Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients With Metastatic Hormone-Refractory Prostate Cancer

Fred Saad, Donald M. Gleason, Robin Murray, Simon Tchekmedyian, Peter Venner, Louis Lacombe, Joseph L. Chin, Jeferson J. Vinholes, J. Allen Goas, Ming Zheng

For the Zoledronic Acid Prostate Cancer Study Group

In a placebo-controlled randomized clinical trial, zoledronic acid (4 mg via a 15-minute infusion every 3 weeks for 15 months) reduced the incidence of skeletal-related events (SREs) in men with hormone-refractory metastatic prostate cancer. Among 122 patients who completed a total of 24 months on study, fewer patients in the 4-mg zoledronic acid group than in the placebo group had at least one SRE (38% versus 49%, difference = –11.0%, 95% confidence interval [CI] = –20.2% to –1.3%; *P* = .028), and the annual incidence of SREs was 0.77 for the 4-mg zoledronic acid group versus 1.47 for the placebo group (*P* = .005). The median time to the first SRE was 488 days for the 4-mg zoledronic acid group versus 321 days for the placebo group (*P* = .009). Compared with placebo, 4 mg of zoledronic acid reduced the ongoing risk of SREs by 36% (risk ratio = 0.64, 95% CI = 0.485 to 0.845; *P* = .002). Patients in the 4-mg zoledronic acid group had a lower incidence of SREs than did patients in the placebo group, regardless of whether they had an SRE prior to entry in the study. Long-term treatment with 4 mg of zoledronic acid is safe and provides sustained clinical benefits for men with metastatic hormone-refractory prostate cancer. [J Natl Cancer Inst 2004;96:879–82]

Bone metastasis occurs in a majority of patients with advanced prostate cancer and represents a clinically significant issue in the management of these patients *(1)*. Metastatic bone disease is associated with substantial morbidity, including severe bone pain and pathologic fractures. Bisphosphonates have become an integral tool in the management of malignant bone disease, but they had not demonstrated clinical benefit in men with prostate cancer until recently. We previously reported the results of a 15-month analysis from a randomized placebo-controlled clinical trial of the bisphosphonate zoledronic acid in men with bone metastases secondary to hormone-refractory prostate cancer *(2)*. The 15-month analysis of this trial demonstrated that, compared with placebo, a 4-mg dose of zoledronic acid resulted in a statistically significant reduction in the incidence of skeletal-related events (SREs) and delayed the onset of SREs *(2)*. Here we present results of an analysis of zoledronic acid in these patients over a time course of 24 months.

In this multicenter, placebo-controlled trial, 643 men with metastatic hormone-refractory prostate cancer were randomly assigned to receive intravenous zoledronic acid (4 mg or 8 mg) or placebo every 3 weeks for 15 months (core phase), with an option to continue for an additional 9-month extension phase (total study time of 24 months). Patients treated with 8 mg of zoledronic acid had a higher incidence of elevated serum creatinine levels than did patients treated with 4 mg of zoledronic acid *(2)*. Therefore, zoledronic acid doses greater than 4 mg are not recommended, and a protocol amendment to ensure renal safety reduced the 8-mg dose to 4 mg (hereinafter referred to as the 8/4-mg group). Per a protocol amendment, no efficacy conclusions were drawn from the results of this group. The primary efficacy endpoint was the proportion of patients having at least one SRE, which was prospectively defined as a pathologic fracture, spinal cord compression, radiation therapy or surgery to bone, or change in the antineoplastic therapy to treat bone pain. Prospectively planned secondary efficacy endpoints included time to the first SRE, annual incidence of SREs, multiple event analysis using the Andersen–Gill model *(3)*, and mean change from baseline brief pain inventory (BPI) score. All analyses presented here include data from randomization to the end of the extension phase (i.e., 24 months) unless otherwise specified. To avoid counting possibly linked SREs more than once, we counted only one event in any 21-day window for the annual incidence endpoint and the multiple event analysis. In exploratory analyses, we examined the proportion of patients that had an SRE excluding asymptomatic fractures, the proportion with an SRE from months 15 to 24 (i.e., the extension phase only), and the proportion with an SRE stratified by prior history of SREs. We also analyzed the proportion of patients with an SRE and the median time to the first SRE for the 4- and 8/4-mg zoledronic acid groups combined.

Of the 208 patients who completed the 15-month core phase of this study, 186 patients continued in the study, and 122 patients completed 24 months of study treatment (Fig. 1). Baseline demographic and disease characteristics for the patients included in the safety analysis were reported previously *(2)*. Treatment groups were well balanced at baseline for all patient variables, including chemotherapy. A similar percentage of patients in each treatment group received mitoxantrone during the trial (25% for 4 mg of zoledronic acid, 20% for 8/4 mg of zoledronic acid, and 24% for placebo). At the 24-month analysis, the overall and renal safety profiles of the 4-mg zoledronic acid group were similar to those of placebo and were not

Affiliations of authors: Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Québec, Canada (FS); Advanced Clinical Therapeutics, Tucson, AZ (DMG); Division of Hematology and Medical Oncology, Peter MacCallum Cancer Institute, East Melbourne, Victoria, Australia (RM); Pacific Shores Medical Group, Long Beach, CA (ST); Cross Cancer Institute, Edmonton, Alberta, Canada (PV), Le Centre de Recherche en Cancerologie del Université Laval, Québec, Québec, Canada (LL); London Health Sciences Centre, East London, Ontario, Canada (JLC); Irmandade de Santa Casa de Misericordia de Porto Alegre, Rio Grande do Sul, Brazil (JJV); Novartis Pharmaceuticals Corporation, East Hanover, NJ (JAG, MZ).

Correspondence to: Fred Saad, MD, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, 1560 Rue Sherbrooke E., Montréal, PQ H2L 4M1 Québec, Canada (e-mail: fred.saad@ssss.gouv.qc.ca).

See "Notes" following "References."

DOI: 10.1093/jnci/djh141

Journal of the National Cancer Institute, Vol. 96, No. 11,

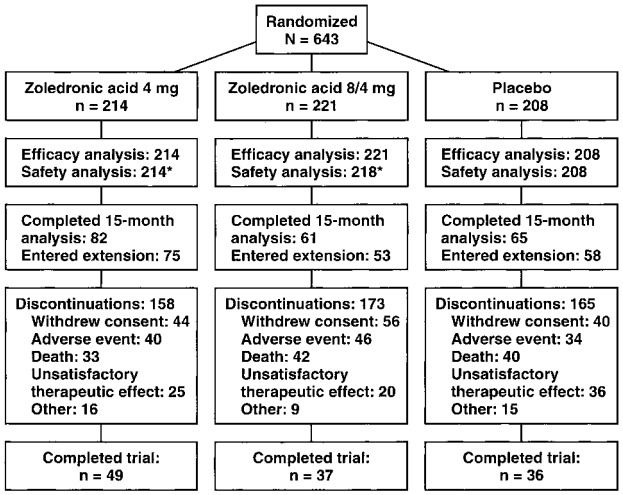

Fig. 1. CONSORT flow diagram. *Three patients, one randomly assigned to receive zoledronic acid at 4 mg and two randomly assigned to receive zoledronic acid at 8/4 mg, never received the study drug and were not included in the safety analysis. One patient randomly assigned to receive zoledronic acid at 8/4 mg incorrectly received 4 mg; this patient was included in the 8/4-mg group for efficacy and in the 4-mg group for safety analysis. Adapted with permission of Saad et al. *(2)*

different from those reported at the 15-month analysis (data not shown).

Table 1 summarizes the efficacy data at 24 months for the preplanned analyses, and Table 2 summarizes the efficacy data at 24 months for the exploratory analyses. During the entire 24-month study, statistically significantly fewer patients in the 4-mg zoledronic acid group than in the placebo group had at least one SRE (38% versus 49%, difference = –11.0%, 95% CI = –20.2% to –1.3%; $P = .028$). The annual incidence of SREs was 0.77 for the 4-mg zoledronic acid group versus 1.47 for the placebo group ($P = .005$). The median time to the first SRE was reached in both treatment groups and was approximately 6 months longer for patients in the 4-mg zoledronic acid group than for patients in the placebo group (488 days versus 321 days; $P = .009$). Moreover, when asymptomatic fractures were excluded from the 24-month analysis of SREs, statistically significantly fewer patients in the 4-mg zoledronic acid group than in the placebo group had at least one SRE (30% versus 41%, difference = –11.0%, 95% CI = –20.1% to –1.8%; $P = .019$) (Table 2). Zoledronic acid also demonstrated continued benefit among patients who remained in the study. During the extension phase of the trial (i.e., from 15 to 24 months after randomization), fewer patients in the 4-mg zoledronic acid group than in the placebo group had at least one SRE (19% versus 38%, difference = –19.0%, 95% CI = –34.3% to –3.7%; $P = .017$) (Table 2).

Patients in the 8/4-mg zoledronic acid group had fewer SREs than did patients in the placebo group for all comparisons tested; however, many of the differences between these treatment groups failed to reach statistical significance even though these two treatment arms had similar discontinuation rates. The reasons for this lack of statistical significance are unclear, especially because the 4-mg zoledronic acid and 8/4-mg zoledronic acid groups had similar pharmacologic effects on biochemical markers of bone resorption *(2)*. We therefore analyzed the combined 4-mg and 8/4-mg zoledronic acid groups and

Table 1. Twenty-four-month analysis of prospectively planned efficacy endpoints*

	Zoledronic acid treatment group			4-mg zoledronic acid versus placebo				8/4-mg zoledronic acid versus placebo			
Endpoint	4 mg (n = 214)	8/4 mg (n = 221)	Placebo (n = 208)	Difference (95% CI), %	P†	HR (95% CI)	P†	Difference (95% CI), %	P†	HR (95% CI)	P†
Patients with ≥1 SRE during the study n (%)‡	81 (38)	91 (41)	101 (49)	−11.0 (−20.2 to −1.3)	.028			−8.0 (−16.8 to 2.0)	.129		
Median time to first SRE, days	488	363	321			0.677 (0.505 to 0.908)	.009			0.892 (0.671 to 1.187)	.434
Mean annual incidence of SREs‡	0.77	1.05	1.47	NA	.005			NA	.098		
Multiple event analysis, HR§	0.640	0.836	1.00 (referent)			0.640 (0.485 to 0.845)	.002			0.836 (0.641 to 1.090)	.186
BPI, mean least-squares change from baseline value at											
18 mo	0.58	0.45	0.95	−0.37 (−0.78 to −0.04)	.075			−0.50 (−0.91 to −0.09)	.016		
21 mo	0.56	0.50	1.07	−0.51 (−0.91 to −0.10)	.014			−0.57 (−0.98 to −0.17)	.005		
24 mo	0.58	0.54	1.05	−0.47 (−0.88 to −0.06)	.024			−0.51 (−0.92 to −0.11)	.013		
Mean change from baseline analgesic score at 24 mo	1.04	1.05	1.17	NA	.491			NA	.438		

*CI = confidence interval; HR = hazard ratio; SRE = skeletal-related event; BPI = brief pain inventory score; NA = not applicable.

†*P* values (two-sided) for between–study arm comparisons of percentage of patients with at least one SRE and annual incidence of SREs are from the Cochran–Mantel–Haenszel test. Cox proportional hazards regression analyses were used to compare the time to first SRE. Analysis of covariance was used to compare the mean change from baseline in bone pain scores of each treatment group, with baseline value as a covariate and treatment and stratum as factors.

‡All incident SREs (0–24 months).

§Multiple event analysis was performed by using the Andersen–Gill model *(3)*.

Table 2. Results of exploratory analyses*

Outcome	Treatment group: 4 mg zoledronic acid (n = 214)	Treatment group: 8/4 mg zoledronic acid (n = 218)	Treatment group: Placebo (n = 208)	4-mg zoledronic acid versus placebo: Difference (95% CI), %	4-mg zoledronic acid versus placebo: P†	8/4-mg zoledronic acid versus placebo: Difference (95% CI), %	8/4-mg zoledronic acid versus placebo: P†
Patients with ≥1 SRE during the study, n (%)							
Excluding asymptomatic fractures	64 (30)	74 (33.5)	85 (41)	−11.0 (−20.1 to −1.8)	.019	−7.4 (−16.5 to 1.8)	.125
15–24 months‡ (extension phase only)	14/74 (19)	13/54 (24)	22/58 (38)	−19.0 (−34.3 to −3.7)	.017	−13.9 (−31.0 to 3.3)	.121
Prior SRE at study entry	27/66 (41)	35/71 (49)	40/78 (51)	−10.4 (−26.7 to 6.0)	.215	−2.0 (−18.1 to 14.1)	.809
No prior SRE at study entry	54/147 (37)	56/149 (38)	61/130 (47)	−10.2 (−21.8 to 1.4)	.087	−9.3 (−20.9 to 2.3)	.116

Outcome	Zoledronic acid§ (n = 435)	Placebo (n = 208)	Zoledronic acid versus placebo: Difference (95% CI), %	Zoledronic acid versus placebo: P†	Zoledronic acid versus placebo: HR (95% CI)	Zoledronic acid versus placebo: P†
Patients with ≥1 SRE during the study, n (%)	172 (40)	101 (49)	−9.0% (−17.2% to −0.9%)	.031		
Median time to first SRE, days	423	321			0.779 (0.609 to 0.996)	.047

*CI = Confidence Interval; SRE = Skeletal related event; HR = hazard ratio.

†P values (two sided) for between-treatment comparisons are from the Cochran–Mantel–Haenszel test.

‡From randomization.

§Data reflect 4-mg and 8/4-mg groups combined.

found that statistically significantly fewer patients who received zoledronic acid had SREs than did patients who received placebo (40% versus 49%, difference = –9.0%, 95% CI = –17.2% to –0.9%; $P = .031$), and the median time to the first SRE was more than 3 months longer for patients who received zoledronic acid than for patients who received placebo (423 days versus 321 days; $P = .047$) (Table 2).

We also examined whether patients with a history of SREs were predisposed to subsequent SREs and whether the slight imbalance between treatment groups with respect to history of SREs affected the outcome of this trial. At study entry, 30.8% and 32.1% of patients in the 4- and 8/4-mg zoledronic acid groups, respectively, had experienced an SRE, compared with 37.5% of patients in the placebo group. We therefore performed a stratified analysis to examine the incidence of SREs during the trial among patients with and without an SRE before study entry and the treatment benefit in each subgroup. This analysis showed that patients with an SRE before study entry had a higher incidence of SREs during the study than patients without an SRE before study entry (Table 2). Nevertheless, compared with patients in the placebo group, fewer patients in either zoledronic acid group had an SRE during the 24 months on study, regardless of their history of SREs prior to study entry. Compared with placebo, 4 mg of zoledronic acid also extended the median time to the first on-study SRE in both subgroups (data not shown). These results are consistent with the findings of a recent report demonstrating that zoledronic acid provides statistically significant ongoing treatment benefits for patients who experienced a first SRE while on study *(4)*.

Because prostate cancer patients often experience multiple SREs over the course of the disease *(5)*, we also conducted an Andersen–Gill multiple-event analysis, which accounts for all clinically relevant SREs during the 24-month study and the timing of events, to provide a more comprehensive assessment of skeletal morbidity *(5)*. Results of this analysis revealed that 4 mg of zoledronic acid produced a statistically significant 36% reduction in the ongoing risk of SREs, based on a risk ratio of 0.640 (95% CI = 0.485 to 0.845; $P = .002$) compared with results of placebo (Table 1).

Periodic measures of BPI scores (at 3-month intervals) also demonstrated statistically significant and durable palliation of bone pain for patients treated with zoledronic acid (both 4- and 8/4-mg groups) compared with results of the placebo group. In fact, changes from baseline pain scores showed a clear dose response (Table 1).

As previously reported *(2)*, adverse events (e.g., mild-to-moderate fatigue, myalgia, and fever) occurred more frequently in patients treated with zoledronic acid than with placebo during the core phase; the incidence of these adverse events was similar between the zoledronic acid and placebo groups during the extension phase (data not shown). Moreover, the rate of study discontinuation due to adverse events did not differ substantially among the three treatment groups.

In conclusion, long-term treatment with 4 mg of zoledronic acid is safe, has demonstrated statistically significant reductions in skeletal complications, and provides durable palliation of bone pain in patients with bone metastases secondary to hormone-refractory prostate cancer. Zoledronic acid is the only bisphosphonate that has demonstrated a

statistically significant reduction in skeletal complications in a randomized, placebo-controlled trial. Results of exploratory analyses suggest that zoledronic acid provided ongoing clinical benefit—regardless of the patient's history of SREs before study entry—throughout the 24-month study period. Although the optimal duration of zoledronic acid therapy is not known, the available evidence suggests that patients continue to receive benefit for as long as they are treated. Therefore, similar to the treatment guidelines for breast cancer *(6)*, it is reasonable to treat patients with zoledronic acid for as long as it is tolerated or until the patient experiences a substantial decline in performance status.

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NOTES

The following have conducted or are currently conducting research sponsored by Novartis Pharmaceuticals: F. Saad, D. M. Gleason, R. Murray, L. Lacombe, J. L. Chin, and J. J. Vinholes. J. A. Goas and D. M. Gleason hold shares of Novartis stock. F. Saad, L. Lacombe, and J. L. Chin are consultants on an advisory board to Novartis Pharmaceuticals.

Manuscript received November 20, 2003; revised March 26, 2004; accepted April 2, 2004.