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ORIGINAL REPORT

Skeletal Health After Continuation, Withdrawal, or Delay of Alendronate in Men With Prostate Cancer Undergoing Androgen-Deprivation Therapy

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ABSTRACT

Purpose
Androgen-deprivation therapy (ADT) for prostate cancer is associated with bone loss and osteoporotic fractures. Our objective was to examine changes in bone density and turnover with sustained, discontinued, or delayed oral bisphosphonate therapy in men receiving ADT.

Patients and Methods
A total of 112 men with nonmetastatic prostate cancer receiving ADT were randomly assigned to alendronate 70 mg once weekly or placebo in a double-blind, partial-crossover trial with a second random assignment at year 2 for those who initially received active therapy. Outcomes included bone mineral density and bone turnover markers.

Results
Men initially randomly assigned to alendronate and randomly reassigned at year 2 to continue had additional bone density gains at the spine (mean, 2.3% ± 0.7) and hip (mean, 1.3% ± 0.5%; both $P < .01$); those randomly assigned to placebo in year 2 maintained density at the spine and hip but lost (mean, −1.9% ± 0.6%; $P < .01$) at the forearm. Patients randomly assigned to begin alendronate in year 2 experienced improvements in bone mass at the spine and hip, but experienced less of an increase compared with those who initiated alendronate at baseline. Men receiving alendronate for 2 years experienced a mean 6.7% (± 1.2%) increase at the spine and a 3.2% (± 1.5%) at the hip (both $P < .05$). Bone turnover remained suppressed.

Conclusion
Among men with nonmetastatic prostate cancer receiving ADT, once-weekly alendronate improves bone density and decreases turnover. A second year of alendronate provides additional skeletal benefit, whereas discontinuation results in bone loss and increased bone turnover. Delay in bisphosphonate therapy appears detrimental to bone health.

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INTRODUCTION

Androgen-deprivation therapy (ADT) is commonly used for nonmetastatic and advanced prostate cancer, and use has increased two- to four-fold in the last 10 years.[1-3] We and others have previously reported that men with prostate cancer receiving ADT have significant bone loss across all skeletal sites compared with men with prostate cancer who are not receiving ADT.[4-10] Bone loss is greatest within the first 12 months after initiation of treatment.[11] Long-term ADT is associated with a double to quadruple increase in fracture risk.[12-16]

We recently reported that once-weekly oral alendronate prevents bone loss across 1 year in men receiving ADT.[17] Other investigators have also demonstrated that intravenous bisphosphonates maintain bone mass in these patients.[18-20] Little information is available on changes in bone mass or turnover after discontinuation of bisphosphonate therapy or whether a second year of oral therapy provides additional skeletal benefit. This trial was designed a priori to include a second year of therapy to determine whether men needed to continue therapy to prevent bone loss and whether a second year of therapy resulted in additional gain in bone mass. We also examined the duration of ADT before bisphosphonate therapy on skeletal health.

PATIENTS AND METHODS

Participant Characteristics

Men age 85 years or younger receiving ADT for nonmetastatic prostate cancer were enrolled.[17] ADT included

gonadotropin-releasing hormone agonists, antiandrogens, or combinations of the two. Men were excluded if they were receiving medications or had diseases known to affect bone metabolism, had an elevated prostate-specific antigen (PSA) level, had a testosterone not in castrate range, or were previously or currently on a bisphosphonate. The protocol was approved by the institutional review board. Participants provided written informed consent.

Study Design

This study was a randomized, double-blind, placebo-controlled, partial-crossover trial. We previously reported the results of the first year.[17] This report focuses on the second year of oral therapy. After the first year, participants in the placebo arm were crossed over to receive 1 year of alendronate. Participants in the alendronate arm were randomly reassigned to receive alendronate or matching placebo.

Treatments

Participants received alendronate 70 mg orally once per week or matching placebo (Merck & Co, Rahway, NJ). Baseline total daily calcium intake was assessed with a food frequency questionnaire,[21] and men received supplements with calcium carbonate and vitamin D (Oscal 500 Plus D, GlaxoSmith Kline, Pittsburgh, PA) to ensure that their daily calcium intake was greater than 1,000 mg/d.

We screened 126 men, 112 men were randomly assigned, 56 were treated with alendronate, and 56 received placebo[17](Fig 1). At the end of year 1, 51 patients remained on alendronate, 25 were randomly assigned to continue active treatment (alendronate-alendronate), and 26 were randomly assigned to placebo (alendronate-placebo). Of the 56 men in placebo arm at baseline, 52 men remained in the trial and were crossed to alendronate (placebo-alendronate).

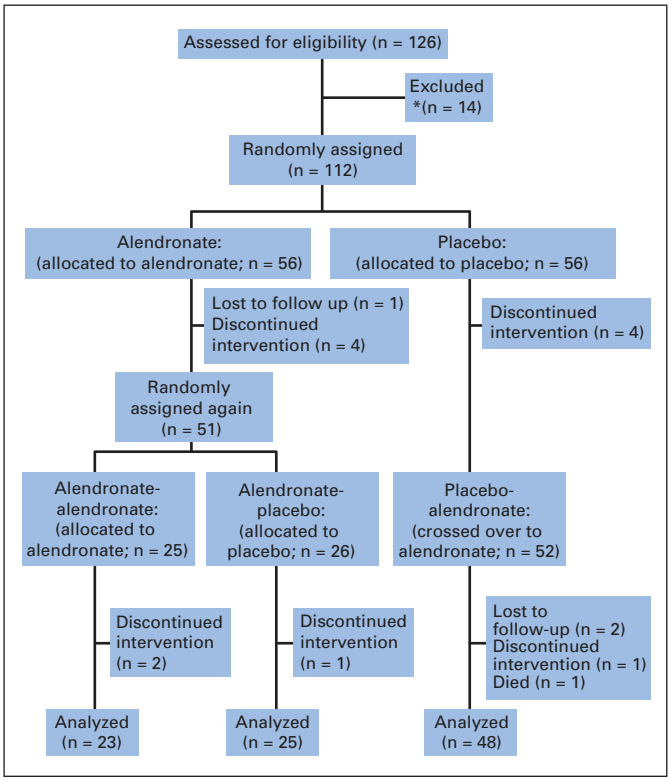

Fig 1. Flow diagram of the progress through the phases of the clinical trial. (*) Participants were excluded if they dropped out during the initial screening (n = 6), were not hypogonadal (n = 3), were too ill (n = 1), had metastatic disease at baseline (n = 1), an elevated prostate-specific antigen (n = 1), were on glucocorticoids (n = 1) or had another cancer (n = 1). During the 2-year follow-up, the reasons for attrition in each group included lost to follow-up, discontinued intervention, died, refused, or medical exclusion.

Protocol and Outcome Variables

Height (cm) and weight (kg) were assessed at each visit, and PSA, testosterone and 25-hydroxyvitamin were measured at baseline.[17] Bone mineral density (BMD) of the hip (total hip, femoral neck, and trochanter), lumbar spine (posteroanterior [PA] and lateral), and radius (one-third ultradistal, and total) were measured by dual-energy x-ray absorptiometry (QDR-4500A; Hologic Inc, Bedford, MA) at baseline, 6, 12, 18, and 24 months. The coefficient of variation (CV) is 1.3% and 1.4% for the spine and total hip BMD, respectively.[11]

Markers of bone formation included serum intact *N*-terminal propeptide of type I procollagen (P1NP, μg/L; DiaSorin Inc, Saluggia [Vercelli], Italy), bone-specific alkaline phosphatase (Alkphase-B, U/L; Quidel Corp, San Diego, CA) and osteocalcin (Novocalcin, ng/mL; Quidel Corp). Markers of bone resorption included serum C-telopeptide crosslinked collagen type 1 (CTX, nmol/L BCE; Crosslaps; Osteometer Biotech, Hawthorne, CA) and urinary *N*-telopeptide crosslinked collagen type 1 (NTX, nmol bone collagen equivalents/mmol creatinine; Osteomark; Ostex International, Princeton, NJ).

Adherence assessed by return of unused tablets was defined as taking 80% of the medication during the study. Adverse events were coded using the Medical Dictionary for Regulating Activities (MedDRA).

Statistical Analysis

Subject characteristics were compared across the three groups using analysis of variance or Kruskal-Wallis tests. Within-group changes over time were assessed using paired samples *t* tests. A mixed model was fitted using SAS MIXED (SAS Institute, Cary, NC) procedure with change in each BMD measure and marker of bone turnover as the response variable; treatment group, time, and their interaction as main fixed effects of interest; baseline value of the response variable as a covariate; and a participant random effect to account for multiple measurement from the same participants over time. Appropriate contrasts were used to make various between-group comparisons of interest. Specifically, the alendronate-alendronate and alendronate-placebo groups were compared in terms of 12- to 24-month change to assess the effect of sustained treatment. Baseline to 12-month change in the alendronate-alendronate and alendronate-placebo groups was compared with baseline to 24-month change in the placebo-alendronate group to assess the effect of delaying treatment by 1 year. Both raw and percentage changes were used as response variables to assess the robustness of the results. A post hoc analysis was conducted using an alternative method to more appropriately assess the effect of ADT duration before commencement of alendronate treatment. Specifically, because all patients received 1 year of alendronate therapy regardless of the randomized group assignment, our data could be considered as having come from a 1-year prospective cohort study of patients. A series of mixed models were fitted with raw BMD at each site as the response variable; time (0/6/12 months of alendronate) and ADT duration before starting alendronate ($<$ 12/12 to 24/24 to 36/36-48/ $\geq$ 48 months) as fixed effects of interest; and a participant random effect. On observing a discriminating threshold around 36 months of prior ADT use, the mixed models were refitted with the appropriate dichotomized version of prior ADT duration ($<$ 36/$\geq$ 36 months). The gain in BMD was estimated after receiving alendronate for 12 months among those with less than 36 and 36 or more months of prior ADT, and the difference in BMD between those with less than 36 and 36 or more months of prior ADT, after 12 months of alendronate therapy. Compliance and adverse event rates across the groups were compared using Fisher's exact test.

RESULTS

There were no significant differences in baseline clinical characteristics[17] (Table 1). At baseline, the average age was a mean of 71.4 years ($\pm$ 8.6 years) , duration of ADT was a mean of 25.5 months ($\pm$ 29.3 months; median, 14.0 months), and PSA level was a mean of 1.1 ng/mL ($\pm$ 4.3 ng/mL; median, 0.10 ng/mL). Sixty percent of men were receiving gonadotropin-releasing hormone agonists, 38% were receiving combination with an antiandrogen, and 2% were receiving

Table 1. Baseline Clinical Characteristics of Those on Study at Year 2

Characteristic	Alendronate-Alendronate (n = 25) No.	%	Alendronate-Placebo (n = 26) No.	%	Placebo-Alendronate (n = 52) No.	%	*P*
Age, years							.605
Mean	71.9		70.0		71.9		
SD	7.1		9.1		9.0		
Body mass index, kg/m^2	29.5		27.2		28.9		.090
Mean	4.1		2.5		4.4		
SD							
ADT							.276
GnRH agonists	15	60	12	46	34	65	
Antiandrogen	0	0	0	0	2	4	
Combination therapy	10	40	14	54	16	31	
Duration of ADT, months							.234
Mean	16.8		27.9		28.5		
SD	5.4		29.7		33.5		
Median	11.0		15.0		14.5		
< 36	21	84.0	19	73.1	39	75.0	.600
≥ 36	4	16.0	7	26.9	13	25.0	
Calcium intake, mg/d							.464
Mean	1,007.9		851.4		1,055.7		
SD	572.1		623.4		763.1		
Vitamin D intake, U/d							.049
Mean	718.2		550.2		479.1		
SD	479.8		385.3		350.2		
Serum 25 hydroxy vitamin D, ng/mL							.774
Mean	33.4		34.0		32.5		
SD	8.2		9.3		9.5		
Bone mineral density, g/cm^2							
Posterior anterior spine							.012
Mean	1.14		1.01		1.04		
SD	0.17		0.14		0.17		
Lateral spine							.163
Mean	0.74		0.70		0.67		
SD	0.12		0.16		0.14		
Total hip							.003
Mean	1.03		0.94		0.92		
SD	0.11		0.12		0.13		
Femoral neck							.027
Mean	0.79		0.75		0.72		
SD	0.10		0.10		0.10		
Trochanter							<.001
Mean	0.82		0.72		0.70		
SD	0.13		0.12		0.11		
One-third distal radius							.017
Mean	0.77		0.74		0.72		
SD	0.07		0.08		0.09		
Markers of bone turnover							
Urinary NTX, nmol BCE/mmol Cr							.96
Mean	53.1		53.5		52.0		
SD	19.8		20.9		26.2		
Serum CTX, nmol/BCE							.45
Mean	0.60		0.64		0.56		
SD	0.25		0.26		0.26		
P1NP, ng/L							.18
Mean	55.3		71.0		59.6		
SD	25.2		42.1		28.2		
Osteocalcin,(ng/mL							.46
Mean	14.5		16.3		15.4		
SD	5.0		4.9		5.7		

(continued on following page)

Table 1. Baseline Clinical Characteristics of Those on Study at Year 2 (continued)

Characteristic	Alendronate-Alendronate (n = 25) No.	%	Alendronate-Placebo (n = 26) No.	%	Placebo-Alendronate (n = 52) No.	%	*P*
BSAP, U/L							.47
Mean	26.5		30.0		28.2		
SD	8.7		13.2		9.2		
Osteoporosis classification*							.051
Normal	5	20	3	11.5	3	5.8	
Low bone mass (osteopenia)	14	56	15	57.7	21	40.4	
Osteoporosis	6	24	8	30.8	28	53.9	

Abbreviations: SD, standard deviation; ADT, androgen-deprivation therapy; GnRH, gonadotropin-releasing hormone; NTX, *N*-telopeptide crosslinks of type 1 collagen; BCE, bone collagen equivalence; Cr, creatinine; CTX, C-telopeptide cross-links of type 1 collagen; P1NP, *N*-terminal propeptide of type 1 procollagen; BSAP, bone-specific alkaline phosphatase.

*Osteoporosis classification by spine, hip, and femoral neck according to WHO and International Society of Clinical Densitometry.[22,23,33]

only an antiandrogen. At baseline, there were small differences in BMD across the three groups, but no differences in markers of bone turnover (Table 1), for which the main analyses were adjusted. According to WHO classification,[22,23] 41% had osteoporosis, 49% had low bone mass, and 11% were normal. Adherence was 74% in the alendronate-alendronate group, 83% in the alendronate-placebo group, and 77% in the placebo-alendronate group ($P = .767$).

Changes in Year 2

At the beginning of year 2, the men randomly reassigned to the alendronate-alendronate group did not differ from the alendronate-placebo group in BMD at the lateral spine, femoral neck, one-third distal radius, total radius, or bone markers. There were small differences in spine (1.19 ± 0.19 *v* 1.04 ± 0.14 g/cm^2; $P = .002$) and hip (1.03 ± 0.11 *v* 0.95 ± 0.12 g/cm^2; $P = .015$) BMD.

During year 2, BMD in the men in the alendronate-alendronate group increased by a mean of 2.3% ($\pm$ 3.4%) at the spine ($P = .005$) and 1.3% ($\pm$ 2.2%) at the total hip ($P = .010$; Fig 2) relative to their 12-month measurements. BMD remained stable at the femoral neck and one-third distal radius. In comparison, BMD in the alendronate-placebo group, decreased a mean 1.9% ($\pm$ 3.1%; $P = .006$) at the one-third distal radius and 2.1% ($\pm$ 2.6%; $P < .001$) at the total radius, whereas bone density remained stable at the spine and hip.

Serum CTX in the men in the alendronate-alendronate group decreased a mean of 18.6% ($\pm$ 28.4%; $P = .008$), and other bone markers remained stable (Fig 2). In the alendronate-placebo group, urinary NTX increased a mean of 70.5% ($\pm$ 126.2%; $P = .010$) with significant increases also observed in P1NP and bone-specific alkaline phosphatase (Fig 2).

Within-Group Changes After 2 Years

After 2 years of study, men in the alendronate-alendronate group had the greatest increases in BMD relative to baseline including mean increases of 6.7% ($\pm$ 5.6%) at the spine ($P < .001$), 1.6% ($\pm$ 2.7%) at the total hip ($P = .011$) and 3.2% ($\pm$ 7.1%) at the femoral neck ($P = .041$; all $P < .05$; Fig 3). The alendronate-placebo group and the placebo-alendronate group also had increases at the spine (mean, 3.3% $\pm$ 3.6% and mean, 2.4% $\pm$ 4.8%, respectively; both $P < .002$), but the changes from baseline at the total hip and femoral neck for both groups were not significant (Fig 3). At the one-third distal radius, bone density decreased in all groups except for men who received alendronate for 2 years. A similar pattern of decreased bone density was observed at the total radius (Fig 3).

After 2 years, biochemical markers of bone turnover were significantly below baseline in all three groups (Fig 3). For example, at 24 months, CTX was decreased by a mean of 60.7% ($\pm$ 21.5%) in

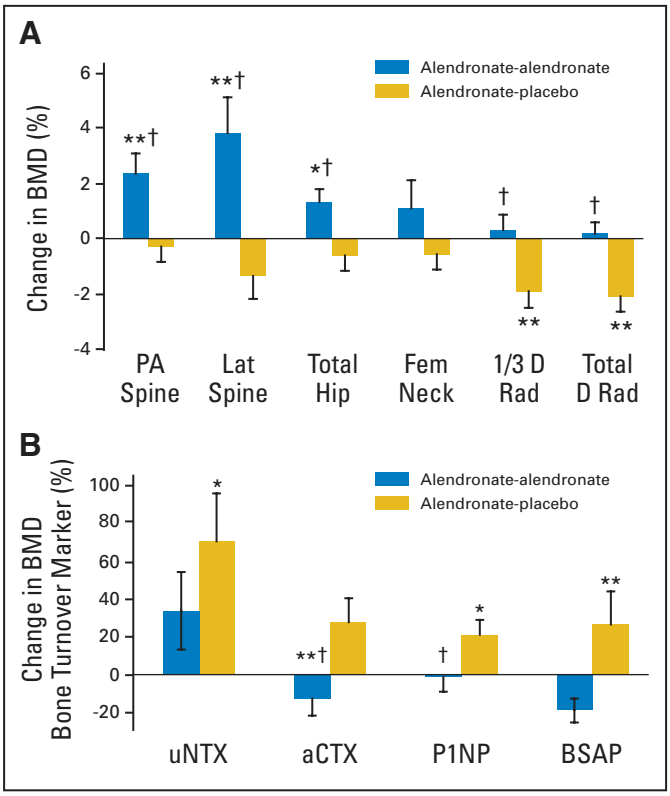

Fig 2. Mean percentage change (with SEM) in (A) bone mineral density (BMD) during the second year of the trial and (B) bone turnover markers during the second year of the trial. (*) $P < .05$; (**) $P < .01$ change from month 12 to 24; (†) $P < .05$ comparison between alendronate-alendronate versus alendronate-placebo groups. PA, posteroanterior; Lat, lateral; Fem, femoral; 1/3 D Rad, one-third distal radius; D Rad, distal radius; uNTX, urinary *N*-telopeptide croslinked collagen type 1; aCTX, cerum C-telopeptide crosslinked collagen type 1; P1NP, type I procollagen; BSAP, bone-specific alkaline phosphatase.

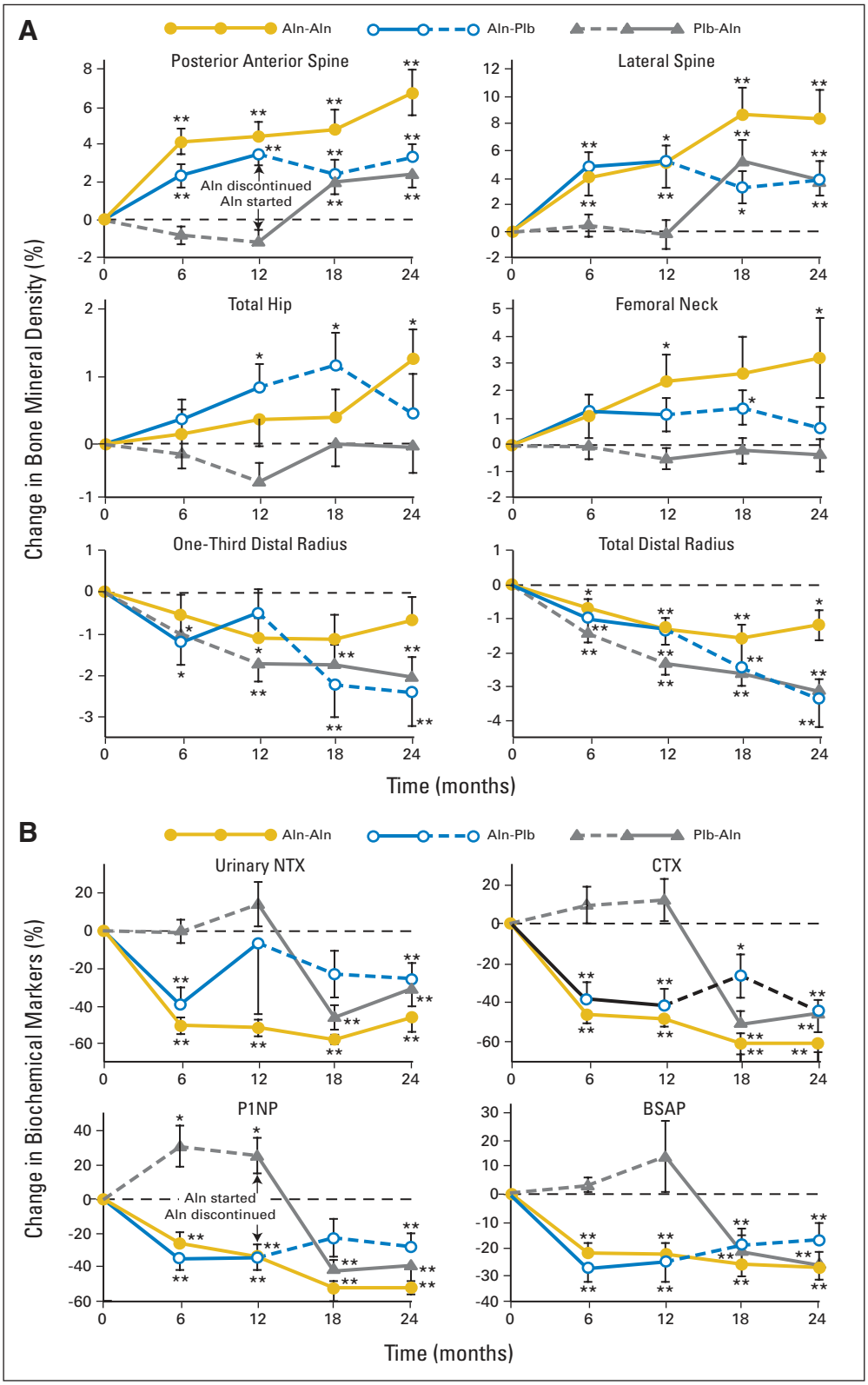

Fig 3. Mean percentage change (with SEM) in (A) bone mineral density from baseline to 24 months and (B) bone turnover markers from baseline to 24 months. (*) $P < .05$; (**) $P < .01$ change from baseline. Aln-Aln, alendronate-alendronate; Aln-Plb, alendronate-placebo; Plb-Aln, placebo-alendonate; NTX, *N*-telopeptide crosslinked collagen type 1; CTX, C-telopeptide crosslinked collagen type 1; P1NP, type I procollagen; BSAP, bone-specific alkaline phosphatase.

the alendronate-alendronate group, 44.6% (± 28.6%) in the alendronate-placebo group, and 45.8% (± 64.3%) in the placebo-alendronate group (all $P < .001$). Similar significant decreases in all three treatment groups were seen with urinary NTX, P1NP, and bone-specific alkaline phosphatase (Fig 3).

Between-Group Differences in Changes After 2 Years

The increases in BMD in the alendronate-alendronate group were greater than the alendronate-placebo group at the PA spine (mean, 3.79% ± 1.22%; $P = .002$), lateral spine (mean, 4.97% ± 2.13%; $P = .021$), femoral neck (mean, 2.59% ± 1.17%; $P = .028$), ultradistal and total distal radius (mean, 2.34% ± 0.98% and 2.25% ± 0.68%, respectively; both $P < .02$; Table 2). The alendronate-alendronate group also had greater increases compared with the placebo-alendronate group at the PA spine (mean, 4.66% ± 1.07%; $P < .001$), lateral spine (mean, 4.64% ± 1.98%; $P = .02$), femoral neck (mean, 3.75% ± 1.04%; $P < .001$), trochanter (mean, 1.92% ± 0.89%; $P = .032$), total hip (mean, 1.92% ± 0.68%; $P = .005$), and ultradistal and total radius (both $P < .001$; Table 2). At 2 years, there were no significant differences in BMD between the alendronate-placebo group and the placebo-alendronate group. Furthermore, there were no differences in the bone markers between any groups at 2 years (Table 2). Using the WHO classification,[22,23] at the end of 2 years there were no differences in the osteoporosis classification between the alendronate-alendronate group (normal, 21.7%; low bone mass, 56.5%; osteoporosis, 21.7%), the alendronate-placebo group (normal, 12.0%; low bone mass, 52.0%; osteoporosis, 36.0%) and the placebo-alendronate group (normal, 10.4%; low bone mass, 35.4%; osteoporosis, 54.2%; $P = .097$).

Effect of Sustained Treatment

To determine whether there was evidence for an additional benefit by sustaining treatment for 24 months versus treatment of only 12 months, 12- to 24-month gains in bone mineral density were compared between alendronate-alendronate and alendronate-placebo groups by mixed-model analysis adjusted for baseline. The alendronate-alendronate group that sustained treatment had a significantly greater percentage point increase in BMD compared with the alendronate-placebo group at the spine (adjusted means difference, 2.6 ± 1.0; $P = .009$), lateral spine (adjusted means difference, 5.1 ± 1.7; $P = .004$), total hip (adjusted means difference, 1.7 ± 0.7; $P = .019$), trochanter (adjusted means difference, 2.1 ± 0.8; $P = .010$), and the one-third distal, ultradistal and total radial sites (adjusted means difference, 2.1 to 2.2; all $P < .021$; Table 3).

Effect of Delaying Treatment

To determine whether a delay in treatment by 12 months was detrimental, differences in BMD, after being on treatment for the same length of time, were compared between men who initiated treatment at baseline (alendronate-alendronate and alendronate-placebo groups) versus those who delayed treatment (placebo-alendronate) by 1 year using mixed-model analysis. On average, men who did not delay treatment compared with men who delayed had a gain in BMD that was greater at the spine, femoral neck, ultradistal radius and total radius (all $P < .05$; Table 3) at 12 months.

To further explore the question of delay of treatment with alendronate, we examined the change in BMD on the basis of duration of ADT before alendronate treatment. When men were categorized as having had ADT for less than 36 months versus at least 36 months, men who had been receiving ADT for less than 36 months and then treated with alendronate for 12 months had a gain of 0.043 g/cm^2 ($P < .001$) of BMD at the spine compared with a gain of 0.030 g/cm^2 ($P < .001$) for men who had prior ADT for greater than 36 months. After 12 months of alendronate treatment, men with a shorter duration of ADT treatment had a 0.101 g/cm^2 greater BMD compared with those with a longer duration ($P = .008$). Similar additional gains were also observed at the lateral spine, hip trochanter, one-third distal radius, and total radius.

Adverse Events

Over the 2 years there were four participants experiencing clinical fractures including one in the alendronate-alendronate group, two in the alendronate-placebo group, and one in the placebo-alendronate group. During year 2, there were no differences

Table 2. Between-Group Differences in Change ± SE After 2 Years, Adjusted for Baseline Measurement of Outcome

	Alen/Alen *v* Alen/Placebo			Alen/Alen *v* Placebo/Alen			Alen/Placebo *v* Placebo/Alen		
Outcome	Percentage Point Difference Change	SE	*P*	Percentage Point Difference Change	SE	*P*	Percentage Point Difference Change	SE	*P*
PA spine	3.79	1.22	.002	4.66	1.07	< .001	0.87	1.01	.392
Lateral spine	4.97	2.13	.021	4.64	1.98	.020	−0.33	1.87	.862
Femoral neck	2.59	1.17	.028	3.75	1.04	< .001	1.16	1.00	.247
Trochanter	0.67	0.99	.500	1.92	0.89	.032	1.25	0.82	.131
Total hip	1.26	0.77	.101	1.92	0.68	.005	0.67	0.65	.303
One-third distal radius	1.50	0.90	.096	1.15	0.80	.151	−0.34	0.77	.653
Ultradistal radius	2.34	0.98	.018	2.90	0.86	< .001	0.56	0.83	.502
Total distal radius	2.25	0.68	.001	2.07	0.60	< .001	−0.18	0.58	.762
Urine NTX	−20.43	20.28	.315	−14.36	17.78	.420	6.08	17.33	.726
Serum CTX	−17.16	14.28	.231	−11.79	12.51	.347	5.37	12.09	.657
BSAP	−12.83	13.30	.335	−5.53	11.62	.634	7.31	11.20	.515
Osteocalcin	−16.85	8.26	.042	−10.22	7.22	.158	6.63	6.97	.342
P1NP	−31.8	15.06	.036	−17.27	13.13	.190	14.54	12.67	.252

Abbreviations: Alen, alendronate; PA, posteroanterior; NTX, *N*-telopeptide crosslinks of type 1 collagen; BSAP, bone-specific alkaline phosphatase; CTX, C-telopeptide crosslinks of type 1 collagen; P1NP, *N*-terminal propeptide of type 1 procollagen.

Table 3. Effects of Sustained Treatment and Delaying Treatment

Effect	Sustained Treatment Effect After 12 Months*			Effect of Delaying Treatment for 12 Months†		
	Percentage Point Change From 12 to 24 Months	SE	*P*	Percentage Point Change From Baseline	SE	*P*
PA spine	2.63	1.00	.009	1.75	0.84	.038
Lateral spine	5.10	1.74	.004	1.11	1.59	.489
Femoral neck	1.48	1.07	.171	2.21	0.83	.009
Trochanter	2.07	0.79	.010	1.14	0.70	.103
Total hip	1.67	0.71	.019	1.01	0.54	.064
One-third distal radius	2.24	0.80	.005	1.19	0.63	.062
Ultradistal radius	2.09	0.90	.021	2.76	0.68	< .0001
Total distal radius	2.20	0.61	< .0001	1.88	0.48	.0001

Abbreviation: PA, posteroanterior.
*Sustained treatment effect: Alendronate-alendronate versus alendronate-placebo.
†Effect of delaying treatment by 1 year: baseline to 12 months percentage change in combined alendronate-alendronate and alendronate-placebo groups *v* baseline to 24 months percentage change in placebo-alendronate group. Assessed after receiving treatment for 12 months.

in the proportions of patients experiencing total or serious adverse events (Table 4). There were no differences in the proportions of patients experiencing adverse events associated with alendronate except for myalgias and arthralgias, which were rare in the group randomly reassigned to placebo in year 2 but were reported in the groups assigned to alendronate.

DISCUSSION

This double-blind, placebo-controlled, randomized, partial-crossover clinical trial was designed to examine once-weekly oral alendronate for the prevention and treatment of androgen deprivation-induced bone loss in men with prostate cancer. In the first year, we reported that alendronate improved BMD in the spine and hip and prevented loss at the distal radius.[17] During the second year, our goal was to determine whether an additional year of oral bisphosphonate treatment resulted in continued improvement in bone density and whether withdrawal of the treatment resulted in a decline. We also examined whether a delay in alendronate treatment by 12 months was detrimental to bone mass and the impact of duration of ADT before alendronate therapy. Results of this trial support our a priori hypothesis that a second year of alendronate therapy provides continued skeletal benefit and suppression of bone turnover. Discontinuation of alendronate however, resulted in maintenance of bone mass at the spine and hip coupled with a significant decrease in bone density at the forearm. However, a delay in bisphosphonate treatment was detrimental compared with early treatment. These results suggest that the oral bisphosphonate is needed to provide continued benefit to the skeleton during ADT and should be considered when androgen deprivation is initiated.

Although previous reports have demonstrated the benefits of intravenous bisphosphonates after 48 weeks,[18,20] the impact of withdrawal from either intravenous or oral therapy has not been examined in men with prostate cancer. In postmenopausal women, after 2 or 5 years of oral alendronate therapy, bone density at the spine and hip remained stable after the first year of discontinuation.[24-26] The decline in the radius observed in men has not been previously reported in women. Men experience bone loss at the forearm with initiation and continuation of androgen deprivation.[11] Because the forearm is strongly associated with fracture risk in men,[27] these findings may be clinically relevant.

Little data are available on the consequences of delaying treatment with bisphosphonate after initiation of ADT for prostate cancer. We examined this using several methods. Men who delayed alendronate therapy had a smaller gain in BMD at 2 years compared with men who initiated alendronate at the beginning of the study. Furthermore,

Table 4. Participants Experiencing Adverse Events

Event	During the Second Year							After 2 Years						
	Alendronate-Alendronate		Alendronate-Placebo		Placebo-Alendronate			Alendronate-Alendronate		Alendronate-Placebo		Placebo-Alendronate		
	No.	%	No.	%	No.	%	*P*	No.	%	No.	%	No.	%	*P*
Any adverse events	22	88.0	19	73.1	41	78.8	.409	23	92.0	23	88.5	50	96.2	.449
Serious adverse events	5	20.0	5	19.2	10	19.2	.996	11	44.0	7	26.9	18	34.6	.440
Known associations with alendronate														
Gastric	1	4.0	0	0.0	1	1.9	.490	1	4.0	2	7.7	4	7.7	.99
Esophageal	1	4.0	1	3.8	1	1.9	.805	1	4.0	1	3.8	2	3.8	.99
Constipation	0	0.0	1	3.8	2	3.8	.99	2	8.0	2	7.7	8	15.4	.558
Myalgia	5	20.0	0	0.0	6	11.5	.038	6	24.0	1	3.8	10	19.2	.096
Arthralgia	10	40.0	4	15.4	16	30.8	.144	15	60.0	5	19.2	18	34.6	.009

regardless of ADT duration, alendronate was effective. However, after 1 year of alendronate treatment, men who had been receiving ADT for less than 3 years had a greater gain in BMD compared with those who had been receiving ADT for more than 36 months. Because of the post hoc secondary nature of analysis, these results should be interpreted with caution. Nonetheless, our results provide preliminary evidence in support of initiating bisphosphonate therapy early in the course of ADT.

Our study has several limitations. This study was not designed to examine clinical fractures. The occurrence of fractures may require several years of androgen deprivation. We chose to examine surrogate outcomes of osteoporosis using bone mass and turnover that provide supportive evidence for fracture reduction as suggested by the Surgeon General.[28] Second, because only 11% were classified with a normal BMD at baseline, we felt we could not perform a complete double-blind, placebo-controlled trial because it would be inappropriate to withhold treatment for 2 years in hypogonadal men who had low bone mass or osteoporosis. All men received at least 1 year of therapy. Despite blinded randomization, we observed a chance difference in baseline BMD between groups with the greatest BMD in men who received therapy for 2 years. To address such differences, we adjusted our analyses for baseline BMD by including it as a covariate in our mixed models. Moreover, such differences should make the percentage change analyses more conservative because the same magnitude of absolute change will be interpreted as a smaller degree of percentage change in the group that received alendronate during the entire 2-year period. Finally, we included both men who were receiving chronic androgen deprivation and those who were initiating therapy. Although, this broader inclusion increases the variability among our participants, it also makes the results more generalizable and makes a secondary analysis on effect of prior ADT duration on outcomes possible.

Because the greatest bone loss occurs on initiation of ADT,[11] early screening with BMD assessment and preventive measures (calcium, vitamin D, exercise) would be encouraged.[9,10,29] Suggested guidelines have been generated from expert panels and reviews and recommend treatment for men with prostate cancer receiving ADT with (1) an adult fragility fracture, (2) osteoporosis, or (3) low bone mass by bone density with a risk factor for fracture.[9,10,29-32] Men should also be evaluated for other secondary causes of bone loss. Currently bisphosphonates are the recommended therapy.[9,10,29,32]

In summary, improvements in bone mineral density in men with prostate cancer on androgen deprivation are greatest in men who continue to receive alendronate therapy. Furthermore, delay in treatment is detrimental to skeletal integrity. In men with low bone mass or osteoporosis, once-weekly oral therapy with alendronate should be considered early and continued for at least 2 years in men with prostate cancer who are receiving ADT to gain maximum benefit to the skeleton.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Cooperberg MR, Lubeck DP, Meng MV, et al: The changing face of low-risk prostate cancer: Trends in clinical presentation and primary management. J Clin Oncol 22:2141-2149, 2004
2. Cooperberg MR, Grossfeld GD, Lubeck DP, et al: National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Can Inst 95:981-989, 2003
3. Zeliadt SB, Potosky AL, Etzioni R, et al: Racial disparity in primary and adjuvant treatment for nonmetastatic prostate cancer: SEER-Medicare trends 1991 to 1999. Urology 64:1171-1176, 2004
4. Stoch SA, Parker RA, Chen L, et al: Bone loss in men with prostate cancer treated with gonadotropin-releasing hormone agonists. J Clin Endocrinol Metab 86:2787-2791, 2001
5. Daniell HW: Osteoporosis after orchiectomy for prostate cancer. J Urol 157:439-444, 1997
6. Wei JT, Gross M, Jaffe CA, et al: Androgen deprivation therapy for prostate cancer results in significant loss of bone density. Urology 54:607-611, 1999
7. Kiratli BJ, Srinivas S, Perkash I, et al: Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. Urology 57:127-132, 2001
8. Berruti A, Dogliotti L, Terrone C, et al: Changes in bone mineral density, lean body mass and fat content as measured by dual energy X-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol 167:2361-2367, 2002
9. Eastham J: Bone health in men receiving androgen deprivation therapy for prostate cancer. J Urol 177:17-24, 2007
10. Greenspan SL: Approach to the prostate cancer patient with bone disease. J Clin Endocrinol Metab 93:2-7, 2008
11. Greenspan SL, Coates P, Sereika SM, et al: Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J Clin Endocrinol Metab 90:6410-6417, 2005
12. Shahinian VB, Kuo Y-F, Freeman JL, et al: Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 352:154-164, 2005
13. Krupski TL, Smith MR, Lee WC, et al: Natural history of bone complications in men with prostate carcinoma initiating androgen deprivation therapy. Cancer 101:541-549, 2004

14. Townsend MF, Sanders WH, Northway RO, et al: Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate cancer. Cancer 79:545-550, 1997

15. Hatano T, Oishi Y, Furuta A, et al: Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. BJU Int 86:449-452, 2000

16. Oefelein MG, Ricchuiti V, Conrad W, et al: Skeletal fracture associated with androgen suppression induced osteoporosis: The clinical incidence and risk factors for patients with prostate cancer. J Urol 166:1724-1728, 2001

17. Greenspan SL, Nelson JB, Trump DL, et al: Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: A randomized trial. Ann Intern Med 146:416-424, 2007

18. Smith MR, Eastham J, Gleason DM, et al: Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 169:2008-2012, 2003

19. Michaelson MD, Kaufman HL, Lee H, et al: Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol 25:1038-1042, 2007

20. Smith MR, McGovern FJ, Zietman AL, et al: Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med 345:948-955, 2001

21. Dawson-Hughes B, Jacques P, Shipp C: Dietary calcium intake and bone loss from the spine in healthy postmenopausal women. Am J Clin Nutr 46:685-687, 1987

22. Kanis JA, Melton LJ III, Christiansen C, et al: The diagnosis of osteoporosis. J Bone Miner Res 9:1137-1141, 1994

23. Kanis JA: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report. Osteoporos Int 4:368-381, 1994

24. Greenspan SL, Emkey RD, Bone HG III, et al: Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis: A randomized, double-blind, placebo-controlled trial. Ann Intern Med 137:883, 2002

25. Tonino RP, Meunier PJ, Emkey R, et al: Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. J Clin Endocrinol Metab 85:3109-3115, 2000

26. Bone HG, Hosking D, Devogelaer J-P, et al: Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350:1189-1199, 2004

27. Melton LJ III, Atkinson EJ, O'Connor MK, et al: Bone density and fracture risk in men. J Bone Miner Res 13:1915-1923, 1998

28. US Department of Health and Human Services: Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD, US Department of Health and Human Services, Office of the Surgeon General, 2004

29. Smith MR: Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. Cancer 97:789-795, 2003 (suppl)

30. Higano CS: Understanding treatments for bone loss and bone metastases in patients with prostate cancer: A practical review and guide for the clinician. Urol Clin North Am 31:331-352, 2004

31. Diamond TH, Higano CS, Smith MR, et al: Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy. Cancer 100: 892-899, 2004

32. Saad F, Schulman CC: Role of bisphosphonates in prostate cancer. Eur Urol 45:26-34, 2004

33. Binkley N, Bilezikian JP, Kendler DL, et al: Official positions of the International Society for Clinical Densitometry and Executive Summary of the 2005 Position Development Conference. J Clin Densitom 9:4-14, 2006

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