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Weekly Oral Alendronic Acid in Male Osteoporosis

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Abstract

Objective: To evaluate the efficacy and tolerability of alendronic acid 70mg once weekly for the treatment of male osteoporosis.

Patients and methods: This randomised, double-blind, placebo-controlled, 12-month trial compared the effect of alendronic acid 70mg once weekly or placebo (randomised 2 **:** 1) on bone mineral density (BMD) in 167 men with spine or hip BMD at least 2 standard deviations (SD) below the mean for young normal white males or nontraumatic fracture. All patients received calcium and vitamin D (colecalciferol). We measured lumbar spine, hip and total body BMD, and biochemical markers of bone turnover. Fractures were collected as adverse events.

Results: Alendronic acid 70mg once weekly produced significant BMD increases from baseline of 4.3% at the spine, 2.1% at the femoral neck, 2.4% at the trochanter, and 1.4% at the total body, which were all significantly greater than placebo ($p < 0.05$). The increase at the lumbar spine was significant relative to baseline and placebo after 6 months of treatment ($p < 0.001$). The treatment effect was consistent regardless of BMD, age, height, weight, body mass index (BMI) and hypogonadal status at baseline. Alendronic acid significantly decreased biochemical markers of bone turnover relative to baseline and placebo. Alendronic acid was generally well tolerated, with an incidence of gastrointestinal adverse events similar to placebo.

Conclusion: Alendronic acid 70mg administered once weekly is an effective and convenient alternative to daily dosing for the treatment of male osteoporosis.

Male osteoporosis is a common and important clinical problem, associated with significant morbidity, mortality and societal expense. Approximately 10% of men ≥65 years of age are osteoporotic.[1] Causes of male osteoporosis may include excess corticosteroids, various androgen deprivation therapies or hypogonadism, but often no specific aetiology is identified. The absolute number of osteoporotic fractures in men is also rising in part because of the 'graying' of the population. It is estimated that 30% of hip fractures worldwide will occur in men.[2]

Alendronic acid (Fosamax®, Whitehouse Station, NJ, USA)[1] is a potent antiresorptive agent that acts by inhibiting osteoclast activity,[3] while allowing the continued mineralisation of bone matrix. Alendronic acid reduces bone turnover in postmenopausal women with osteoporosis, increases bone mineral density (BMD), and reduces the risk of vertebral and nonvertebral fracture, including those of the hip, by approximately 50%.[4] Previous studies have demonstrated that alendronic acid 70mg administered once weekly is as effective as the 10mg daily dose in treating postmenopausal women with osteoporosis.[5,6] Furthermore, women who compared use of daily and weekly alendronic acid regimens in a crossover, open-label study indicated a strong preference for the once-weekly 70mg dose (86.4% vs 9.2%; $p < 0.001$).[7]

In men with osteoporosis, alendronic acid 10mg daily prevented bone loss, vertebral fractures and height loss.[8] Although not powered to be a fracture endpoint study, the current investigation was conducted to evaluate the efficacy and tolerability of alendronic acid 70mg once weekly for the treatment of male osteoporosis.

Patients and Methods

Subjects

Men aged 25–90 years with hypogonadal or idiopathic osteoporosis were studied at 13 centres in the US. Inclusion in the trial was based on: (a) BMD at least 2 standard deviations (SD) below the mean at the femoral neck (≤0.658 g/cm^2 [Hologic] or ≤0.867 [Lunar]) and at least 1 SD below the mean at the lumbar spine (≤1.005 g/cm^2 [Hologic] or ≤1.135 [Lunar]) for young normal white males; (b) BMD at least 2 SD below the mean at the lumbar spine (≤0.895 g/cm^2 [Hologic] or ≤1.015 [Lunar]) and at least 1 SD below the mean at the femoral neck (≤0.794 g/cm^2 [Hologic] or ≤0.987 [Lunar]), for young normal white males; or (c) documented nontraumatic (osteoporotic) fracture, including spinal fractures diagnosed on screening lateral radiograph, and femoral neck BMD at least 1 SD below the mean for young normal white males.

Patients were considered hypogonadal if serum free testosterone was below the age-specific normal range, as determined by the central laboratory at screening (ages 20–39 years: 18–39 pg/mL; ages 40–59 years: 13–33 pg/mL; ages 60–79 years: 9–26 pg/mL). Patients were excluded if osteoporosis was secondary to corticosteroids, metabolic bone disorders, vitamin D (colecalciferol) deficiency (as measured by 25-OH vitamin D <11 ng/dL at the screening visit), or testosterone deficiency if replacement therapy had been initiated within 1 year of enrolment. Other exclusion criteria included: any prior use of bisphosphonates; use of calcitonin within 6 months or fluoride within 24 months prior to screening; a history of recent (within 1 year) major upper gastrointestinal (GI) disease, such as peptic ulcer, malabsorption, oesophageal disease or active GI bleeding; any known oesophageal conditions leading to delayed emptying; and prostate cancer or elevated prostatic-specific antigen at baseline.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

The study was approved by the appropriate local ethics committees and institutional review boards at each centre. All participants provided written informed consent to participate in the study.

Treatment

Patients were stratified by hypogonadal status and randomly assigned in a 2 : 1 ratio to receive oral alendronic acid 70mg once-weekly tablets or placebo using a computer-generated, blinded allocation schedule. Patients were instructed to take one tablet of study medication once per week, with 177–237mL of plain water, at least 30 minutes before any other medication, food or drink of the day, and not to lie down until 30 minutes after dosing. Patients were instructed to take any missed weekly doses up to 1 day before the next scheduled weekly dose. In addition, 500mg of calcium as carbonate + 200 IU vitamin D (Os-cal® 500+D, SmithKline Beecham, Pittsburgh, PA, USA) was provided, to be taken twice daily with food, at least 30 minutes after study medication.

Study Procedures

Dual-energy x-ray absorptiometry measurement of BMD was conducted at the investigational sites, using Hologic (Hologic Corporation, Waltham, MA, USA) or Lunar (Lunar Corporation, Madison, WI, USA) densitometers. A central quality assurance centre, BioImaging Technologies, Inc. (BITI, Newtown, PA, USA), provided and monitored standardised procedures to obtain and submit BMD scans, and to maintain equipment. The local sites scanned a standard hydroxyapatite phantom as a quality control procedure each day that BMD measurements were obtained. BMD at the lumbar spine, hip and total body was measured at baseline and at 6 and 12 months. Baseline spine and hip BMD scans were analysed locally, then sent to BITI to confirm eligibility. All subsequent BMD scans were analysed centrally, and investigators were not provided with the results until the study ended.

Urinary N-telopeptides of type I collagen (NTx) corrected for creatinine (Osteomark™, Ostex International, Seattle, WA, USA) was selected as the bone resorption marker, and serum bone specific alkaline phosphatase (BSAP) [Ostase™, Beckman-Coulter, San Diego, CA, USA] as the bone formation marker in this study. Biochemical markers of bone turnover were collected at baseline and at 3, 6 and 12 months. All samples were collected fasting in the morning and assayed by a central laboratory (Medical Laboratory International) blinded to patient treatment assignment.

Safety Analysis

Lateral spine x-rays were obtained at baseline and at 12 months or early discontinuation. Morphometric assessment of individual vertebral heights was performed by the blinded, central radiologist (Dr C. Van Kujik, University of Amsterdam, Amsterdam, The Netherlands), according to established procedures.[9] An incident (new or worsening) vertebral fracture was defined as a decrease ≥20% and ≥4mm in any vertebral height between the baseline and subsequent radiographs. Symptomatic vertebral and nonvertebral fractures that occurred during the study were confirmed locally, radiographically and reported as clinical adverse experiences. Height (without shoes) was measured at baseline and at 12 months using a Harpenden stadiometer (Holtein Limited, UK). Three measurements taken at each visit were averaged. All clinical and laboratory adverse events were monitored throughout the study.

Statistical Planning and Analysis

A sample size of 80 patients in the alendronic acid group and 40 patients in the placebo group was planned to detect a difference of 3% for change in spine BMD between the two treatment groups with a power of 97%, given a two-sided test of hypotheses performed at $\alpha = 0.05$. Treatment comparisons for BMD, biochemical markers and stature were made using analysis of variance (ANOVA) techniques,

with treatment, study centre and hypogonadal status as terms in the main model. Percentage change from baseline, natural log (fraction of baseline) and change from baseline were analysed for BMD parameters, biochemical marker measurements and stature, respectively. BMD and stature data were analysed using a modified intention-to-treat (ITT) approach (last post-baseline measurement on treatment carried forward to impute missing values) and included all patients with a baseline and at least one post-baseline measurement in the treatment period. For BMD, a per-protocol analysis was performed as prespecified, and did not show a difference from the ITT approach. Biochemical markers were analysed using the per-protocol approach. The proportions of patients achieving thresholds ranging from −6% to 8% (by 1% intervals) for percentage change from baseline in lumbar spine BMD were tabulated. Fisher's Exact Test was used to compare adverse experience rates between treatment groups and the proportion of patients who exceeded predefined limits of change in laboratory safety parameters. Because of the small number of fractures expected to occur in this study, no statistical testing was performed on fracture data.

Results

Subject Participation

Of the 167 patients enrolled, 85.6% completed the study (figure 1). A greater proportion of placebo-treated patients discontinued early (21% vs 11% in the alendronic acid group), but no meaningful reason for this difference was identified.

Baseline Characteristics

Treatment groups were similar at baseline (table I). About 40% of men were hypogonadal; 57% were ≥65 years of age. Only four patients were non-White. More than 60% of the men reported prior nontraumatic osteoporotic fractures, and a similar number had a vertebral fracture based on local interpretation of baseline spine radiographs. Mean BMD T-score (± SD) was −1.8 (± 1.3) at the lumbar spine and −2.1 (± 0.6) at the femoral neck (data not shown), with no meaningful differences in BMD measurements or T-scores between treatment groups. About 24% of patients reported a history of upper GI disease, with a similar proportion in each treatment group.

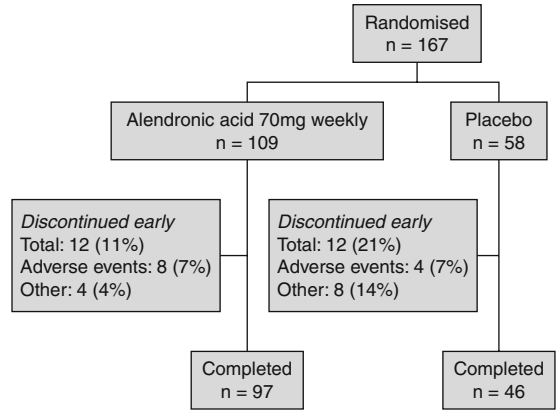

Fig. 1. Flow chart illustrating the number of patients who were randomised and completed the trial in each treatment group.

Bone Mineral Density

At all skeletal sites, alendronic acid 70mg once weekly produced significant BMD increases at 12 months relative to baseline and placebo (table II). After 6 months of treatment, increases in lumbar spine BMD were significant relative to baseline and placebo ($p < 0.001$) [figure 2]. In the alendronic acid group at 12 months, 95% of patients had a BMD increase (>0) from baseline at the lumbar spine; 66% of alendronic acid patients gained at least 3% BMD at the lumbar spine, in contrast to 26% of patients in the placebo group.

The treatment effect on lumbar spine BMD was consistent across prespecified subgroups, including baseline lumbar spine and femoral neck BMD, height, weight, body mass index (BMI), history of prior osteoporotic fracture, presence of prevalent vertebral fractures, age (<65 or ≥65 years and <75 or ≥75 years) and hypogonadal status (data not shown).

Table I. Baseline patient characteristics by treatment group[a]

	Alendronic acid 70mg once weekly (n = 109)		Placebo (n = 58)	
	mean	SD	mean	SD
Age (y)	65.8	10.7	66.7	12.4
Weight (kg)	78.7	11.7	79.1	13.0
Height (mm)	1743.7	67.8	1713.7	62.4
BMI (kg/m^2)	25.8	3.5	26.9	4.5
Serum free testosterone (pg/mL)	9.9	3.6	10.1	3.7
Lumbar spine BMD (g/cm^2)				
(n) Hologic	(75) 0.87	0.14	(42) 0.91	0.17
(n) Lunar	(12) 1.04	0.16	(8) 1.07	0.15
Femoral neck BMD (g/cm^2)				
(n) Hologic	(76) 0.64	0.06	(44) 0.67	0.09
(n) Lunar	(14) 0.79	0.08	(8) 0.78	0.06
White race (%)	97		98	
Age ≥65y (%)	60		52	
Hypogonadal (%)	41		41	
Alcohol ≥7 drinks/wk (%)	17		16	
Current smoker	11		12	
Pre-existing vertebral fracture (local reading) [%]	62		66	
Prior osteoporotic fracture (%)	59		67	

a Baseline characteristics were similar between treatment groups.

BMD = bone mineral density; **BMI** = body mass index; **SD** = standard deviation.

Bone Turnover Markers

NTx decreased by 42% at 3 months in the alendronic acid group, and this reduction was maintained through 12 months; the placebo group showed little change over the course of the study (table III, figure 3). BSAP levels decreased in the alendronic acid group by 24% at 3 months and 33% at 6 months; this reduction was maintained through 12 months. Declines in bone turnover markers were significant relative to placebo and to baseline at all timepoints (figure 3).

Safety

Fractures

Morphometric vertebral fractures occurred in nine patients: six (7.5%) in the alendronic acid group and three (7.3%) in the placebo group. Clinical vertebral fractures occurred in 4.6% of alendronic acid-treated patients versus 5.2% of the pla-

Table II. Mean percentage change from baseline in bone mineral density at month 12 (modified intention-to-treat approach)[a]

	Alendronic acid 70mg once weekly (n = 109)			Placebo (n = 58)		
	n	mean change (%)	95% CI	n	mean change (%)	95% CI
Lumbar spine†	82	4.28*	3.43, 5.12	46	1.45**	0.37, 2.53
Femoral neck†	84	2.07*	1.18, 2.95	46	0.17	−0.97, 1.31
Hip trochanter†	84	2.35*	1.77, 2.93	45	0.34	−0.42, 1.10
Total hip†	84	1.70*	1.23, 2.16	46	−0.17	−0.77, 0.43
Total body‡	90	1.40*	0.78, 2.01	48	0.20	−0.62, 1.02

a At all skeletal sites, alendronic acid treatment produced significant bone mineral density increases relative to baseline and placebo. Means are adjusted for centre and hypogonadal status.

CI = confidence interval. Between-treatment group comparison: † $p < 0.010$, ‡ $p < 0.05$; within-treatment test of mean = 0: * $p < 0.001$, ** $p < 0.01$.

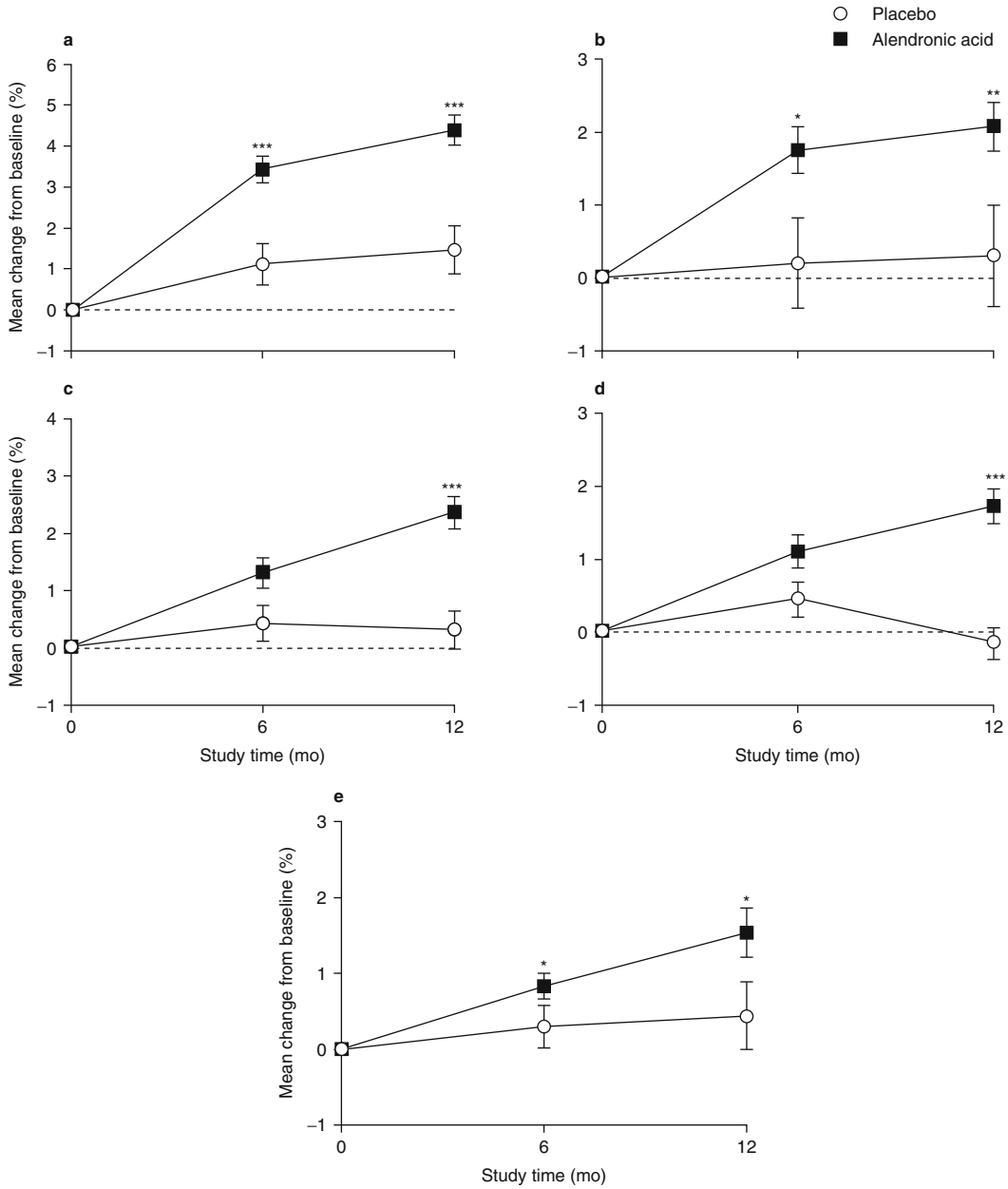

Fig. 2. Mean percentage changes from baseline in bone mineral density at 6 and 12 months of the lumbar spine (**a**), femoral neck (**b**), hip trochanter (**c**), total hip (**d**), and total body (**e**) in the placebo and alendronic acid groups. p-Value for between-treatment comparison: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Bars represent standard errors.

cebo group. Six patients in the alendronic acid group and one in the placebo group experienced nonvertebral fractures (2 **:** 1 randomisation); in five of the alendronic acid-treated patients, the fractures were associated with excessive trauma (e.g. a fall from a roof, and a skiing accident). Two

Table III. Mean percentage change[a] from baseline in markers of bone turnover at month 12 (per-protocol approach)[b]

	Alendronic acid 70mg once weekly (n = 109)			Placebo (n = 58)		
	n	mean change (%)[a]	95% CI	n	mean change (%)[a]	95% CI
Urinary NTx (pmol BCE/μmol)‡	90	−51.1*	−56.5, −45.0	45	−4.5	−16.6, 9.5
Serum BSAP (ng/mL)‡	90	−34.3*	−38.2, −30.1	45	−9.9**	−15.3, −4.2

a Transformed from Ln (fraction of baseline): (geometric mean-1) • 100.

b At all skeletal sites, alendronic acid treatment produced significant declines in bone turnover markers relative to baseline and placebo.

BCE = bone collagen equivalent; **BSAP** = serum bone-specific alkaline phosphatase; **CI** = confidence interval; **NTx** = urinary N-telopeptide of type I collagen. Between-treatment group comparison: ‡ $p < 0.001$; within-treatment test of mean = 0: * $p < 0.001$, ** $p < 0.05$.

nonvertebral fractures were considered nontraumatic (osteoporotic) by investigators, a finger fracture in an alendronic acid-treated patient, and a wrist fracture in a placebo-treated patient. Both treatment groups had a mean decrease of 1.67mm in stature.

General Safety

The safety profile of alendronic acid 70mg once weekly was similar to placebo (table IV). Similar proportions of patients in each treatment group experienced serious adverse events, and no death was considered drug related. Proportions of patients experiencing abdominal pain or gastrointestinal complaints, including drug-related GI complaints, were similar between treatment groups. For instance, 26.6% of patients in the alendronic acid group and 22.4% of patients in the placebo group experienced upper GI adverse events. Use of NSAIDs and/or aspirin-containing products was reported by 75 (68.8%) and 38 (65.5%) of the patients in the alendronic acid 70mg once weekly and placebo groups, respectively.

Discussion

In the present study, alendronic acid 70mg once weekly for 1 year significantly increased BMD at the lumbar spine, hip and total body, both from baseline and compared with placebo, in men with spine or hip BMD at least 2 SDs below the mean for young normal white males or nontraumatic fracture. Increases in lumbar spine BMD were observed 6 months after initiating treatment. Bone turnover markers decreased as early as 3 months after initiating treatment, contributing to subsequent increases in BMD. The magnitude of reductions in bone turnover markers and increases in BMD were very similar to those previously observed in osteoporotic men treated with alendronic acid 10mg daily.[8] Similar

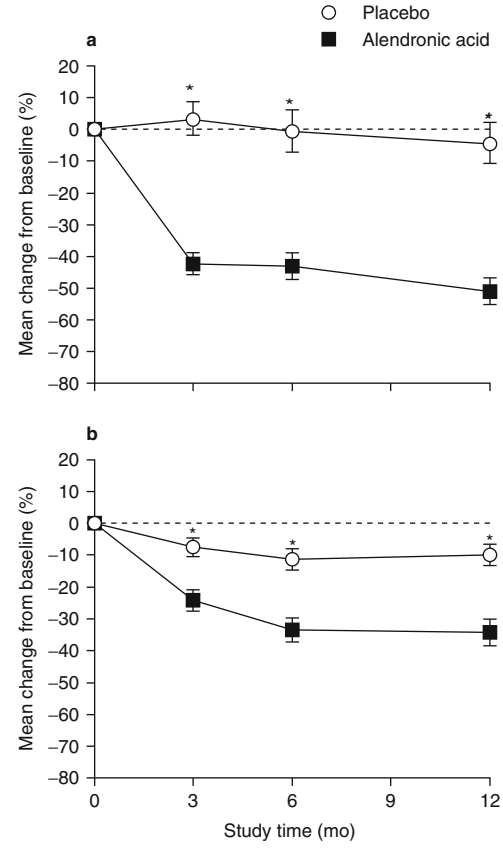

Fig. 3. Mean percentage changes from baseline at 6 and 12 months in urinary N-telopeptides of type I collagen corrected for creatinine (**a**) and serum bone specific alkaline phosphatase (**b**) in the alendronic acid and placebo groups. p-Value for between-treatment comparison: * $p < 0.001$. Bars represent standard errors.

Table IV. Summary of adverse events[a]

Adverse event	Alendronic acid (n = 109) [% of patients]	Placebo (n = 58) [% of patients]	Between-treatment differences [% (95% CI)]
Any AE	70.6	81.0	−10.4 (−22.6, 3.8)
Drug related[b] AE	13.8	8.6	5.1 (−6.2, 14.3)
Discontinued due to AE	6.4	8.6	−2.2 (−12.7, 5.7)
Serious AE	12.8	13.8	−0.9 (−13.2, 9.1)
Abdominal pain	2.8	5.2	−2.4 (−11.6, 3.6)
Digestive system AE	26.6	22.4	4.2 (−10.1, 16.8)

a The safety profile of alendronic acid 70mg once weekly was similar to placebo

b Possibly, probably or definitely drug related as determined by the investigator.

AE = adverse event; **CI** = confidence interval.

treatment effects were noted regardless of baseline BMD, age, height, BMI and other characteristics.

It is estimated that hypogonadism may exist in about 10% of male osteoporosis cases,[10] but testosterone replacement does not consistently increase BMD.[11-13] In contrast, skeletal response to alendronic acid was consistent, regardless of baseline gonadal function. Similarly, response was independent of hypogonadal status in a previous male osteoporosis study that evaluated alendronic acid 10mg daily over 2 years.[8]

The present study was designed with BMD as the primary endpoint. Fractures were collected only to monitor safety. In women, antifracture efficacy is related to the magnitude of changes in BMD and bone turnover.[14-16] Daily alendronic acid reduces the risk of both vertebral and nonvertebral fractures, including hip fractures, by about 50% in women with osteoporosis.[4] The therapeutic equivalence of daily versus weekly dosing was confirmed in a clinical trial in postmenopausal women with osteoporosis.[5,6] In the current study, approximately two-thirds of alendronic acid-treated patients experienced a BMD increase of 3% or more. The magnitudes of change in BMD and bone turnover markers observed in this small study, coupled with the similar pharmacokinetic profile of alendronic acid among men and women, suggest that alendronic acid treatment should result in fracture risk reductions in men similar to those observed in women. This is consistent with the similar effects of alendronic acid in animal studies, irrespective of gender, that demonstrate a dose-related increase in bone strength.[17]

Alendronic acid 70mg once weekly was generally well tolerated. There were no differences in adverse experiences between the alendronic acid and placebo groups. The incidence of upper GI experiences, including those considered drug related by the investigator, was similar between treatment groups. These findings concur with the safety and tolerability profile of alendronic acid comparable to placebo in large clinical trials in women,[18] and in endoscopic studies that included men.[19]

Progressive loss of trabecular volume with aging occurs in both genders, but unlike women, men generally do not experience accelerated midlife bone loss. Despite this, fractures are common in both women and men, and fracture risk increases exponentially with age and is strongly associated with low BMD irrespective of gender.[20] Indeed, although hip fracture is commonly considered a condition of older women, about one-third of all hip fractures occur in men,[21] and are associated with a higher mortality than in women.[22] Unfortunately, awareness of osteoporosis in men remains low. For example, a recent study showed that even after hip fracture, only a minority of men received any treatment for osteoporosis, and most of those men received only calcium and vitamin D.[23] Thus, there is a need to increase recognition of male osteoporosis, and to encourage initiation of effective therapy.

Conclusion

The results of this randomised, double-blind, placebo-controlled, 12-month trial demonstrate that alendronic acid 70mg once weekly offers a convenient option for the treatment of male osteoporosis that is effective in increasing bone density and reducing the bone turnover rate, and is generally well tolerated.

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K. Vandormael and A. Daifotis are employees of Merck & Co., Inc., and potentially own stock and/or hold stock options in the Company.

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