see commentary on page 557

Renal safety of annual zoledronic acid infusions in osteoporotic postmenopausal women

Steven Boonen[1,2], Deborah E. Sellmeyer[3], Kurt Lippuner[4], Alexander Orlov-Morozov[5], Ken Abrams[6], Peter Mesenbrink[6], Erik F. Eriksen[7] and Paul D. Miller[8] for the HORIZON Pivotal Fracture Trial

[1]Leuven University Center for Metabolic Bone Diseases and Division of Geriatric Medicine, Department of Internal Medicine, Katholieke Universiteit Leuven, Leuven, Belgium; [2]Bone Research Unit, Laboratory for Experimental Medicine and Endocrinology, Department of Experimental Medicine, Katholieke Universiteit Leuven, Leuven, Belgium; [3]Division of Endocrinology, University of California, San Francisco, California, USA; [4]Osteoporosis Policlinic, Osteoporosis Unit, University Hospital, University of Berne, Berne, Switzerland; [5]Department of Rheumatology, Clinical Hospital 23, Moscow, Russia; [6]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [7]Novartis Pharma AG, Basel, Switzerland and [8]Colorado Center for Bone Research, Lakewood, Colorado, USA

Intravenous bisphosphonates reduce fracture risk but have been associated in rare cases with deteriorating renal-function in cancer patients. The renal effects of zoledronic acid were assessed in osteoporotic postmenopausal women from 27 countries who received three annual infusions of zoledronic acid or a placebo in a randomized, double-blind trial. Serum creatinine, estimated creatinine clearance and urinary protein were measured before and after at least one infusion in a predefined renal safety cohort of 5035 equally divided patients. This group was compared to 7714 patients whose parameters were measured annually. Significantly more transient pre- to post-infusion increases in serum creatinine occurred in zoledronic acid than placebo-treated patients with significant elevations, relative to pre-infusion, only in the second year. All 31 zoledronic acid and 8 of 10 patients on placebo recovered their pre-infusion serum creatinine value within 12 months. No differences in mean changes in serum creatinine, estimated creatinine clearance or adverse renal events were found. We found that transient changes in renal function can occur following an annual zoledronic acid infusion but, in the long term, renal function was not different from control patients.

Kidney International (2008) **74,** 641–648; doi:10.1038/ki.2008.193; published online 28 May 2008

KEYWORDS: osteoporosis; postmenopausal; renal; safety; zoledronic acid

Correspondence: *Paul D. Miller, Medical Director, Colorado Center for Bone Research, 3190 S. Wadsworth Boulevard, Lakewood, Colorado 80227, USA. E-mail: millerccbr@aol.com*

The data reported in this manuscript were presented, in part, at the 7th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, Porto, Portugal, on March 29, 2007.

Received 26 October 2007; revised 5 February 2008; accepted 5 March 2008; published online 28 May 2008

Oral bisphosphonate therapy has been shown to effectively reduce fracture risk in postmenopausal women with osteoporosis[1–3] but requires frequent administration and is associated with complex dosing instructions, variable absorption, gastrointestinal intolerance and poor compliance.[4,5] Intravenous (IV) administration avoids these disadvantages while ensuring full compliance, which may provide improved efficacy and fracture reduction.[6–9] All IV bisphosphonates are associated with mild-to-moderate post-infusion symptoms, occurring most commonly after the first infusion and typically resolving within 3 days of onset. However, bisphosphonates are exclusively excreted via the kidneys[10] and the use of high-dose IV bisphosphonates administered over a period of less than 15 min has been associated with deterioration of renal function, primarily in the oncology setting where other exacerbating factors, such as preexisting renal disease and concomitant use of nephrotoxic agents, may contribute to this impairment.[11–13] Understanding the renal impact of IV bisphosphonates in the postmenopausal osteoporosis population thus forms an important component in their safety evaluation.

Despite the extensive recycling of drug from plasma to bone storage and back to plasma, bisphosphonates do not undergo biotransformation and are mostly excreted unchanged in urine.[14] Clearance of the drug, both total and renal, is significantly correlated with creatinine clearance. This close correlation is most likely related to the fact that for both bisphosphonates and creatinine, the vast majority of renal clearance occurs via glomerular ultrafiltration.

Clinical trials have shown that, irrespective of renal function, plasma accumulation of zoledronic acid does not occur appreciably with sequential infusions of zoledronic acid.[13] In addition, although plasma levels of zoledronic acid in patients with mild-to-moderate renal impairment (estimated creatinine clearance 30–60 ml/min) are approximately 30–40% higher relative to patients with normal renal function, this difference is small and nonsignificant; therefore, adjustment of zoledronic acid dosage is not necessary

in a postmenopausal osteoporotic population. Bisphosphonates are not advised in patients with estimated creatinine clearance <35 ml/min because of lack of clinical data.[15]

As is typically observed with all bisphosphonates, plasma concentrations of zoledronic acid peak rapidly post-infusion and decline in a multiphasic fashion to 1% of peak concentrations within 24 h. This is followed by prolonged, very low drug plasma concentrations, which represent the recycling of drug from plasma to bone and back to plasma by the ongoing remodeling mechanisms.[14–16] Increasing the infusion time from 5 to 15 min has been shown to lower the peak zoledronic acid level by approximately 30% without affecting the level of drug exposure, and results in less adverse effects on renal function.[17] Therefore, an infusion time of no less than 15 min is strongly recommended.

This article reports the renal safety of once-yearly zoledronic acid 5 mg given over at least 15 min in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly–Pivotal Fracture Trial (HORIZON-PFT),[8] a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of zoledronic acid (5 mg) in the treatment of osteoporosis in postmenopausal women.

RESULTS

Study population and patient disposition

The intention-to-treat, safety, and renal safety populations comprised 7736, 7714, and 5035 patients, respectively.[8] The renal safety population included 2521 patients in the zoledronic acid group and 2514 patients in the placebo group. Baseline demographic and disease-related characteristics for the safety population were similar for the two treatment groups (Table 1). Patients in the renal safety cohort had similar baseline characteristics to the overall population. A total of 1219 patients (15.8%) discontinued the study. The rates of study discontinuation (zoledronic acid, 16.2%; placebo, 15.3%) and study discontinuation due to adverse events (zoledronic acid, 2.1%; placebo, 1.8%) were similar in the two treatment groups.

General safety

Zoledronic acid was generally safe and well tolerated. The percentages of patients experiencing any adverse event (zoledronic acid, 95.5%; placebo, 93.9%), serious adverse events including death (zoledronic acid, 29.2%; placebo, 30.1%), and death (zoledronic acid, 3.4%; placebo, 2.9%) were similar between treatment groups. Of 7736 randomized patients, 22 did not receive any study medication, 7714 received the first infusion, 6926 received the second infusion (88.3% of zoledronic-acid treated patients and 91.3% of patients treated with placebo), and 6297 were administered the third infusion (80.5% of zoledronic acid-treated patients and 82.8% of patients treated with placebo).

Short-term renal safety

Measurement of serum creatinine levels 9–11 days after each infusion showed that, overall, increases >0.5 mg/100 ml from the pre-infusion value occurred in 0.4% (10/2338) of placebo-treated patients and 1.3% (31/2320) of patients treated with 5 mg of zoledronic acid ($P=0.001$; Table 2). Only 2/31 of the patients treated with 5 mg of zoledronic acid had a change >0.5 mg/100 ml relative to their pre-infusion measurement at more than one time point. The incidence of increases by infusion with zoledronic acid 5 mg or placebo was 0.6 vs 0.3% ($P=$NS), 0.7 vs 0.1% ($P=0.002$), and 0.5 vs 0.2% ($P=$NS) after infusions 1, 2, and 3, respectively. The percentage of patients experiencing an increase >0.5 mg/100 ml from the pre-infusion value in the zoledronic acid group was greatest in those with baseline estimated creatinine clearance between 30 and 34 ml/min (10.6%) (more than four times greater incidence than the nearest baseline estimated creatinine clearance subgroup (35–39 ml/min)). Increased serum creatinine levels returned to within 0.5 mg/100 ml of the pre-infusion value in all affected patients treated with 5 mg of zoledronic acid ($n=31$) and in 8 of the 10 affected placebo-treated patients within 12 months. For the 31 patients treated with 5 mg of zoledronic acid, the mean serum creatinine levels at 9–11 days post-infusion and at 12 months post-infusion were similar after each infusion (Figure 1).

The number of patients in whom urinary protein levels increased from a pre-infusion level ≤2+ to a level >2+ 9 to 11 days post-infusion was low. Overall, this occurred in 0.58% (13/2244) of patients treated with 5 mg of zoledronic acid compared with 0.22% (5/2262) of the placebo group

Table 1 | Patient baseline characteristics (safety population and renal safety population)

	Safety population		Renal safety population	
Characteristic	Zoledronic acid N=3861	Placebo N=3853	Zoledronic acid N=2521	Placebo N=2514
Race, *n* (%)				
Caucasian	3042 (78.8)	3048 (79.1)	2105 (83.5)	2119 (84.3)
Hispanic	226 (5.9)	215 (5.6)	66 (2.6)	57 (2.3)
Other[a]	594 (15.4)	589 (15.3)	350 (13.9)	338 (13.4)
Age (years)				
Mean (s.d.)	73 (5.3)	73 (5.4)	73 (5.4)	73 (5.4)
Range	64–89	64–89	64–89	64–89
Number of years postmenopausal, n (%)				
≤5	1 (<0.1)	3 (0.1)	1 (<0.1)	1 (<0.1)
>5–30	2994 (77.5)	3005 (78.0)	1954 (77.5)	1940 (77.2)
>30	856 (22.2)	830 (21.6)	558 (22.1)	563 (22.4)
Missing data	11 (0.3)	14 (0.4)	8 (0.3)	10 (0.4)
Creatinine clearance (ml/min)				
Mean (s.d.)	63 (17.3)	64 (17.6)	64 (17.3)	64 (17.7)
Range	30.5–184.8	25.3–180.9	30.5–169.5	25.3–164.7
Urinary protein (dipstick) n (%)				
<1+	3808 (98.6)	3777 (98.1)	2481 (98.4)	2463 (98.0)
1+	38 (1.0)	58 (1.5)	30 (1.2)	38 (1.5)
≥2+[b]	15 (0.4)	16 (0.4)	10 (0.4)	12 (0.5)
Missing data	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (0.1)

[a]Includes 'Black', 'Japanese', 'other Asian', and 'other' races.
[b]Protocol violation.

Table 2 | Short-term renal safety: pre- to post-infusion changes in serum creatinine level and in urinary protein level (renal safety population)

Timing of visit	Zoledronic acid		Placebo		P-value
	N	n (%)	N	n (%)	
9–11 days after 1st infusion					
Increase in serum creatinine >0.5 mg/100 ml	2114	13 (0.61)	2130	6 (0.28)	0.113
Urinary protein level >2+[a]	2086	6 (0.29)	2101	3 (0.14)	0.342
9–11 days after 2nd infusion					
Increase in serum creatinine >0.5 mg/100 ml	1663	12 (0.72)	1721	1 (0.06)	0.002
Urinary protein level >2+[a]	1645	5 (0.30)	1706	2 (0.12)	0.280
9–11 days after 3rd infusion					
Increase in serum creatinine >0.5 mg/100 ml	1560	8 (0.51)	1600	3 (0.19)	0.141
Urinary protein level >2+[a]	1468	3 (0.20)	1515	1 (0.07)	0.367
Overall (that is, any 9–11 day post-infusion visit)					
Increase in serum creatinine >0.5 mg/100 ml	2320	31 (1.34)	2338	10 (0.43)	0.001
Urinary protein level >2+[a]	2244	13 (0.58)	2263	5 (0.22)	0.062

[a]Evaluation restricted to patients with pre-infusion reading ⩽2+; evaluated using dipstick.
N: number of patients with evaluable data.
n: number of patients affected.
Serum creatinine levels (mean [s.d.], max) 9–11 days post-infusion.
Zoledronic acid 1st infusion: 0.774 [0.210] mg/100 ml, 4.005 mg/100 ml; 2nd infusion: 0.805 [0.199] mg/100 ml, 2.195 mg/100 ml; 3rd infusion: 0.828 [0.203] mg/100 ml, 2.500 mg/100 ml.
Placebo 1st infusion: 0.803 [0.193] mg/100 ml, 3.495 mg/100 ml; 2nd infusion: 0.812 [0.181] mg/100 ml, 1.900 mg/100 ml; 3rd infusion: 0.836 [0.188] mg/100 ml, 2.104 mg/100 ml.

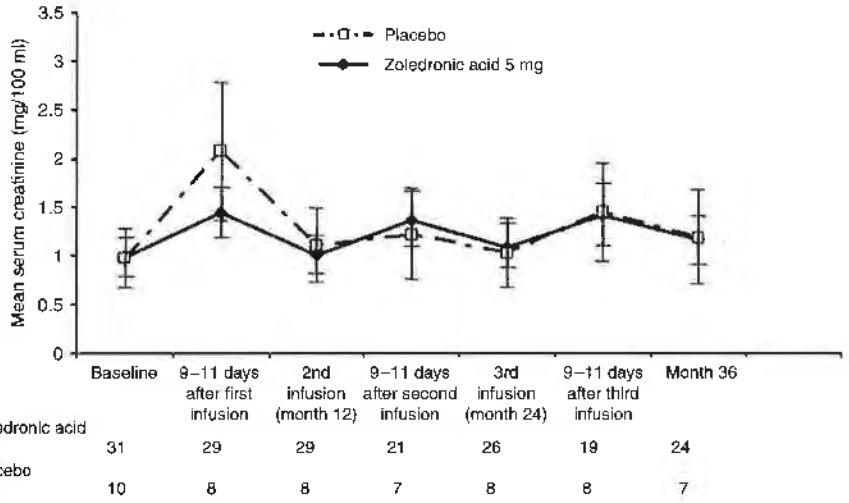


Figure 1 | Mean serum creatinine levels from baseline to 36 months in patients with pre- to post-infusion change of >0.5 mg/100 ml. For each infusion, the patients treated with 5 mg of zoledronic acid showed similar mean serum creatinine levels at 9–11 days post-infusion and also at 12 months post-infusion.

($P = 0.062$). In patients treated with 5 mg of zoledronic acid, the frequency of post-infusion urinary dipstick protein increases to >2+ was low after all infusions with a maximum incidence of 0.30% after infusion 2.

Long-term renal safety

No long-term differences in renal function were observed between the patients treated with 5 mg of zoledronic acid and those treated by placebo. Mean changes from baseline in serum creatinine level (zoledronic acid, 0.1 ± 0.14 mg/100 ml; placebo, 0.1 ± 0.15 mg/100 ml) and estimated creatinine clearance (zoledronic acid, −8.8 ± 9.58 ml/min; placebo, −8.7 ± 9.62 ml/min; Figure 2) were almost identical in the two treatment groups over the 3 years of the study. Moreover, at month 36, 3.2% of patients in both groups had estimated creatinine clearance <30 ml/min.

Overall, at any time during the study, the incidence of renal abnormalities was similar between treatment groups (Table 3). These included reported renal adverse events (zoledronic acid, 4.9%; placebo, 4.4%), estimated creatinine

clearance <30 ml/min (zoledronic acid, 4.4%; placebo, 4.2%; P=NS), estimated creatinine clearance decreases ≥30% in patients with baseline value ≤60 ml/min (zoledronic acid, 5.0%; placebo, 4.8%; P=NS), and increased proteinuria (zoledronic acid, 0.5%; placebo, 0.5%; P=NS) (>2+ in patients with baseline level ≤2+; zoledronic acid, 0.5%; placebo, 0.5%; P=NS). Increases from baseline in serum creatinine level >0.5 mg/100 ml were 2.8% with zoledronic acid and 2.0% with placebo (P=NS).

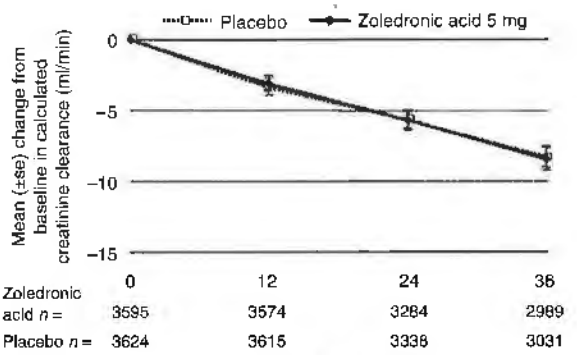


Figure 2 | Long-term renal safety: mean change in estimated creatinine clearance from baseline to 36 months (safety population). At month 36, the mean (± s.e.m.) decrease from baseline in estimated creatinine clearance was similar in the patients treated with 5 mg of zoledronic acid (−8.75 ± 0.175 ml/min) and in the placebo group (−8.67 ± 0.175 ml/min).

Renal safety in patients with mild-to-moderate renal impairment

Renal safety in patients with mild-to-moderate renal impairment was evaluated in patients with baseline estimated creatinine clearance between 30 and 60 ml/min. Overall, for zoledronic acid-treated patients, the incidence of an increase in serum creatinine >0.5 mg/100 ml relative to baseline was similar in patients whose baseline estimated creatinine clearance was <60 ml/min compared with those whose baseline estimated creatinine clearance was ≥60 ml/min (21 (1.99%) of 1053 patients vs 21 (1.66%) of 1267 patients, respectively; Table 4).

Moreover, in the short term, no differences were observed in the incidence of an increase in serum creatinine >0.5 mg/100 ml in patients with an estimated creatinine clearance of 35 to ≤60 ml/min and >60 ml/min administered 5 mg of zoledronic acid compared with placebo. In patients with an estimated creatinine clearance between 30 and 35 ml/min, five patients in the group treated with 5 mg of zoledronic acid had an increase in serum creatinine >0.5 mg/100 ml compared with one patient in the placebo group.

The incidence of patients developing treatment-emergent estimated creatinine clearance <30 ml/min was greater for patients with a baseline calculated estimated creatinine clearance <40 ml/min in both treatment groups and is consistent with the average decline in renal function of the overall population—approximately 8 ml/min over 3 years.

Table 3 | Long-term renal safety: changes from baseline in estimated creatinine clearance, serum creatinine, and urinary protein levels (safety population)

Endpoint Timing of data collection	Zoledronic acid *N*	Zoledronic acid *n* (%)	Placebo *N*	Placebo *n* (%)	*P*-value
Increase in serum creatinine >0.5 mg/100 ml					
Before 2nd infusion (month 12)	3595	19 (0.53)	3624	9 (0.25)	0.060
Before 3rd infusion (month 24)	3289	16 (0.49)	3345	20 (0.60)	0.617
Month 36	3022	36 (1.19)	3066	38 (1.24)	0.907
Overall (that is, at any time during the study)	3752	104 (2.77)	3767	77 (2.04)	0.042
Urinary protein level >2+[a]					
Before 2nd infusion (month 12)	3581	1 (0.03)	3606	3 (0.08)	0.625
Before 3rd infusion (month 24)	3277	3 (0.09)	3323	5 (0.15)	0.482
Month 36	2980	2 (0.07)	3021	5 (0.17)	0.453
Overall (that is, at any time during the study)	3749	19 (0.51)	3758	19 (0.51)	1.000
Estimated creatinine clearance <30 ml/min					
Before 2nd infusion (month 12)	3574	49 (1.37)	3615	44 (1.22)	0.602
Before 3rd infusion (month 24)	3284	57 (1.74)	3337	63 (1.89)	0.647
Month 36	2994	97 (3.24)	3035	96 (3.16)	0.884
Overall (that is, at any time during the study)	3621	160 (4.42)	3658	152 (4.16)	0.603
Estimated creatinine clearance decreased by ≥30%[b]					
Before 2nd infusion (month 12)	3574	40 (1.12)	3615	35 (0.97)	0.563
Before 3rd infusion (month 24)	3284	63 (1.92)	3338	69 (2.07)	0.725
Month 36	2994	110 (3.67)	3035	98 (3.23)	0.359
Overall (that is, at any time during the study)	3621	182 (5.03)	3658	177 (4.84)	0.745

[a]Evaluation restricted to patients with baseline reading ≤2+; evaluated using dipstick.
[b]Evaluation restricted to patients with baseline value ≤60 ml/min.
N: number of patients with evaluable data.
n: number of patients affected.

Table 4 | Patients developing increases in serum creatinine >0.5 mg/100 ml relative to baseline 9–11 days post-infusion, and those developing treatment-emergent estimated creatinine clearance <30 ml/min or a decrease in estimated creatinine clearance >30% during the trial

	Zoledronic acid						Placebo					
	Serum creatinine increase >0.5 mg/100 ml		Estimated CrCl <30 ml/min		Estimated CrCl decrease >30%		Serum creatinine increase >0.5 mg/100 ml		Estimated CrCl <30 ml/min		Estimated CrCl decrease >30%	
Baseline CrCl	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)
<30 ml/min	0	0	0	0	0	0	3	0 (0.00)	3	3 (100.00)	3	1 (33.33)
30–35 ml/min	47	5 (10.64)	68	38 (55.66)	68	6 (8.82)	65	1 (1.54)	84	53 (63.10)	84	9 (10.71)
35–40 ml/min	84	2 (2.38)	146	52 (35.62)	146	23 (15.75)	95	3 (3.16)	133	42 (31.58)	133	18 (13.53)
40–50 ml/min	372	7 (1.88)	573	49 (8.55)	573	70 (12.22)	358	4 (1.12)	589	42 (7.13)	589	64 (10.87)
50–60 ml/min	550	7 (1.27)	861	16 (1.86)	891	83 (9.32)	513	2 (0.39)	803	8 (1.00)	834	85 (10.19)
>60 ml/min	1267	21 (1.66)	1973	5 (0.25)	1678	182 (10.85)	1304	9 (0.69)	2064	4 (0.20)	1634	177 (10.77)
All patients	2320	42 (1.81)	3621	160 (4.42)			2338	19 (0.81)	3658	152 (4.16)		

CrCl: creatinine clearance.
N: number of patients with evaluable data.
n: number of patients affected.

There was no relationship between the percentage change in creatinine clearance and baseline creatinine clearance (Table 4).

Renal failure

Acute renal failure (that is, serious adverse event requiring hospitalization) was reported in four patients treated with 5 mg zoledronic acid (0.10%) and in three placebo-treated patients (0.08%), based on an investigator's judgement of whether changes in creatinine clearance constituted an adverse event. That is, the determination of acute renal failure was subjective and was not based on any prespecified criteria, as evidenced by the fact that two of the four zoledronic acid-treated patients considered to have developed renal failure had baseline creatinine clearances of 31 ml/min and had only small changes below 30 ml/min. The overall incidence of reported renal failure was also similar between groups (zoledronic acid, 0.10%; placebo, 0.18%).

DISCUSSION

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly–Pivotal Fracture Trial was a large, randomized, double-blind, placebo-controlled trial that monitored short-term renal function in more than 5000 patients, and long-term renal function in the entire safety population of 7714 patients.[8] The results showed no association between annual infusions of 5 mg of zoledronic acid and long-term deterioration of renal function in osteoporotic postmenopausal women with estimated creatinine clearance ⩾30 ml/min at baseline: long-term changes in renal function, renal adverse events and renal impairment occurred with similar frequency in the zoledronic acid- and placebo-treated groups. Gradual deterioration of renal function with time was observed in both the active treatment and placebo groups in the HORIZON-PFT study (Figure 2),[8] consistent with age-related effects on renal function.

This study demonstrated that annual infusions of 5 mg of zoledronic acid may be associated with transient, short-term increases in serum creatinine only, as demonstrated by the similar long-term changes in calculated creatinine clearance observed in both treatment groups. Follow-up of the 31 patients treated with 5 mg of zoledronic acid who experienced short-term significant increases in serum creatinine showed that the increased serum creatinine levels had returned to within 0.5 mg/100 ml of the pre-infusion values within 12 months, demonstrating no cumulative effect on renal function in this population when multiple annual infusion doses of 5 mg of zoledronic acid are administered over a period no shorter than 15 min. Further corroborating this notion are the results obtained in the analyses of patients with mild-to-moderate renal impairment (estimated creatinine clearance between 30 and 60 ml/min). The proportion of patients whose estimated creatinine clearance decreased to <30 ml/min or decreased >30% from baseline during the study was similar between treatment groups for all categories of baseline creatinine clearance.

The change in renal function was determined by changes in serum creatinine values >0.5 mg/100 ml higher than the value at pre-infusion or at baseline. These changes, rather than changes in creatinine clearance, were used because they require practical and less expensive methods of measurement for the non-nephrology clinical setting used in the study.[18]

Treatment of postmenopausal osteoporosis is only one of the several indications for bisphosphonates and for zoledronic acid in particular. For example, zoledronic acid is approved for the treatment of Paget's disease of bone,[19] hypercalcemia of malignancy, multiple myeloma, and bone metastases of solid tumors.[20]

Several case reports have shown changes in renal function in association with zoledronic acid infusion in oncology patients, particularly with more rapid infusions (of 5 min duration), although the specific role of zoledronic acid treatment is difficult to determine in the presence of various risk factors in these patients.[21–23] Most oncology regimens[20] are considerably more intensive than the single, annual administration of 5 mg of zoledronic acid used in this trial,[8] and in addition, dehydration, renal dysfunction, and the use of nephrotoxic drugs are common in cancer patients.[12,24,25]

Data from short- and long-term studies have shown that the renal safety profile of high-dose zoledronic acid is similar to IV pamidronate in breast cancer and multiple myeloma, and to placebo in prostate cancer, lung cancer, and other solid tumors.[26] Interpretation of the results from this study in the context of existing published safety data should recognize the inherent differences in baseline characteristics between cancer and osteoporosis patients and take into account the different zoledronic acid dosing regimens used in these two patient populations.

Both equations for estimating glomerular filtration rate, that is, Cockcroft–Gault and modification of diet in renal disease, are useful in clinical practice to estimate renal function.[27] When compared to one of the 'gold standards' for measuring glomerular filtration rate (^{51}Cr-EDTA), both estimated equations show very limited biases and fit closely on a line of unity in a linear manner to true glomerular filtration rate measurements in large population studies. Both formulae may have limited precision in subgroups, particularly in younger subjects (<65 years of age), or very thin subjects for modification of diet in renal disease (<18 kg/m^2), and obese individuals for Cockcroft–Gault (BMI >30 kg/m^2). As the cohort of the zoledronic acid patients in the HORIZON-PFT study were mainly aged above 65 years and not obese, the Cockcroft–Gault formula provided a valid estimation for glomerular filtration rate in this study population.

The results of this study show that the transient short-term changes that may occur with annual infusions of 5 mg of zoledronic acid over 15 min are not associated with long-term detrimental effects in postmenopausal osteoporotic patients who have normal renal function or mild-to-moderate renal dysfunction at baseline. This is important from a clinical standpoint, as it confirms that modifying the present treatment regimen (5 mg of zoledronic acid annually, infused over a minimum period of 15 min) is not necessary in patients with a baseline estimated creatinine clearance ≥30 ml/min and removes the need to place further restrictions on the osteoporotic population that can benefit from this treatment.

As annual administration of zoledronic acid for 3 years has been shown to reduce the risk of new vertebral and hip fractures by 70 and 41%, respectively,[8] the benefits of treatment are substantial. However, for patients with increased risk for adverse events, that is, those with reduced renal function (estimated creatinine clearance between 30 and 35 ml/min), and for those at increased risk of renal adverse events (for example, elderly patients and those with hypertension or diabetes mellitus), sound clinical management is advised. In particular, this should involve ensuring that the patient is well hydrated before and after infusion of zoledronic acid and that the infusion time is not less than 15 min.

In conclusion, we have shown that multiple annual infusions of 5 mg of zoledronic acid, when infused over a minimum period of 15 min, are safe and generally well tolerated in women with postmenopausal osteoporosis. Although zoledronic acid administration may be associated with short-term effects on renal function, especially in patients with estimated creatinine clearance between 30 and 35 ml/min, these changes are very uncommon, mild, and transient and are not associated with any long-term detrimental effect. As the gradual reductions in renal function that occurred in the zoledronic acid and placebo treatment groups in this study were of identical magnitude, we can conclude that three annual zoledronic acid infusions have no long-term detrimental effect on renal function in patients with postmenopausal osteoporosis with baseline estimated creatinine clearance >30 ml/min.

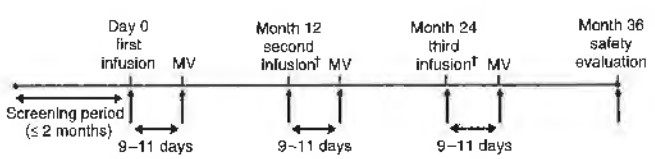
MATERIALS AND METHODS

Study design and subjects

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly–Pivotal Fracture Trial was an international, multicenter, randomized, double-blind, placebo-controlled trial carried out in 239 centers in 27 countries.[8] The study population comprised 7736 postmenopausal women aged 65–89 years with osteoporosis documented by either: (i) femoral neck bone mineral density T-score ≤−2.5 with or without evidence of vertebral fracture; or (ii) a bone mineral density T-score of ≤−1.5 with radiologic evidence of at least two mild or one moderate existing (prevalent) vertebral fracture(s). Exclusion criteria included use of IV bisphosphonates in the 2 years before randomization, use of oral bisphosphonates not in accordance with the washout schedule, previous use of strontium, hypercalcemia, hypocalcemia, and renal disease (estimated creatinine clearance <30.0 ml/min, urinary protein ≥2+ (dipstick reading), or increase of >0.5 mg/100 ml in serum creatinine between the two screening visits). Creatinine clearance was estimated using the Cockcroft–Gault equation:

$$C_{Cr}(\text{ml/min}) = \frac{(140 - \text{age[years]}) \times \text{body weight (kg)} \times 0.85}{72 \times S_{Cr}(\text{mg/100ml})}$$

After a screening period of up to 2 months, patients were randomized to receive placebo or 5 mg of zoledronic acid as a 15 min IV infusion on day 0, and approximately 12 and 24 months later, a total of three annual treatments (Figure 3). Serum creatinine and estimated creatinine clearance were determined in all patients within 3 weeks before any dose of study medication. No patient was dosed if their estimated creatinine clearance decreased to <30 ml/min. All participants were instructed to take 1000–1500 mg of elemental calcium and 400–1200 IU of vitamin D daily. Patients were placed into one of two strata on the basis of whether they were taking any osteoporosis medications at baseline. Patients in stratum one were not taking any osteoporosis medications at the time of



MV, monitoring visit
†Included pre-treatment assessment of renal function

Figure 3 | Renal safety monitoring schedule during the HORIZON-PFT study.

randomization, whereas patients in stratum two were permitted to receive concomitant osteoporosis medication, which included hormone replacement therapy, raloxifene, calcitonin, tibolone, tamoxifen, ipriflavone, dehydroepiandrosterone(s), and medroxyprogesterone.

Safety monitoring

General safety was assessed by routine monitoring of adverse events, clinical laboratory evaluations, measurement of vital signs, and physical examination. Patients who discontinued from study drng were encouraged to remain in the stndy for follow-up efficacy and safety evaluations. Specific monitoring of renal function was also carried ont. Short-term renal effects were evaluated by measuring serum creatinine and urinary dipstick protein levels 9–11 days after each infusion in a subset of patients designated as the 'renal safety cohort'. A patient was included in this cohort if they had at least one baseline and at least one post-randomization measurement of serum creatinine or a urine dipstick (zoledronic acid, $n = 2521$; placebo, $n = 2514$). Post-infnsion sernm creatinine values were compared with valnes obtained at baseline and with the pre-infusion valne. Baseline values of serum creatinine and estimated creatinine clearance were defined as the average of the last twn measurements taken before randomization. For all other parameters, the baseline value was the last measurement obtained before administration of the first dose of study medication. On subsequent visits, if more than one pre-infusion serum creatinine measurement was taken, the most recent was used. All post-infusion nrinary dipstick protein values were compared with data obtained at baseline and the pre-infusion value. Long-term renal effects were evalnated in all patients by determining estimated creatinine clearance, serum creatininc, and nrinary protein levels before treatment administration of infusion 2 (month 12) and infusion 3 (month 24), and at the final visit (month 36 or early termination). These valnes were compared with those obtained at baseline.

All potential renal events were assessed by a three-member panel of renal experts who were independent of the clinical trial team. The panel predefined search terms on the basis of codes from the Medical Dictionary for Regulatory Activity-preferred terms. Investigators at each clinical center collected medical documentation for the cases. The docnmentation was forwarded to the expert panel for blinded event adjndication to determine if they met the criteria of a clinically relevant change in renal function. Adjudication of individnal events was triggered by the following: (i) serum creatinine value >0.5 mg/100 ml higher than the value obtained pre-infusion or at baseline; (ii) estimated creatinine clearance <30 ml/min; (iii) $\geqslant 30\%$ decrease in estimated creatinine clearance when baseline value was $\leqslant 60$ ml/min; and (iv) any reported adverse event associated with a change in renal function.

Statistical analysis

The analyses of renal safety involved two populations: the safety population (all subjects in the intention-to-treat population who received at least one infusion of study drug), and the renal safety population (a subset of the safety population that included all patients with a baseline serum creatinine measnrement and at least one post-treatment measurement of serum creatinine or urinary protein 9–11 days after treatment). All safety analyses were performed using observed data, and there was no impntation of missing data. Descriptive statistics were used to describe patient characteristics at baseline (intention-to-treat and renal safety population) and renal safety data (short-term, renal safety population; long-term, safety population). P values were calculated using the Fisher's exact test, as appropriate.

DISCLOSURE

SB reports having received research funding and consulting fees from Novartis. DES worked on a research project that received funding from Novartis. PDM reports receiving research funding and consulting fees from Novartis. KA, PM, and EFE are employees of Novartis and own stock in the company. All of the other authors declared no competing interests.

ACKNOWLEDGMENTS

We thank Duncan Pennington of BioScience Communications for editorial support. SB is senior clinical investigator of the Fund for Scientific Research (FWO—Vlaanderen) and is holder of the Leuven University Chair in Metabolic Bone Diseases.
Special thanks are due to Zeb Horowitz (now at Savient Pharmaceuticals), John Orloff (Novartis), and the following: Steering Committee members—Dennis Black, Steven Cummings, Pierre Delmas, Richard Eastell, Ian Reid, SB, Jane Cauley, Felicia Cosman, Péter Lakatos, Ping C Leung, Zulema Man, EFE (Novartis), PM (Novartis); Past Steering Committee members—Edith Lau, Saloman Jasqui, Carlos Mautalen, Theresa Rosario-Jansen (Novartis), John Caminis (Novartis); Data Safety Monitoring Board—Lawrence Raisz (chairman), Peter Bauer, Juliet Compston, David DeMets, Raimund Hirschberg, Olof Johnell, Stuart Ralston, Robert Wallace; DSMB Consultants—Michael Farkough; Novartis—Mary Flood; University of California, San Francisco (UCSF) Coordinating Center—Douglas Bauer, Lisa Palermo; UCSF Radiology (QCT analysis)—Thomas Lang.
We are indebted to the HORIZON-PFT Clinical Site Investigators—Argentina: Eduardo Kerzberg, Zulema Man, Carlos Mautalen, Maria Ridruejo, Guillermo Tate, Jorge Velasco; Australia: Michael Hooper, Mark Kotowicz, Peter Nash, Richard Prince, Anthony Roberts, Philip Sambrook; Austria: Harald Dobnig, Gerd Finkenstedt, Guenter Hoefle, Klaus Klaushofer, Martin Pecherstorfer, Peter Peichl; Belgium: Jean Body, Steven Boonen, Jean-Pierre Devogelaer, Piet Geusens, Jean Kaufman; Brazil: João Brenol, Jussara Kochen, Rubem Lederman, Sebastiao Radominski, Vera Szejnfeld, Cristiano Zerbini; Canada: Jonathan Adachi, Jacques Brown, Denis Choquette, David Hanley, Robert Josse, David Kendler, Richard Kremer, Frederic Morin, Wojciech Olszynski, Alexandra Papaioannou, Chiu KinYuen; China: Baoying Chen, Shouqing Lin; Colombia: Nohemi Casas, Monique Chalem, Juan Jaller, Jose Molina; Finland: Hannu Aro, Jorma Heikkinen, Heikki Kröger, Lasse Mäkinen, Juha Saltevo, Jorma Salmi, Matti Välimäki; France: Claude-Laurent Benhamou, Pierre Delmas, Patrice Fardellone, Georges Werhya; Germany: Bruno Allolio, Dieter Felsenberg, Joachim Happ, Manfred Hartard, Johannes Hensen, Peter Kaps, Joern Kekow, Ruediger Moericke, Bernd Ortloff, Peter Schneider, Siegfried Wassenberg; Hong Kong: Ping Chung Leung; Hungary: Adam Balogh, Bela Gornor, Tibor Hidvégi, Laszlo Koranyi, Péter Lakatos, Gyula Poór, Zsolt Tulassay; Israel: Rivka Dresner Pollak, Varda Eshed, A. Joseph Foldes, Sophia Ish-Shalom, Iris Vered, Mordechai Weiss; Italy: Silvano Adami, Antonella Barone, Gerolamo Bianchi, Sandro Giannini, Giovanni Carlo Isaia, Giovanni Luisetto, Salvatore Minisola, Nicola Molea, Ranuccio Nuti, Sergio Ortolani, Mario Passeri, Alessandro Rubinacci, Bruno Seriolo, Luigi Sinigaglia; Korea (Republic of): Woong-Hwan Choi, Moo-Il Kang, Ghi-Su Kim, Hye-Soon Kim, Yong-Ki Kim, Sung-Kil Lim, Ho-Young Son, Hyun-Koo Yoon; Mexico: Carlos Abud, Pedro Garcia, Salomon Jasqui, Luis Ochoa, Javier Orozco, Javier Santos; New Zealand: Ian Reid; Norway: Sigbjørn Elle, Johan Halse, Arne Høiseth, Hans Olav, Hølvik Ingun Røed, Arne Skag, Jacob Stakkestad, Unni Syversen; Poland: Janusz Badurski, Edward Czerwinski, Roman Lorenc, Ewa Marcinowska-Suchowierska, Andrzej Sawicki, Jerzy Supronik; Russia: Eduard Ailamazyan, Lidiya Benevolenskaya, Alexander Dreval, Leonid Dvoretsky, Raisa Dyomina, Vadim Mazurov, Galina Melnichenko, Ashot Mkrtoumyan, Alexander Orlov-Morozov,

Olga Ostroumova, Eduard Pikhlak, Tatiana Shemerovskaya, Nadezhda Shostak, Irina Skripnikova, Vera Smetnik, Evgenia Tsyrlina, Galina Usova, Alsu Zalevskaya, Irina Zazerskaya, Eugeny Zotkin; Sweden: Osten Ljunggren, Johan Lofgren, Mats Palmér, Maria Saaf, Martin Stenström; Switzerland: Paul Hasler, Olivier Lamy, Kurt Lippuner, Claude Merlin, René Rizzoli, Robert Theiler, Alan Tyndall, Daniel Uebelhart; Taiwan: Jung-Fu Chen, Po-Quang Chen, Lin-show Chin, Jawl-Shan Hwang, Tzay-Shing Yang, Mayuree Jirapinyo; Thailand: Mayuree Jirapinyo, Rojanasthien Sattaya, Sutin Sriussadaporn, Soontrapa Supasin, Nimit Taechakraichana, Kittisak Wilawan; United Kingdom: Hugh Donnachie, Richard Eastell, William Fraser, Alistair McLellan, David Reid; United States: John Abruzzo, Ronald Ackerman, Robert Adler, John Aloia, Charles Birbara, Barbara Bode, Henry Bone, Donald Brandon, Jane Cauley, Felicia Cosman, Daniel Dionne, Robert Downs, Jr., James Dreyfus, Victor Elinoff. Ronald Emkey, Joseph Fanciullo, Darrell Fiske, Palmieri Genaro, M Gollapudi, Richard Gordon, James Hennessey, Paul Howard, Karen Johnson, Conrad Johnston, Risa Kagan, Shelly Kafka, Jeffrey Kaine, Terry Klein, William Koltun, Meryl Leboff, Bruce Levine, E Michael Lewiecki, Cora Elizabeth Lewis, Angelo Licata, Michael Lillestol, Barry Lubin, Raymond Malamet, Antoinette Mangione, Velimir Matkovic, Daksha Mehta, Paul Miller, Sam Miller, Frederik T Murphy, Susan Nattrass, David Podlecki, Christopher Recknor, Clifford Rosen, Daniel Rowe, Robert Rude, Thomas Schnitzer, Yvonne Sherrer, Stuart Silverman, Kenna Stephenson, Barbara Troupin, Joseph Tucci, Reina Villareal, Nelson Watts, Richard Weinstein, Robert Weinstein, Michael Weitz, Richard White.

REFERENCES

1. Black DM, Thompson DE, Bauer DC *et al.* Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. *J Clin Endocrinol Metab* 2000; **85**: 4118–4124.
2. Cranney A, Tugwell P, Adachi J *et al.* III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev* 2002; **23**: 517–523.
3. Bone HG, Hosking D, Devogelaer JP *et al.* Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004; **350**: 1189–1199.
4. Ezra A, Golomb G. Administration routes and delivery systems of bisphosphonates for the treatment of bone resorption. *Adv Drug Deliv Rev* 2000; **42**: 175–195.
5. Cramer JA, Amonkar MM, Hebborn A. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin* 2005; **21**: 1453–1460.
6. Reid IR, Brown JP, Burckhardt P *et al.* Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med* 2002; **346**: 653–661.
7. Croom KF, Scott LJ. Intravenous ibandronate: in the treatment of osteoporosis. *Drugs* 2006; **66**: 1593–1601.
8. Black DM, Delmas PD, Eastell R *et al.* Once-yearly zoledronic acid 5 mg for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356**: 1809–1822.
9. Lyles KW, Colón-Emeric CS, Magaziner JS *et al.* Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; **357**: 1799–1809.
10. Green JR, Seltenmeyer Y, Jaeggi KA. Renal tolerability profile of novel, potent bisphosphonates in two short-term rat models. *Pharmacol Toxicol* 1997; **80**: 225–230.
11. Weinman EJ, Patak RV. Acute renal failure in cancer patients. *Oncology* 1992; **6**: 47–52.
12. Kintzel PE. Anticancer drug-induced kidney disorders. *Drug Saf* 2001; **24**: 19–38.
13. Markowitz GS, Appel GB, Fine PL *et al.* Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. *J Am Soc Nephrol* 2001; **12**: 1164–1172.
14. Chen T, Berenson J, Vescio R *et al.* Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002; **42**: 1228–1236.
15. Skerjanec A, Berenson J, Hsu C *et al.* The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol* 2003; **43**: 154–162.
16. Nancollas GH, Tang R, Phipps RJ *et al.* Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. *Bone* 2006; **38**: 617–627.
17. Zometa [package insert]. *Zoledronic Acid Prescribing Information*. Novartis Pharmaceuticals Corporation: East Hanover, NJ, 2003.
18. Delanaye P, Radermecker RP, Rorive M *et al.* Indexing glomerular filtration rate for body surface area in obese patients is misleading: concept and example. *Nephrol Dial Transplant* 2005; **20**: 2024–2028.
19. European Agency for the Evaluation of Medicinal Products. http://www.emea.europa.eu/humandocs/PDFs/EPAR/aclasta/H-595-PI-en.pdf. Site accessed February 22nd, 2007.
20. Food and Drug Administration. http://www.fda.gov/cder/foi/label/2006/021223s012lbl.pdf. Site accessed, February 22nd, 2007.
21. Chang JT, Green L, Beitz J. Renal failure with the use of zoledronic acid. *N Engl J Med* 2003; **349**: 1676–1679.
22. Markowitz GS, Fine PL, Stack JI *et al.* Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int* 2003; **64**: 281–289.
23. Munier A, Gras V, Andrejak M *et al.* Zoledronic acid and renal toxicity: data from French adverse effect reporting database. *Ann Pharmacother* 2005; **39**: 1194–1197.
24. Ritch PS. Treatment of cancer-related hypercalcemia. *Semin Oncol* 1990; **17**(2 Suppl 5): 26–33.
25. Knudsen LM, Hippe E, Hjorth M *et al.* Renal function in newly diagnosed multiple myeloma—a demographic study of 1353 patients. The Nordic Myeloma Study Group. *Eur J Haematol* 1994; **53**: 207–212.
26. Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. *Oncologist* 2004; **9**(Suppl 4): 28–37.
27. Stevens LA, Coresh J, Greene T *et al.* Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; **354**: 2473–2483.