fraction of the zoledronic acid is reversibly taken up by the skeleton, and elimination of drug is mainly by renal excretion [Weiss *et al.* 2008]. Disposition of the drug in blood and noncalcified tissue is governed by extensive uptake into and slow release from bone. Together, these characteristics allow zoledronic acid to achieve prolonged therapeutic concentrations when given as a single annual infusion. A dose-finding study, for example, showed that a 4-mg infusion was as effective as more frequent administration in improving bone density and reducing bone resorption [Reid *et al.* 2002]. Furthermore, onset of activity with zoledronic acid is rapid. In a 24-week trial in postmenopausal women with low bone mineral density (BMD), a single 5-mg zoledronic acid infusion reduced bone resorption markers more rapidly than weekly oral alendronate (70 mg) [Saag *et al.* 2007a]. Importantly, once-yearly dosing with zoledronic acid offers a treatment option that provides greater convenience for patients and ensures treatment adherence.

This review presents the current efficacy and safety data for zoledronic acid in treatment of primary and secondary osteoporosis and prevention of fractures.

Postmenopausal osteoporosis

The ability of an annual administration of zoledronic acid (5 mg) to reduce the risk of vertebral, hip and other types of fracture has been demonstrated in a large, randomized, double-blind, placebo-controlled trial: the Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly (HORIZON) Pivotal Fracture Trial (PFT) [Black *et al.* 2007]. In this 3-year study, 3889 patients (mean age 73 years) were randomly assigned to receive a single 15-minute infusion of zoledronic acid (5 mg) at baseline, 12 months and 24 months, and 3876 were assigned to receive placebo. There were two strata, one with osteoporosis-treatment-naïve patients and, uniquely for a bisphosphonate clinical trial, one in which concomitant therapy with 'usual' osteoporosis therapies (e.g. hormone-replacement therapy, tibolone, selective estrogen receptor modulators, and calcitonin) were allowed. Patients were

followed for 36 months. There were two coprimary endpoints, including new vertebral fracture (in patients not taking concomitant osteoporosis medications) and hip fracture (in all patients). Secondary endpoints included changes in BMD and bone turnover markers in the serum (C-terminal telopeptide [β -CTX], bone-specific alkaline phosphatase, N-terminal propeptide), as well as safety outcomes. Results from HORIZON-PFT showed that treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% during the 3-year study period compared with placebo [Black *et al.* 2007]. Fracture rates were 3.3% in patients receiving zoledronic acid *versus* 10.9% in the placebo group (relative risk [RR], 0.30; 95% confidence interval [CI], 0.24–0.38) (Figure 1). Zoledronic acid also reduced the risk of hip fracture by 41%, with fracture rates of 1.4% and 2.5% in the zoledronic acid and placebo groups, respectively (hazard ratio [HR], 0.59; 95% CI, 0.42–0.83) (Figure 1). In this study, all of the secondary endpoints were met; for example, nonvertebral fractures, clinical fractures and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively ($p < 0.001$ for all comparisons) (Figure 1). Notably, the effect of zoledronic acid was

independent of concomitant administration of other osteoporosis therapies, including hormone-replacement therapy, selective oestrogen-receptor modulators, calcitonin and tibolone [Reid *et al.* 2008]. The effect of zoledronic acid on nonvertebral fracture was evaluated further in a *post-hoc* analysis of the so-called ‘super six’ fracture sites (wrist, hip, pelvis, humerus, leg and clavicle) [Black *et al.* 2009]. The incidence of nonvertebral ‘super six’ fractures at 3 years in the zoledronic acid and placebo groups were 5.7% and 8.6%, respectively, equivalent to a 34% reduction in fracture risk (HR, 0.66; 95% CI, 0.55–0.78; $p < 0.0001$).

In HORIZON-PFT, zoledronic acid was also associated with a significant increase in BMD and a decrease in bone turnover markers [Black *et al.* 2007]. In the zoledronic-acid group, BMD increased significantly at the total hip (6.02%; 95% CI, 5.77–6.28), lumbar spine (6.71%; 95% CI, 5.69–7.74), and femoral neck (5.06%; 95% CI, 4.76–5.36) compared with placebo ($p < 0.001$ for all comparisons). All three biochemical markers of bone turnover decreased significantly in patients in the zoledronic acid group compared with those in the placebo group.

*In patients not taking concomitant osteoporosis medications (Stratum I); ** $p < 0.001$; *** $p < 0.002$.
HR, hazard ratio; RR, relative risk

Figure 1. Relative risk of fracture incidence in a 3-year study of once-yearly zoledronic acid (5 mg) *versus* placebo in women with postmenopausal osteoporosis (HORIZON-PFT) [Black *et al.* 2007].

At 12 months, levels of serum β -CTx, bone-specific alkaline phosphatase and N-terminal propeptide were 59% (95% CI, 55–63), 30% (95% CI, 27–32) and 58% (95% CI, 55–60) lower, respectively, in the zoledronic acid group ($p < 0.001$ for all comparisons). Further analysis of 147 bone samples using microcomputed tomography (μ CT) and histomorphometry confirmed the decrease of bone turnover produced by zoledronic acid [Recker *et al.* 2008]. Zoledronic acid induced a 63% median reduction of activation frequency ($p < 0.0001$), with reduced mineralizing surface and volume referent bone formation rate *versus* placebo, indicating reduced bone turnover. μ CT analysis also revealed that patients in the zoledronic-acid group had higher median trabecular bone volume ($p = 0.020$), higher trabecular numbers ($p = 0.008$) and decreased trabecular separation ($p = 0.011$) than those receiving placebo, indicating better preservation of trabecular structure. In a subgroup analysis of the HORIZON-PFT, reduction in fracture risk and treatment-by-factor interactions were evaluated across 14 determinants of response. Of these, nine were preplanned subgroups (age, BMD T-score and baseline vertebral fracture status, race, weight/body mass index, geographical region, prior bisphosphonate use, creatinine clearance, and baseline use of osteoporosis medications) and five were *post hoc* (hip BMD, smoking, height loss since age 25 years, fall in past 12 months, and daily activity). The analysis revealed that zoledronic acid significantly reduced the risk of vertebral fractures regardless of age group, creatinine clearance status and BMI (all $p < 0.0001$). Zoledronic acid had greater effects on vertebral fracture risk in younger women (adjusted odds ratio [OR], 0.18 [95% CI, 0.10–0.31] in the <70 years age group *versus* 0.37 [95% CI, 0.27–0.52] in ≥ 75 years age group), overweight women (OR, 0.22 [95% CI, 0.15–0.31] in women with body mass index (BMI) ≥ 25 kg/m² *versus* 0.38 [95% CI, 0.27–0.53] in those with BMI 19–24.9 kg/m²), and women with better baseline renal function (OR, 0.21 [95% CI, 0.14–0.29] in women with creatinine clearance ≥ 60 mL/min *versus* 0.35 [95% CI, 0.25–0.48] in <60 mL/min group). There were significant treatment-by-factor interactions ($p \leq 0.05$) with zoledronic acid with age, creatinine clearance and BMI [Eastell *et al.* 2009], indicating that zoledronic acid-treated subjects who were younger, more overweight, or with better creatinine clearance were significantly

less likely to experience a vertebral fracture than placebo-treated subjects.

In patients previously receiving oral bisphosphonate therapy, studies have shown that they can be safely switched to annual zoledronic acid without compromising therapeutic efficacy. In 225 postmenopausal women with low BMD on alendronate who were randomized to oral weekly alendronate (70 mg) continuation ($n = 112$) or switched to zoledronic acid ($n = 113$), BMD values remained stable during the 12-month study in both groups, demonstrating maintenance of bone mass [McClung *et al.* 2007]. Mean bone turnover marker levels in patients switched to zoledronic acid were reduced from baseline after 3 months although, in contrast to the HORIZON-PFT, levels returned to baseline after 6 months, and increased thereafter, yet remained within the premenopausal range. The benefits of zoledronic acid on vertebral fractures in patients who had previously received other bisphosphonates compared with those who were bisphosphonate naïve were evaluated in a *post-hoc* analysis of the HORIZON-PFT [Lippuner *et al.* 2008]. Among bisphosphonate-naïve patients, the incidence of vertebral fracture over 3 years was 10.7% with placebo and 3.2% with zoledronic acid (RR, 0.29; 95% CI, 0.23–0.38; $p < 0.0001$). In patients with previous bisphosphonate experience, 12.1% of those receiving placebo had a vertebral fracture compared with 4.2% of those receiving zoledronic acid (RR, 0.35; 95% CI, 0.19–0.62; $p < 0.0001$).

Recent hip fracture patients

The previous occurrence of a hip fracture is an important risk factor for future osteoporotic fractures [Ryg, 2009; Colón-Emeric *et al.* 2003]. Zoledronic acid is the only osteoporosis therapy that has been evaluated to assess its efficacy in preventing new fractures following an incident hip fracture in the HORIZON-Recurrent Fracture Trial (RFT) [Lyles *et al.* 2007]. Men and women aged ≥ 50 years who had experienced a low-trauma hip fracture were randomized to an annual infusion of zoledronic acid (5 mg) or placebo, within 90 days of their original fracture. Overall, the rates of any new clinical fracture were just 8.6% in the zoledronic acid group, compared with 13.9% in the placebo group, demonstrating a 35% reduction in risk with zoledronic acid ($p = 0.001$) [Figure 2]. The respective rates of a new clinical vertebral fracture were 1.7% and 3.8% ($p = 0.02$), while those for new

Figure 2. Relative risk of new fracture occurrence in patients receiving once-yearly zoledronic acid (5 mg) or placebo within 90 days of a low-trauma hip fracture (HORIZON-RFT) [Lyles *et al.* 2007].

nonvertebral fractures were 7.6% and 10.7% ($p=0.03$) [Figure 2] [Lyles *et al.* 2007]. When the secondary efficacy variables of total hip and femoral neck BMD were evaluated by gender, zoledronic acid was shown to significantly increase total hip BMD (Table 1) and femoral neck BMD at 36 months in men as well as in women [European Medicines Agency, 2008]. There was no evidence for delayed healing of the original fracture in either of the treatment groups. Interestingly, 101 of 1054 patients in the zoledronic acid group (9.6%) died compared with 141 of 1057 patients in the placebo group (13.3%), demonstrating a 28% reduction in risk of deaths from any cause in the zoledronic acid group ($p=0.01$). The underlying cause of the difference in mortality between the two treatment arms is unknown [Lyles *et al.* 2007].

A prespecified secondary analysis and subsequent *post-hoc* analyses of HORIZON-RFT data showed that timing of therapy-influenced efficacy and suggested that 2 or more weeks after fracture repair is the optimal time for zoledronic acid infusion [Eriksen *et al.* 2009]. In total, 46% of patients were dosed within 6 weeks of surgical

hip fracture repair, and 54% were dosed after. In all, patients dosed later than 6 weeks demonstrated greater increases in total hip and femoral neck BMD at 12 months than those dosed within 6 weeks. When an analysis was performed based on infusion time divided into 2 week intervals, at 12 months, there were significant increases in total hip BMD at all timepoints except for in those patients dosed at less than 2 weeks. There was also a consistent reduction in clinical fractures at 12 months regardless of timing of infusion, except for in the less-than-2-weeks subgroup. Zoledronic acid had no adverse effects on fracture healing, regardless of the timing of infusion. Based on these findings, it is recommended to give the zoledronic acid infusion 2 or more weeks after hip fracture repair in patients with a recent low-trauma hip fracture [Novartis Europharm Limited, 2008].

The benefits of zoledronic acid in elderly individuals were confirmed in an analysis of pooled data from HORIZON-PFT and HORIZON-RFT showing that the cohort of women aged over 75 years receiving zoledronic acid ($n=1961$) had a reduced incidence of new

Table 1. Between-treatment percentage change in total hip bone mineral density (BMD) in patients receiving once-yearly zoledronic acid (5 mg) or placebo following a low-trauma hip fracture (HORIZON-RFT) [European Medicines Agency, 2008].

Time point Gender	Treatment	n	LS mean*	LS mean difference* [95% CI*]	p value*
Month 12					
Male	Zoledronic acid	154	1.97	2.01 [0.67, 3.35]	0.0032
	Placebo	169	−0.03		
Female	Zoledronic acid	527	2.77	4.15 [3.40, 4.89]	<0.0001
	Placebo	514	−1.38		
Month 24					
Male	Zoledronic acid	85	3.59	3.81 [1.38, 6.23]	0.0021
	Placebo	100	−0.22		
Female	Zoledronic acid	320	4.95	5.88 [4.56, 7.20]	<0.0001
	Placebo	300	−0.93		
Month 36					
Male	Zoledronic acid	33	7.27	7.06 [3.12, 10.99]	0.0005
	Placebo	31	0.22		
Female	Zoledronic acid	95	4.87	6.11 [3.82, 8.39]	<0.0001
	Placebo	93	−1.24		

CI, confidence intervals; LS mean, least squares mean of the percent change from baseline; n, number of patients with evaluable measurements at both baseline and post-baseline visit as determined by efficacy window. *LS mean, LS mean difference, 95% CI and p values were calculated using a contrast from a three-way ANOVA model with treatment, region, sex and treatment-by-sex interaction in the model. Percentage change from baseline, 100x (post-baseline value − baseline value)/baseline value.

fractures compared with those receiving placebo (n=1926) [Boonen *et al.* 2009]. New clinical fracture incidence over 1 year was 4.1% with zoledronic acid *versus* 5.7% with placebo (HR, 0.72; 95% CI, 0.54–0.96; $p=0.026$). The 3-year incidence of new clinical fractures was 10.8% and 16.6%, respectively (HR, 0.65; 95% CI, 0.54–0.78). Significant reductions in 3-year risk of clinical vertebral ($p<0.0001$) and nonvertebral fractures ($p=0.0025$) were also observed in elderly patients receiving zoledronic acid.

Prevention of bone loss

In addition to the fracture outcomes studies, zoledronic acid has also been evaluated to assess the role of preventing bone loss in postmenopausal women with low bone mass (or osteopenia). In a 2-year, randomized, double-blind, placebo-controlled trial, a single infusion of zoledronic acid (5 mg) given once yearly (n=198) or once in 2 years (n=181) was compared with placebo (n=202) for prevention of bone loss in postmenopausal women aged 45 years or older with osteopenia [McClung *et al.* 2009]. The primary endpoint of the study was the percentage change from baseline to month 24 in lumbar spine BMD. Secondary efficacy endpoints included the percentage change in lumbar spine BMD at month 12 and in total hip, femoral neck,

trochanter, and distal radius BMD at months 12 and 24, and changes in markers of bone turnover at months 1, 3, 6, 9, 12, 15, 18, and 24. After 2 years of treatment, both zoledronic acid regimens were more effective than placebo in improving lumbar spine BMD and improving BMD at all other measured sites (Table 2). Furthermore, superiority of zoledronic acid to placebo in terms of lumbar spine BMD and hip BMD was seen at all timepoints (months 12 and 24) [Figure 3]. Levels of β -CTX, N-terminal propeptide and bone-specific alkaline phosphatase decreased significantly from baseline in both zoledronic acid treatment groups relative to placebo at all timepoints ($p<0.0001$). Following the second infusion, bone turnover marker levels decreased significantly in patients receiving zoledronic acid once in 2 years, but continued to increase slowly within the premenopausal reference range for those receiving once-yearly treatment. During the second year of the study, levels of all three bone turnover markers remained significantly reduced in the once-yearly zoledronic acid group compared with the once-in-2-years zoledronic acid and placebo groups at all timepoints. These data demonstrate that although there are differences in biomarker levels between the zoledronic acid once-yearly and once-in-2-years dosing strategies, there is generally no difference in BMD outcomes. Therefore, in patients

Table 2. Between-treatment percentage change in bone mineral density in postmenopausal women with osteopenia receiving one of two zoledronic acid regimens or placebo for 24 months [McClung *et al.* 2009].

Efficacy variable	ZOL 2x5 mg* n = 198	ZOL 1x5 mg [§] n = 181	Placebo n = 202
Lumbar spine BMD LSM (SE)	5.18 (0.272)	4.42 (0.279)	−1.32 (0.268)
Total hip BMD LSM (SE)	2.91 (0.207)	2.28 (0.216)	−1.45 (0.202)
Femoral neck BMD LSM (SE)	2.20 (0.294)	1.64 (0.308)	−1.35 (0.288)
Trochanter BMD LSM (SE)	4.83 (0.278)	4.16 (0.290)	−1.15 (0.272)
Distal radius BMD LSM (SE)	−0.07 (0.255)	−0.18 (0.266)	−2.39 (0.248)

*ZOL 2x5 mg, zoledronic acid received at randomization and at month 12; [§]ZOL 1x5 mg, zoledronic acid received at randomization and placebo received at Month 12.
n, number of subjects; BMD, bone mineral density; LSM, least squares mean; SE, standard error.

(a) Lumbar spine

(b) Total hip

Figure 3. Percentage change in bone mineral density from baseline in postmenopausal women with osteopenia receiving one of two zoledronic acid regimens or placebo at 12 and 24 months [McClung *et al.* 2009].

with low BMD (osteopenia) but not osteoporosis, it is recommended that a zoledronic acid 5-mg infusion is given once, and the patient followed up over time, with BMD and biomarker (if available) monitoring. Individual clinician judgment should be used to determine whether a second dose is necessary. However, if additional risk factors for osteoporosis are present, patients should be treated annually, as in patients with confirmed osteoporosis.

Glucocorticoid-induced osteoporosis

Bisphosphonate treatment is the current standard of care for GIO [Mok *et al.* 2008; Saag *et al.* 2007b]. Randomized clinical trials have demonstrated superiority of alendronate over the vitamin D3 analog alfacalcidol in the treatment of GIO [De Nijs *et al.* 2006], and risedronate is proven to be effective in both the prevention [Cohen *et al.* 1999] and the treatment [Reid *et al.* 2000] of the condition. Zoledronic acid and risedronate are approved by the US Food and Drug Administration (FDA) both for prevention and treatment of GIO, while alendronate is approved for the treatment of GIO.

In a 1-year randomized, double-blind, double-dummy, non-inferiority trial, the efficacy of intravenous zoledronic acid was compared with that of daily oral risedronate for treatment and prevention of GIO [Reid *et al.* 2009]. At baseline,

833 patients were stratified by gender, and by duration of glucocorticoid therapy, with those receiving treatment for 3 months or less assigned to the 'prevention' category, and those having received more than 3 months of treatment assigned to the 'treatment' category. Patients received a single zoledronic acid (5 mg) infusion or oral risedronate 5 mg/day for 12 months. The primary endpoint was the percentage change from baseline in lumbar spine BMD, and secondary endpoints included BMD at other appendicular sites, changes in bone turnover marker levels, and safety outcomes. Results of the study showed that zoledronic acid was not only noninferior, but also superior to risedronate in increasing lumbar spine BMD both in the prevention (zoledronic acid, 2.6%; risedronate, 0.6%; $p < 0.0001$) and treatment (zoledronic acid, 4.1%; risedronate, 2.7%; $p = 0.0001$) subpopulations at 12 months (Figure 4). Zoledronic acid was also significantly more effective than risedronate at 12 months in increasing femoral neck (treatment: 1.5 *versus* 0.4%, $p = 0.005$; prevention: 1.3 *versus* 0.0%, $p = 0.005$), trochanter (treatment: 2.0 *versus* 0.6%, $p = 0.0005$; prevention: 2.8 *versus* 0.5%, $p < 0.0001$), and total hip (treatment: 1.6 *versus* 0.4%, $p < 0.0001$; prevention: 1.5 *versus* 0.0%, $p < 0.0001$) BMD and reducing bone turnover markers (β -CTX and N-terminal propeptide; both $p < 0.05$ in the prevention and treatment subgroups).

Results are shown for least squares mean and 95% confidence intervals.

* $p = 0.0005$, † $p = 0.0001$, § $p < 0.0001$ for between-treatment comparisons of percentage change in bone mineral density relative to baseline, calculated from a three-way analysis of variance with adjustment for drug group, study region, and sex.

Figure 4. Percentage change over time in bone mineral density at the lumbar spine in patients receiving oral risedronate 5 mg/day or a single zoledronic acid 5 mg infusion for (a) treatment or (b) prevention of glucocorticoid-induced osteoporosis [Reid *et al.* 2009]. Reprinted with permission from *The Lancet*.

Rheumatoid arthritis-related bone loss

The efficacy of zoledronic acid in preventing erosions in bone has also been investigated in patients with rheumatoid arthritis, in whom osteoclast activity is central to the development of bone damage. In a proof-of-concept study, patients receiving methotrexate (7.5–20 mg/week) for early rheumatoid arthritis were randomized to receive either adjuvant zoledronic acid (5 mg) or placebo (given at baseline and week 13) [Jarrett *et al.* 2006]. Results showed that zoledronic acid produced a reduction of 61% in bone erosions in the hand and wrist (assessed by magnetic resonance imaging) *versus* placebo (mean $\pm$ SD: 0.9 ± 1.6 *versus* 2.3 ± 3.1). The mean increase in the number of hand and wrist bones with erosions was significantly lower with zoledronic acid compared with placebo (0.3 ± 0.8 *versus* 1.4 ± 1.8 ; $p = 0.029$).

Hormone-ablative therapy-induced bone loss

Hormone-ablative therapies such as gonadotropin-releasing hormone (GnRH), luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogens, and aromatase inhibitors (AIs) are often used in patients with early-stage breast cancer or high-risk prostate cancer to delay progression or prevent recurrence of the disease. However, these therapies can significantly affect estrogen or testosterone levels, leading to loss of bone mass, and zoledronic acid has again proven useful in these patient populations in preserving skeletal integrity [Brufsky, 2008; Pfeilschifter and Diel, 2000].

In the Austrian Breast and Colorectal Cancer Study Group trial, zoledronic acid was found to be effective in counteracting AI-induced bone loss (AIBL) in 401 premenopausal women with hormone-responsive breast cancer treated with adjuvant endocrine therapy (goserelin plus either anastrozole or tamoxifen). The addition of zoledronic acid (4 mg every 6 months over 3 years) demonstrated inhibition of bone loss in the lumbar spine and trochanter and improvements in lumbar spine T-scores that were significantly greater than goserelin plus anastrozole alone ($p < 0.0001$; Figure 5) [Gnant *et al.* 2007]. Similar results were observed in the Zometa/Femara Adjuvant Synergy Trial (ZFAST), where in 602 postmenopausal women with stage I–IIIa estrogen- and/or progesterone-receptor-positive breast cancer receiving adjuvant letrozole therapy, zoledronic acid 4 mg

given every 6 months appeared to prevent AIBL [Brufsky, 2008].

In men with non-metastatic prostate cancer receiving a GnRH agonist, zoledronic acid 4 mg given once every 3 months for 1 year prevented androgen deprivation-induced bone loss at the hip and lumbar spine. Mean lumbar spine BMD was increased by 5.6% in the zoledronic acid group *versus* a 2.2% decrease in the placebo group ($p < 0.001$). Respective values at other measured sites were: femoral neck, 1.2% *versus* -2.1% ; trochanter, 2.2% *versus* -2.7% ; and total hip, 1.1% *versus* -2.8% ($p < 0.001$ for all) [Smith *et al.* 2003]. In a subsequent trial in men with nonmetastatic prostate cancer treated with a GnRH, zoledronic acid had similar effects on BMD [Michaelson *et al.* 2007].

Safety of intravenous bisphosphonate therapy

Zoledronic acid has been generally well tolerated in clinical trials conducted to date [Reid *et al.* 2009; Black *et al.* 2007; Devogelaer *et al.* 2007;

Figure 5. Premenopausal patients with hormone-responsive breast cancer treated with goserelin and anastrozole (a) without zoledronic acid or (b) with zoledronic acid. Graph shows the proportion of patients with normal bone mineral density, osteopenia, or osteoporosis in the lumbar spine [Gnant *et al.* 2007]. Reprinted with permission from the *Journal of Clinical Oncology*.

Lyles *et al.* 2007; McClung *et al.* 2007]. The most common adverse events during treatment with zoledronic acid are pyrexia, influenza-like symptoms, myalgia, headache, and arthralgia, usually occurring within 3 days of infusion. These symptoms affect approximately 30% of patients at the first infusion and less than 7% at the second [Black *et al.* 2007]. Furthermore, there is evidence that patients can be switched safely from other bisphosphonates to zoledronic acid [McClung *et al.* 2007]. In patients switched from weekly oral alendronate (70 mg) to zoledronic acid, the overall incidence of adverse events was similar compared with those who continued alendronate (zoledronic acid, 86.7%; alendronate, 80.4%) [McClung *et al.* 2007], although headache occurred more commonly within the first 3 days after infusion with zoledronic acid (12.4%) than with alendronate (6.3%).

The renal safety of zoledronic acid in women with postmenopausal osteoporosis was investigated in a predefined renal safety cohort of HORIZON-PFT [Boonen *et al.* 2008b]. Short-term measurements (before and after each of the three annual infusions) of serum creatinine, estimated creatinine clearance and urinary protein were made in 5035 patients, and annual measurements over 3 years were taken in 7714 patients. Transient pre- to post-infusion rises in serum creatinine were seen in 31 patients receiving zoledronic acid and 10 receiving placebo. The increases resolved within 12 months in all except two patients who had received placebo. The results showed no cumulative renal toxicity with repeated infusions. The analysis also showed that the skeletal response to zoledronic acid was not affected by renal impairment, with histomorphometry, biomarkers of bone turnover, BMD and antifracture efficacy showing similar results in patients with creatinine clearance <60 mL/min compared with those with higher creatinine clearance [Boonen *et al.* 2008a].

'Real-world' postmarketing data show that in the 17 months since approval (as of February 2009), the US FDA's Adverse Event Reporting System (AERS) received 24 evaluable cases of renal impairment and acute renal failure associated with use of zoledronic acid (Reclast®) for osteoporosis in postmenopausal women and men, Paget's disease of bone, and the prevention and treatment of GIO. Fourteen of the 24 patients had underlying medical conditions associated with risk of renal impairment or acute renal

failure, or had been exposed to nephrotoxic drugs, in spite of label warnings regarding the use of zoledronic acid 5 mg in such patients. In 13 of the 24 cases, patients had documented transient increases in serum creatinine (median increase 4 mg/dL) following drug infusion. Many patients improved following iv fluid administration or other supportive care. Three patients required haemodialysis. Seven patients died; four due to acute renal failure, although any association between zoledronic acid use and these deaths was deemed difficult to establish.

Based on postmarketing reports, the Reclast® label was updated in March 2009 to include data on acute renal failure and to reinforce existing warnings, with recommendations to monitor serum creatinine in patients with pre-existing renal compromise or other risk factors, including concomitant nephrotoxic medications or diuretic therapy, before infusion [US Food and Drug Administration (FDA), 2009].

A notable adverse event that has been reported in cancer patients receiving more frequent dosing regimens of iv bisphosphonates is osteonecrosis of the jaw (ONJ). These reports have prompted intense scrutiny in other patient populations receiving bisphosphonates, to establish the incidence of this event in the absence of anticancer agents or corticosteroids [Rizzoli *et al.* 2008]. In HORIZON-PFT and HORIZON-RFT there were no instances of spontaneously reported ONJ in a total of 4929 women who received three (n=3875) or one infusion (n=1054) of zoledronic acid 5 mg [Grbic *et al.* 2008; Lyles *et al.* 2007]. A detailed analysis of safety data from HORIZON-PFT was carried out by an independent, blinded, expert adjudication committee, who assessed all maxillofacial adverse events [Grbic *et al.* 2008]. Their review showed that one patient in each group (zoledronic acid and placebo) had a lesion meeting a conservative ONJ criteria (exposed bone in the maxillofacial area that does not heal within 6 weeks after identification of the lesion). In both cases, the event resolved with appropriate care (antibiotic therapy, debridement or both). Thus, use of stringent diagnostic criteria and expert adjudication found no evidence for an increased risk of ONJ in patients receiving one to three annual infusions of zoledronic acid in a non-oncology population.

In HORIZON-PFT, serious atrial fibrillation occurred more frequently in the zoledronic acid

group (50 patients [1.3%]) than in the placebo group (20 patients [0.5%]; $p < 0.001$) [Black *et al.* 2007]. These findings were not confirmed in the HORIZON-RFT study, which consisted of patients who were older with greater cardiovascular comorbidity, and who were therefore at greater risk for cardiac complications [Lyles *et al.* 2007]. The potential for a mechanistic association between bisphosphonate use and atrial fibrillation was subsequently investigated and published by the FDA, based on data from 19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients who were followed for 6 months to 3 years [US Food and Drug Administration (FDA), 2008]. The FDA concluded that there is no clear association between bisphosphonate use and atrial fibrillation, and advised that “healthcare professionals should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their bisphosphonate medication”.

Patient preference for intravenous bisphosphonate therapy

Intravenous bisphosphonate therapy is generally preferred by patients to more frequently dosed regimens. In a 24-week, randomized, double-blind clinical trial that assessed the onset of action of a single 15-minute infusion of zoledronic acid 5 mg ($n=69$) compared to oral weekly alendronate 70 mg ($n=59$), at the end of the study, patients were asked to respond to four questions to determine their preference for the different treatment modalities [Saag *et al.* 2007a]. While still blinded to therapy, patients were asked which treatment was (1) more convenient, (2) more satisfying, (3) they would be more willing to take for a long period of time,

and (4) was preferred. Overall, 66.4% of the patients who completed the questionnaire ($n=122$) expressed a preference for a once-yearly iv infusion, compared with 19.7% who preferred a once-weekly pill. In total, 13.9% indicated that both treatment modalities were equal (Table 3). Similarly, in a 1-year, randomized, double-blind clinical trial of postmenopausal women with low BMD on alendronate who were randomized to oral weekly alendronate 70 mg continuation ($n=112$) or switched to zoledronic acid ($n=113$), 78.7% of patients preferred a once-yearly i.v. infusion [McClung *et al.* 2007] (Table 3).

Patient preference was also assessed at the end of the 1-year randomized, double-blind, noninferiority trial of intravenous zoledronic acid versus daily oral risedronate for the treatment and prevention of GIO [Reid *et al.* 2009]. Most patients ($n=785/833$) stated a preference and, of these, 81% preferred the intravenous preparation for convenience, and 78% for satisfaction (Table 3).

Conclusions

Oral bisphosphonates are considered the standard of care for most patients initiating therapy for the management of osteoporosis; however, efficacy can be limited by poor patient compliance, both in the short and long term. This disappointing aspect of oral treatment has fuelled the investigation of more convenient and efficacious dosing regimens, most notably once-yearly administration of zoledronic acid, which has a short infusion time (15 minutes) and a favourable pharmacological profile (rapid uptake, low desorption, high reattachment after release from bone and low diffusion within bone).

Table 3. Patient preference for yearly intravenous *versus* weekly oral treatment regimens.

Patient preference questionnaire [% of responders]									
	Once-yearly iv			Once-weekly pill			Both are equal		
	Saag <i>et al.</i> 2007a	McClung <i>et al.</i> 2007	Reid <i>et al.</i> 2009	Saag <i>et al.</i> 2007a	McClung <i>et al.</i> 2007	Reid <i>et al.</i> 2009	Saag <i>et al.</i> 2007a	McClung <i>et al.</i> 2007	Reid <i>et al.</i> 2009
More convenient	66.4	79.2	81.0	15.6	7.2	9.0	18.0	13.6	10.0
More satisfying	59.8	NA	78.0	18.9	NA	8.0	20.5	NA	14.0
Better fits lifestyle	NA	72.4	NA	NA	8.1	NA	NA	19.5	NA
More willing to take for a long time	68.0	71.5	84.0	15.6	9.0	9.0	16.4	19.5	7.0
Overall preference	66.4	78.7	NP	19.7	9.0	NP	13.9	11.8	NP
NA, not applicable; NP, results not presented.									

Large, randomized, double-blind clinical trials have shown that zoledronic acid is the most effective antiresorptive in reducing fracture risk and prevention of subsequent fractures, as well as demonstrating robust efficacy in a number of allied osteoporosis indications. Importantly, patients can be switched safely from alendronate to zoledronic acid with no loss of efficacy, and the majority of patients stated that they preferred once-yearly iv infusion to weekly oral treatment.

In conclusion, zoledronic acid 5 mg once-yearly infusion has demonstrated marked efficacy in the treatment and prevention of primary and secondary osteoporosis across a broad spectrum of patients, with a combination of fracture risk reduction and prevention of bone loss at key sites, persistent efficacy and good compliance. It is the only agent shown to reduce the incidence of fracture and mortality in patients with a previous low-trauma hip fracture. These efficacy benefits are balanced with a generally well tolerated and manageable safety profile.

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Conflict of interest statement

René Rizzoli has served in the speaker bureau or advisory boards for Amgen, Danone, Eli Lilly, Merck Sharp & Dohme, Novartis, Nycomed Roche-Glaxo-Smith-Klein and Servier.

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