

Once-Weekly Oral Alendronate 70 mg in Patients with Glucocorticoid-Induced Bone Loss: A 12-Month Randomized, Placebo-Controlled Clinical Trial

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ABSTRACT. Objective. Glucocorticoid-induced osteoporosis is the most common iatrogenic form of osteoporosis. We evaluated the efficacy and safety of once-weekly bisphosphonate therapy for prevention and treatment of bone loss in patients on glucocorticoid therapy.

Methods. We conducted a 12-month, multicenter, randomized, double-blind, placebo-controlled trial with 114 and 59 patients in the treatment and placebo arms, respectively. Participants were stratified according to the duration of prior oral glucocorticoid therapy at randomization. Participants received alendronate 70 mg once weekly (ALN OW) or placebo; all received supplemental daily calcium (1000 mg) and 400 IU vitamin D. Clinical evaluations were performed at baseline, 3, 6, 9, and 12 months.

Results. At 12 months, there was a significant mean percentage increase from baseline in the ALN OW group for lumbar spine (2.45%), trochanter (1.27%), total hip (0.75%), and total body (1.70%) bone mineral density (BMD). Comparing ALN OW versus placebo at 12 months, a significant treatment difference for the mean percentage change from baseline was observed for lumbar spine (treatment difference of 2.92%; $p \leq 0.001$), trochanter (treatment difference 1.66%; $p = 0.007$), and total hip (treatment difference 1.19; $p = 0.008$) BMD. Biochemical markers of bone remodeling also showed significant mean percentage decreases from baseline.

Conclusion. Over 12 months ALN OW significantly increased lumbar spine, trochanter, total hip, and total body BMD compared with baseline among patients taking glucocorticoid therapy. A significant treatment difference versus placebo was observed at 12 months for the mean percentage change from baseline for lumbar spine, trochanter, and total hip. (J Rheumatol First Release June 1 2009; doi:10.3899/jrheum.081207)

Key Indexing Terms:
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Glucocorticoids are widely used for the treatment of a multitude of chronic inflammatory diseases. However, chronic use of glucocorticoids results in bone loss and represents the most common type of secondary osteoporosis¹⁻³. Patients receiving glucocorticoids are at increased risk for osteoporotic fractures in both a time- and dose-dependent fashion⁴⁻⁶. Despite efforts to reduce glucocorticoid use

through combination therapy with nonsteroidal antiinflammatory and disease modifying drugs, large numbers of patients continue taking glucocorticoids for extended periods, often for many years. During 1997, approximately 30 million patients in the United States were treated with oral glucocorticoids⁷, and it is estimated that over 1 million Americans take glucocorticoids chronically (≥ 6 mo)¹.

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Glucocorticoids may cause bone loss by decreasing bone formation by direct suppression of osteoblast function and possibly by increasing bone resorption⁸⁻¹⁰.

Daily alendronate (ALN) has been shown to reverse the loss of bone mineral density (BMD) in patients with osteoporosis and to reduce the risk of osteoporosis-related fractures¹¹⁻¹³. Daily ALN therapy has also been shown to be effective for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP), with a favorable safety and tolerability profile¹⁴⁻¹⁶.

Although international clinical guidelines for patients receiving chronic glucocorticoids recommend concomitant therapy with bisphosphonates and supplemental calcium and vitamin D, to prevent bone loss^{15,17-23}, most patients do not receive adequate treatment. Several reports suggest that only 20%–50% of all chronic users of high-dose glucocorticoids in the US are receiving concomitant antiresorptive therapy^{7,24-26}. This underutilization of available therapies may in part reflect the inconvenience associated with daily administration of oral bisphosphonates. Once-weekly bisphosphonate dosing regimens were introduced for the treatment and prevention of osteoporosis in postmenopausal women in 2000, and daily oral bisphosphonate use is now uncommon. Weekly dosing may be more convenient, and might enhance adherence to antiresorptive treatment²⁷. Daily and weekly ALN have been shown to have comparable effects on biochemical markers of bone turnover and BMD in patients with osteoporosis^{28,29}.

The aim of our study was to evaluate the efficacy and safety profile of once-weekly oral alendronate 70 mg (ALN OW) to reduce and prevent bone loss in patients who were being treated with longterm glucocorticoid therapy.

MATERIALS AND METHODS

Study design. All study participants provided written informed consent before enrolment. The protocols were approved by the relevant institutional review board or ethics committee, and performed according to the guidelines of good clinical practice and with ethical standards for human experimentation (established by the Declaration of Helsinki).

This was a 12-month, randomized, double-blind, placebo-controlled trial (Protocol MK-217-193, NTC No. 00480766) conducted at 23 sites in the US between July 2001 and August 2003 to evaluate the efficacy and safety profile of ALN OW to prevent and treat glucocorticoid-induced bone loss. This trial was conducted prior to the availability of the ClinicalTrials.gov Website, and used a prospective data analysis plan that was submitted to the US Food and Drug Administration.

Adults \leq 80 years of age who were taking a mean of \geq 7.5 mg/day of oral prednisone (or equivalent) and were considered by the site investigator to be highly likely to require oral glucocorticoid treatment for \geq 12 consecutive months were eligible to participate. Participants were also required to have serum 25-hydroxyvitamin D [25(OH)D] levels $>$ 15 ng/ml (37.4 nmol/l). Other inclusion criteria required patients to have a lumbar spine anatomy suitable for dual-energy x-ray absorptiometry (DEXA), and hip and lumbar spine BMD T-score more than 2.5 SD below the sex-matched, young adult reference mean (T-score $<$ -2.5). Patients who had prior vertebral or osteoporotic fractures were not eligible, nor were those with certain malignancies, recent major upper gastrointestinal (GI) disease (e.g., significant upper GI bleeding, recurrent ulcer disease, esophageal or gastric

varices, esophageal stricture, achalasia, or severe esophageal motor dysfunction), myocardial infarction, or pregnancy. Patients who were unwilling to take either calcium or vitamin D supplements or those with a history of alcohol or drug abuse were also excluded.

Because duration of prior oral glucocorticoid therapy was expected to be a prognostic factor, participants were stratified according to the duration of prior oral glucocorticoid therapy at randomization. Patients who had initiated oral glucocorticoids \leq 4 months before screening and had a maximum oral glucocorticoid exposure of $>$ 6 months in the past 3 years were assigned to Stratum 1, and patients who had initiated oral glucocorticoids $>$ 4 months prior to screening or had an oral exposure of $>$ 6 months in the previous 3 years were assigned to Stratum 2. All study personnel, patients, monitors, central laboratory, and DEXA facility personnel remained blinded to treatment allocation throughout the study. Blinding of participants and investigational staff was accomplished through the use of exact matching placebo tablets.

Treatment. Patients were randomized in a 2:1 ratio to receive ALN OW or placebo, respectively, in a single, once-weekly oral dose. All patients also received a total of 1000 mg of elemental calcium (calcium carbonate) and 400 IU of vitamin D (cholecalciferol; Merck and Co., Inc., Rahway, NJ, USA) supplementation administered in 2 daily doses. Patients were instructed to take study medication upon rising, at least 1 half-hour before the first food, beverage (except water), or other medication, and to stay upright until consuming the first food of the day. Calcium and vitamin D supplements were to be taken twice daily with food. Patients recorded glucocorticoid use in a diary that was reviewed at each clinic visit.

Measurements. After eligibility screening, randomization, and baseline data acquisition, followup visits were scheduled after 3, 6, 9, and 12 months to dispense study medication, assess adherence, review glucocorticoid use diary, and conduct DEXA scans of spine, hip, and total body. Laboratory tests including assays of biochemical markers of bone turnover [urinary N-telopeptides of Type I collagen corrected for creatinine (NTX) (Osteomark[®], Ostex International, Seattle, WA, USA) and serum bone-specific alkaline phosphatase (BSAP) (Ostase[®], Beckman Coulter, Inc., Fullerton, CA, USA)] were also performed during the baseline (Month 0) and Months 3, 6, and 12 visits, or at early discontinuation. History, examination (including vital signs, height, and weight), and concomitant medication use was recorded at screening and reevaluated at each clinical visit. Safety laboratory evaluations included a chemistry profile, complete blood count, and white blood cell differential. All clinical and laboratory adverse experiences (AE) that occurred after the start of double-blind treatment and within 14 days after the end of treatment were recorded. Lateral spine radiographs were obtained during screening and repeated if there was a clinical suspicion of a possible vertebral fracture. Incident fractures were reported as AE.

Statistical analyses. The primary endpoints were the percentage change from baseline in posterior-anterior BMD of the lumbar spine at Month 12, and the safety and tolerability profile of ALN OW through 12 months. To assess an earlier treatment effect on the lumbar spine BMD, statistical tests were also performed at Months 3, 6, and 9. To adjust for multiplicity over time, a step-down closed-testing procedure was applied. In this procedure, the treatment difference at Month 9 was considered significant only if there was statistical significance ($p \leq 0.050$) at both Months 12 and 9. Similarly, significance at Month 6 was only concluded if there was statistical significance ($p \leq 0.050$) at Months 12, 9, and 6. Finally, statistical significance at Month 3 was only concluded if there was statistical significance ($p \leq 0.050$) at Months 12, 9, 6, and 3.

Secondary endpoints included percentage change from baseline in hip, femoral neck, trochanter, total hip, and total body BMD at 12 months, and the effects of ALN OW after 12 months on biochemical markers of bone turnover (NTX, BSAP). Statistical significance for the secondary endpoints was only considered if the treatment difference for the primary endpoint (lumbar spine BMD at Month 12) was significant ($p \leq 0.050$). To adjust for multiplicity among the secondary endpoints, 2 groups of secondary endpoints were created: the BMD endpoints and the biochemical markers.

Within each group the endpoints were ordered and a closed-test procedure was used on each group to control the type I error. For the adjustment for multiplicity over time, a step-down closed testing procedure (similar to the one used for the primary endpoint) was applied for each secondary endpoint separately. In this approach, significance at earlier timepoints was only concluded if there was also significance at all later timepoints.

The primary analysis method for the BMD endpoints used the modified intent-to-treat (MITT) population, which included all patients who took ≥ 1 dose of study medication and had a baseline and ≥ 1 on-treatment measurement. In the MITT analysis, missing on-treatment values were imputed by carrying forward the last non-missing on-treatment value. However, no baseline values were carried forward to on-treatment timepoints.

The analysis of bone turnover marker data was based on the evaluable per-protocol (PP) population, which excluded all patients who had a major protocol violation as prespecified in the data analysis plan. No bone turnover marker data were imputed. The treatment difference for NTX/creatinine (NTX/Cr) was considered significant if its p value was ≤ 0.050 , and, for BSAP, significance was determined only if there was significance for both NTX/Cr and BSAP ($p \leq 0.050$).

Safety and tolerability were assessed in all patients who received ≥ 1 dose of active study drug or placebo. Treatments were compared using Fisher's exact test for the incidence of any upper gastrointestinal (UGI) AE.

Treatment effect on lumbar spine, femoral neck, trochanter, total hip,

and total body BMD was assessed by an analysis of variance (ANOVA) model on percentage change from baseline with terms for treatment, study center, and stratum (prior glucocorticoid use profile) as factors. The consistency of the treatment effect across strata was evaluated. Treatment differences between ALN OW and placebo were estimated by difference in least-squares (LS) means from the ANOVA model and the 95% confidence intervals (CI) were calculated. For the biochemical marker variables, log-transformed fraction-of-baseline values were analyzed. Treatment differences were assessed using the same model as for the BMD variables.

Sample size and power calculations. Based on data from 3 previous pilot studies^{14,28}, a sample size of 100 patients in the ALN OW group and 50 patients in the placebo group was planned to detect a difference of 2.5% in lumbar spine BMD with a standard deviation (SD) of 4% between groups with a power of 90%, given a 2-sided test of significance performed at $\alpha = 0.05$, and assuming that 20% of the randomized patients would not be included in the MITT analysis. The actual observed treatment difference of 2.92% and SD of 3.5% were well within the estimated values used to calculate sample size.

RESULTS

Patient allocation, demographics, and baseline characteristics. Patient accounting is shown in Figure 1. Of the 278

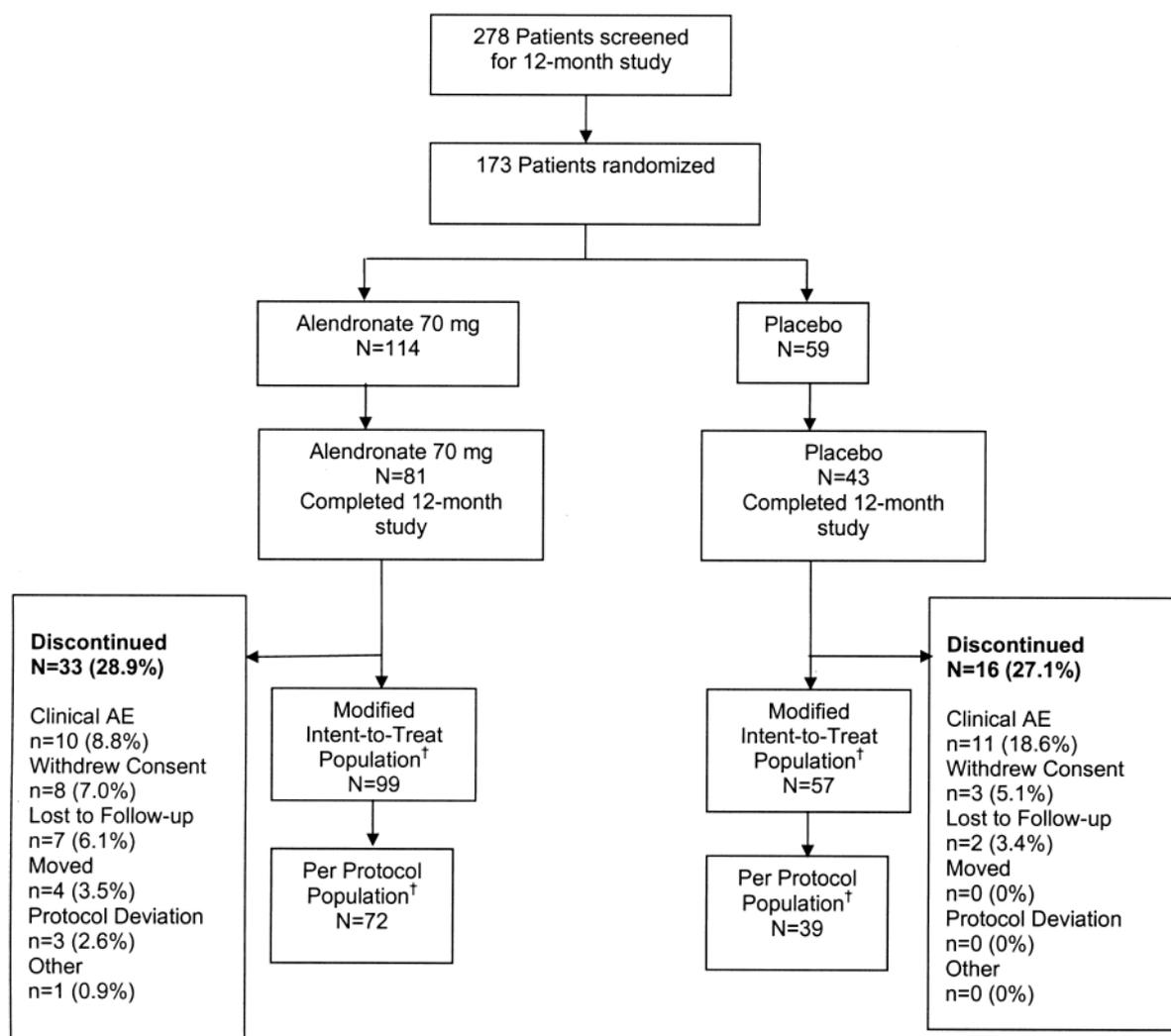


Figure 1. Progress of patients through the trial. †Population related to the lumbar spine BMD analysis.

patients screened for the study, 105 failed to meet eligibility criteria, withdrew consent, or were lost to followup prior to randomization. Of the 173 randomized patients, we observed an equal baseline distribution for 25(OH)D \leq 30 ng/ml: 38% for ALN OW and 37% for placebo. We also observed an equal baseline distribution in terms of T-score and absolute values (g/cm²; data not shown) at all sites between treatment and placebo groups. The majority of patients (74.6%) required glucocorticoid therapy for musculoskeletal and connective tissue disorders. Demographic and baseline data for each group are provided in Table 1.

Prednisone was the most frequently used glucocorticoid in this study. In the ALN OW group all patients received prednisone and 2 received 1 additional concomitant glucocorticoid each (hydrocortisone in 1 and methylprednisolone in the other).

In the placebo group, 54 patients (91.5%) received prednisone, while 4 (6.8%) received methylprednisolone, and 1 (1.7%) received hydrocortisone. The mean daily dose of glucocorticoid treatment at start and end of the trial decreased from 16.5 mg to 10.3 mg in the ALN OW group and from 15.6 mg to 10 mg in the placebo group. Stratum 1 patients decreased from 23.2 mg to 8.2 mg in the ALN OW group and from 20.6 mg to 6.3 mg in the placebo group. Stratum 2 patients decreased from 14.6 mg to 10.9 mg in the ALN OW group and from 13.6 mg to 11.5 mg in the placebo group.

Compliance. For each patient, a compliance measure (percentage compliance) was calculated as a ratio of the actual

Table 1. Baseline patient characteristics by treatment group.

Characteristics, n (%) or mean (SD)	Alendronate 70 mg Once Weekly, n = 114*	Placebo, n = 59*
Female	70 (61.4)	31 (52.5)
Age, yrs	51.9 (14.4)	54.6 (14.8)
Demographics, n (%)		
Asian	4 (3.5)	1 (1.7)
Black	12 (10.5)	8 (13.6)
White	82 (71.9)	45 (76.3)
Other	16 (14.0)	5 (8.5)
Postmenopausal women	29 (25.4)	17 (28.8)
Past glucocorticoid use		
Prior duration of glucocorticoid treatment, mo	54.6 \pm 72.0	44.8 \pm 63.0
Prior daily dose of glucocorticoid treatment, mg	16.5 \pm 11.6	15.6 \pm 12.0
Stratum 1 [†] (n = 42): prior duration of glucocorticoid treatment, mo	1.8 \pm 0.9	2.4 \pm 2.0
Stratum 2 ^{††} (n = 130): prior duration of glucocorticoid treatment, mo	70.2 \pm 75.2	62.0 \pm 67.5
Primary glucocorticoid-requiring illness (Stratum 1), n (%)	n = 26	n = 17
Rheumatoid Arthritis (RA) [#]	3 (11.5)	1 (5.9)
Other rheumatic disorders ^{##}	21 (80.8)	11 (64.7)
Other disorder	2 (7.7)	5 (29.4)
Primary glucocorticoid-requiring illness (Stratum 2), n (%)	n = 88	n = 42
RA [#]	39 (44.3)	15 (35.7)
Other rheumatic disorders ^{##}	32 (36.4)	7 (16.7)
Other disorder	17 (19.3)	20 (47.6)
BMD and biomarker baseline values		
Lumbar spine BMD T-score	-0.33 (1.37) (n = 114)	-0.38 (1.11) (n = 59)
Total hip BMD T-score	-0.40 (1.14) (n = 112)	-0.45 (0.86) (n = 58)
Femoral neck BMD T-score	-0.78 (1.09) (n = 112)	-0.91 (0.79) (n = 58)
Total body BMD T-score	0.07 (0.81) (n = 67)	0.33 (0.84) (n = 31)
NTX/Cr, nmol/mmol	36.56 (19.26) (n = 110)	35.65 (17.97) (n = 57)
BSAP, ng/ml	8.94 (3.97) (n = 109)	9.13 (3.30) (n = 56)

* Number of subjects vary in glucocorticoid stratum. [†] Initiation of glucocorticoids \leq 4 mo before screening and maximum oral glucocorticoid exposure of \leq 6 mo in past 3 yrs. ^{††} Initiation of glucocorticoids > 4 mos before screening or had an oral glucocorticoid exposure of > 6 mos in past 3 yrs. [#] Includes RA and Still's disease. ^{##} Includes arthritis, connective tissue disorder, lupus erythematosus, osteoarthritis, polymyalgia, polymyalgia rheumatica, polymyositis, psoriatic arthritis, scleroderma, and systemic lupus erythematosus. NTX/Cr: N-telopeptides of Type 1 collagen/creatinine; BSAP: bone-specific alkaline phosphatase; BMD: bone mineral density.

number of days with a tablet intake (ALN or placebo) versus the expected number of days with a tablet intake. Mean treatment compliance was ~88% in both treatment groups (87.4% for ALN OW and 88.5% for placebo).

Efficacy. Lumbar spine BMD: Mean percentage change from baseline at Months 3, 6, 9, and 12 in lumbar spine BMD is shown in Figure 2. A significant ($p \leq 0.001$) mean percentage increase from baseline of 2.45% was observed at Month 12 in the ALN OW group, compared with a nonsignificant decrease of -0.57% in the placebo group. The difference between group least-square means (ALN OW – placebo) at 12 months was 2.92% (95% CI 1.76, 4.08; $p \leq 0.001$). A significant treatment difference was also observed at Months 3, 6, and 9.

Mean percentage change from baseline at Months 3, 6, 9, and 12 in hip trochanter, total hip, femoral neck, and total body BMD for ALN OW and placebo are shown in Figures 3A, B, C, and D, respectively. A significant ($p \leq 0.010$) mean percentage increase from baseline in trochanter BMD of 1.27% was observed at Month 12 in the ALN OW group, compared with a nonsignificant mean percentage decrease of -0.33% in the placebo group. The difference between group 1 least-square means for trochanter (ALN OW – placebo) at Month 12 was 1.66% (95% CI 0.46%, 2.86%; $p = 0.007$). A significant ($p \leq 0.010$) mean percentage increase from baseline in total hip BMD of 0.75% was observed at Month 12 in the ALN OW group, compared with a nonsignificant mean decrease of -0.44% in the placebo group. The difference between group least-square means for total

hip (ALN OW – placebo) at Month 12 was 1.19% (95% CI 0.32%, 2.07%; $p = 0.008$). Nonsignificant mean percentage increases from baseline at Month 12 in femoral neck BMD of 0.41% and 0.08% were seen in the ALN OW and placebo groups, respectively. The difference between group least-square means at 12 months for femoral neck (ALN OW – placebo) of 0.44 (95% CI -0.75%, 1.62%; $p = 0.469$) was not significant. A significant ($p \leq 0.050$) mean percentage increase from baseline in total body BMD of 1.70% was observed at Month 12 in the ALN OW group, compared with a nonsignificant increase of 0.60% in the placebo group. However, the least-square mean percentage change from baseline at Month 12 for total body did not differ significantly between groups (0.91%; 95% CI -1.53%, 3.36%; $p = 0.462$).

Biochemical markers of bone turnover. In the ALN OW group, NTX/Cr decreased from baseline by 32.2% at Month 12 ($p \leq 0.001$) compared with a smaller but also significant ($p \leq 0.050$) decrease of -15.9% in the placebo group (Figure 4A). No significant treatment difference was observed between ALN OW and placebo at Month 12 ($p = 0.088$). Since the treatment difference in NTX/Cr did not reach significance at Month 12, the treatment difference was considered not significant at earlier timepoints, due to multiplicity adjustments despite nominal p values ≤ 0.050 .

In the ALN OW group, BSAP decreased from baseline by 14.5% at Month 12 ($p \leq 0.001$), compared with a nonsignificant ($p > 0.050$) increase of 6.7% with placebo (Figure 4B). No significant treatment difference could be

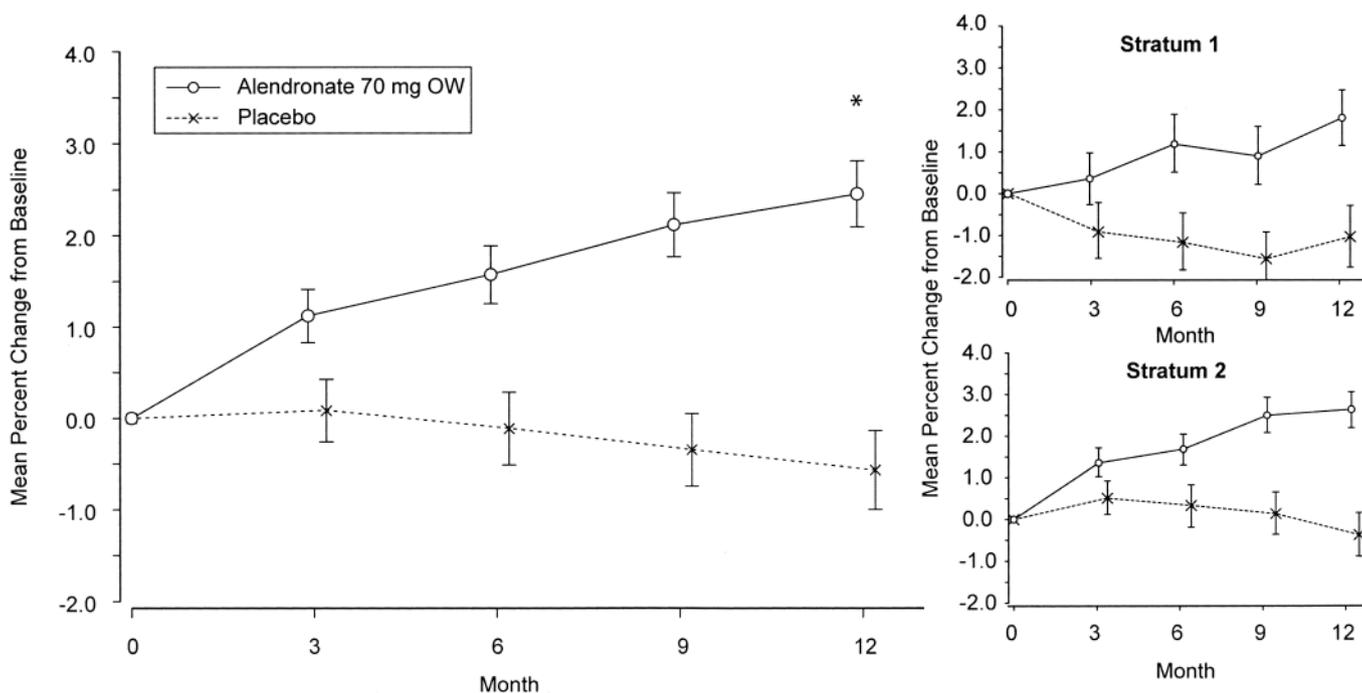


Figure 2. Mean percentage change from baseline (\pm standard error) in lumbar spine BMD (g/cm^2) using the MITT population. Inserts show results by strata. *Between-treatment comparison, $p \leq 0.001$. OW: once weekly.

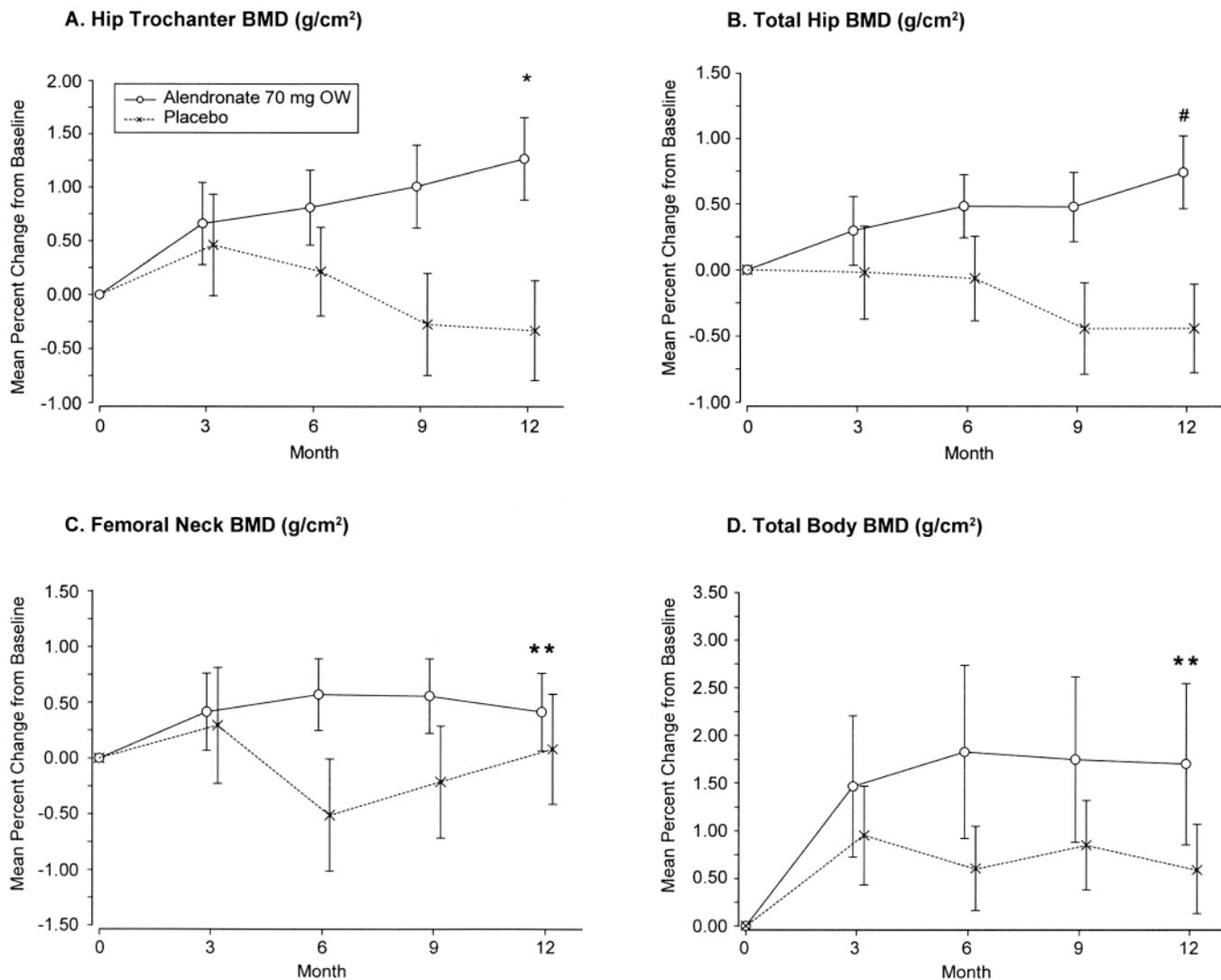


Figure 3. A. Mean percentage change from baseline in hip trochanter BMD (g/cm², ± SE). MITT population. *Between-treatment comparison, p = 0.007. B. Mean percentage change from baseline in total hip BMD (g/cm², ± SE). MITT population. #Between-treatment comparison, p = 0.008. C. Mean percentage change from baseline in femoral neck BMD (g/cm², ± SE). MITT population. **Between-treatment comparison, p is nonsignificant (> 0.05). D. Mean percentage change from baseline in total body BMD (g/cm², ± SE). MITT population. **Between-treatment comparison, p is nonsignificant (> 0.05).

concluded in BSAP at Month 12 (p = 0.001), due to the absence of a significant result in NTX/Cr and the multiplicity adjustment.

Safety. Clinical and UGI and esophageal AE summarized by the number of patients in each treatment group are presented in Table 2. The most commonly reported AE were upper respiratory tract infection (9.6% and 6.8% for ALN OW and placebo, respectively), hypertension (9.6% and 3.4%), and arthralgia (4.4% and 11.9%). The most commonly reported UGI AE were abdominal pain (3.5% and 6.8% in ALN OW and placebo, respectively), dyspepsia (4.4% and 3.4%), nausea (4.4% and 1.7%), and vomiting (3.5% and 1.7%). Two ALN OW and no placebo patients died of cardiac arrest during the treatment period. The investigators reported that

these deaths were not related to study drug. Overall, the incidence of specific clinical AE or specific UGI AE was similar in the ALN OW and placebo groups. Fracture data (vertebral and nonvertebral) were also evaluated separately. Six ALN OW and no placebo patients had a clinical fracture. No patient had more than 1 fracture during the 12-month treatment period, and all fractures were evaluated as being unrelated to study medication. The 6 fractures were not considered fragility fractures and the fractures (3 ankle fractures, 1 clavicle fracture, 1 hip fracture, and 1 spinal compression fracture) were the result of trauma.

A total of 4 (4.0%) ALN OW and 12 (21.1%) placebo patients had excessive bone loss (≥ 5% decrease from baseline in lumbar spine or total hip BMD at least once during

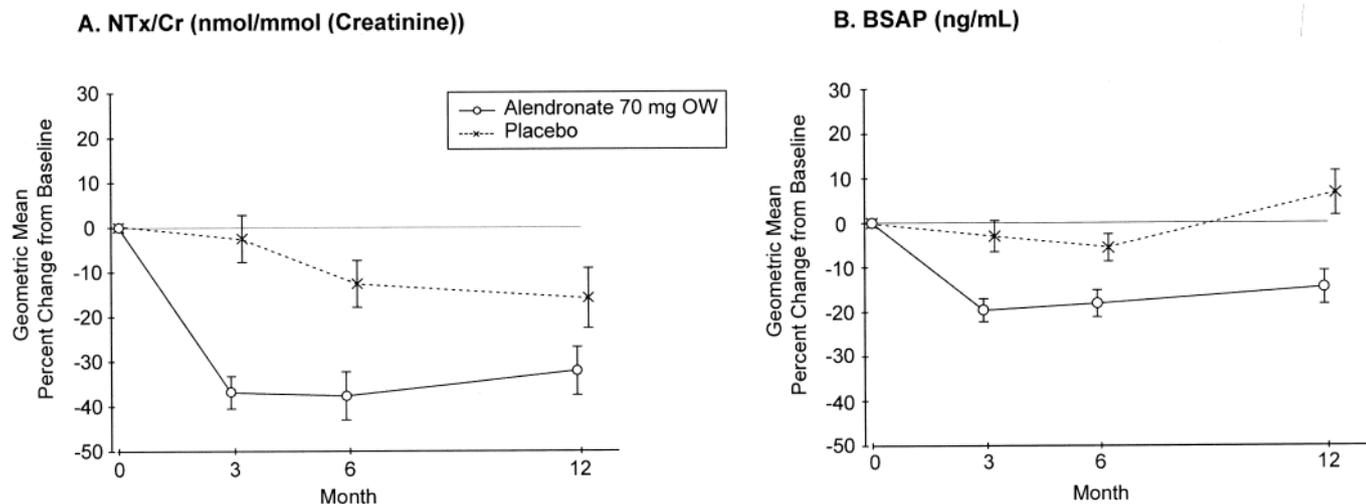


Figure 4. A. Geometric mean percentage change from baseline in NTX/Cr [nmol/mmol (creatinine), \pm SE]. Per-protocol population. Between-treatment comparison is nonsignificant ($p > 0.05$). B. Geometric mean percentage change from baseline in bone-specific alkaline phosphatase (ng/ml, \pm SE). Per-protocol population. Due to multiplicity adjustment no between-treatment statement provided. OW: once weekly.

Table 2. Clinical adverse and upper gastrointestinal (GI) adverse experiences (AE).

Adverse Experiences	ALN OW (n = 114), n (%)	Placebo, (n = 59), n (%)	Difference, %* ALN OW – Placebo Estimated (95% CI)
1 or more AE	86 (75.4)	49 (83.1)	-7.6 (-19.0, 5.9)
Serious AE	21 (18.4)	8 (13.6)	4.9 (-7.7, 15.3)
Deaths	2 (1.8)	0	1.8 (-4.5, 6.2)
Discontinued due to AE	10 (8.8)	10 (16.9)	-8.2 (-20.3, 1.8)
Discontinued due to serious AE	5 (4.4)	1 (1.7)	2.7 (-5.0, 8.3)
Upper GI AE			
1 or more UGI AE	20 (17.5)	12 (20.3)	-2.8 (-16.1, 8.7)
Serious UGI AE	1 (0.9)	1 (1.7)	-0.8 (-8.2, 3.3)
Discontinued due to UGI AE	1 (0.9)	2 (3.4)	-2.5 (-10.7, 2.1)
Discontinued due to serious UGI AE	0	1 (1.7)	-1.7 (-9.0, 1.9)

ALN OW: alendronate 70 mg once weekly. * Difference in percentages and 95% CI based on Wilson's score method.

the treatment period). For 2 ALN OW and 8 placebo patients this bone loss was reported as an AE, and both ALN OW patients and 5 of the 8 placebo patients discontinued.

DISCUSSION

Glucocorticoid treatment continues to be the mainstay of therapy for many chronic inflammatory disorders^{1-3,7}. Glucocorticoid-induced bone loss is a predictable and serious complication of longterm treatment, and, although effective options are available to mitigate bone loss, glucocorticoid-related fractures, notably of the spine and hip, remain common^{30,31}. Bisphosphonate therapy with concomitant calcium and vitamin D supplementation is standard care for osteoporosis; however, this is often overlooked in the case of glucocorticoid-induced bone loss.

In our study we observed a mean 2.45% increase from

baseline in lumbar spine BMD after 12 months in patients treated with ALN 70 mg once weekly. A significant increase from baseline in lumbar spine BMD occurred as early as 3 months. Significant increases from baseline in total hip, hip trochanter, and total body BMD were seen following 12 months of treatment with ALN. Comparing ALN with placebo, a significant treatment difference in BMD was observed at 12 months for lumbar spine, trochanter, and total hip. However, for femoral neck and total body BMD, ALN treatment did not produce a significantly different result compared with placebo treatment at 12 months. As the patients within this study included pre- and postmenopausal women (PMW) in addition to men, we examined whether differences existed in response to treatment between PMW within the study and the overall trial population. Results for PMW at lumbar spine BMD at 12 months were consistent

with the overall trial results. It should be noted that this sub-analysis is based on a small number of patients: 17 placebo and 23 ALN OW.

Prior to entering the trial, patients in our study were assigned to 1 of 2 strata depending on duration of prior use of glucocorticoids, as detailed in the study design. It has been previously demonstrated that rapid bone loss can occur soon after initiating glucocorticoid treatment, which is then followed by a less rapid decline over time³². In this study no significant treatment-by-stratum interaction was observed, indicating that the treatment effect was consistent across the 2 strata. At Month 12, the mean percentage changes from baseline in Stratum 1 were 1.82% and -1.04% for ALN OW and placebo, respectively. The corresponding mean percentage changes in Stratum 2 were 2.64% and -0.36%. Ideally, our study would have included a stratum of patients who were initiating glucocorticoid therapy with concomitant bisphosphonate therapy. However, due to the uncertainty involved in determining whether or not a patient initiating glucocorticoid therapy would continue to be treated long term, it was decided to enroll patients whose treatment was already under way.

Analysis of bone turnover biomarkers revealed a significant decrease ($p \leq 0.001$) in NTX/Cr versus baseline (32.2%) for the ALN OW group; however, there was also a significant, although smaller, decrease ($p \leq 0.050$) in NTX/Cr levels in the placebo group (15.9%). Thus, no significant treatment difference was observed. Due to the lack of a significant treatment difference for NTX/Cr at 12 months and the multiplicity adjustment used in the statistical analysis, no significant treatment differences could be concluded at earlier timepoints for NTX/Cr or for BSAP at Month 12 or earlier.

The observation that levels of NTX/Cr decreased by 15.9% in the placebo group is of interest. Although the precise reason for this is unknown, it is not unreasonable to assume that the decrease in glucocorticoid dose over the course of the trial in combination with vitamin D₃ and calcium supplementation may be a factor in the reduction of bone turnover biomarkers observed in the placebo group. In addition we also actively discontinued any subject who demonstrated excess bone loss > 5% at any timepoint at either the lumbar spine or hip. The number of discontinued patients for this reason was higher in the placebo group (21%) versus the ALN OW group (4%). This may have contributed to an apparent lack of decrease in bone resorption markers. It should also be noted that there were twice as many patients receiving active therapy versus placebo.

Previous studies^{14,33} included participants with a greater number of risk factors for bone loss. Our study was of a lower-risk population: participants were required to have BMD values above osteoporotic thresholds (osteopenic or normal) and be vitamin D-replete [serum 25(OH)D values > 15 ng/ml (37.4 nmol/l)]. However, it should be noted that

since the study was designed and conducted, the prevailing consensus threshold for vitamin D insufficiency has changed, from > 15 ng/ml (37.4 nmol/l) to > 30 ng/ml (75 nmol/l)³⁴. All patients had lateral spine radiographs at baseline and those with prior or baseline fractures were excluded (13/105, 12.4%). Prior studies included patients with osteoporosis and concurrent vertebral fractures^{14,35,36}. Indeed, when we compare the results obtained here we generally observe a smaller increase in BMD at a number of sites when compared to other studies^{14,28,29,37}. The more stringent selection of patients most likely accounts for the majority of this effect. In addition, as patients had been taking glucocorticoids for shorter duration and the dose tapered over the trial, that would also contribute to this observation.

Patients randomized to placebo experienced relatively small losses of BMD at the lumbar spine and hip sites (total hip, trochanter, femoral neck). This lower than anticipated loss may be attributed to the inclusion of a lower-risk population receiving smaller doses of glucocorticoids (mean daily dose 10.0 mg at end of treatment period) and/or the beneficial effects of calcium and vitamin D supplementation³⁸. Although few of the study participants were frankly vitamin D deficient at baseline [25(OH)D \leq 15 ng/ml (37.4 nmol/l)], all received vitamin D (400 IU) and calcium supplementation (1000 mg) daily in divided doses. Similar observations on the potential effects of calcium and vitamin D to mitigate glucocorticoid-induced bone loss have been reported in previous studies^{14,38}. However, in a randomized, double-blind trial comparing activated vitamin D to ALN, ALN was more effective for glucocorticoid-induced osteoporosis^{37,39}.

Although patients in the placebo group generally experienced relatively small losses of BMD, this group experienced a large decrease (0.3 g/cm³) in BMD of the femoral neck at 6 months. Given that the study was not powered to determine whether this observation was statistically relevant and the relatively large standard error, it is not possible to determine whether this finding was clinically relevant.

Another reflection of the efficacy of ALN therapy was demonstrated in the difference in the number of subjects who discontinued as a result of excessive bone loss. Patients were specifically monitored for excess bone loss by BMD measurements every 3 months. Those demonstrating > 5% loss were discontinued in favor of approved available therapies. A total of 5 patients in the placebo group and 2 in the ALN group were discontinued from the study due to excessive bone loss.

Historically, the use of bisphosphonate prophylaxis for GIOP has been low among clinicians⁴⁰⁻⁴² and physicians' awareness may be heightened only after osteoporosis is present and fractures have occurred. Increased fracture risk is reported to occur after initiation of glucocorticoid treatment^{4,35}, so early intervention may optimize treatment outcome. Based on the existing evidence, there is international

consensus that a bisphosphonate as well as supplementation with calcium and vitamin D are the most appropriate therapies for patients requiring glucocorticoids who are at high risk of fractures^{15,18-23}. The increase in lumbar spine BMD observed here with ALN OW treatment as early as 3 months after initiation of therapy may mitigate additional bone loss.

In our study, efficacy of ALN OW on lumbar spine BMD was not related to age, sex, prior duration of glucocorticoid use, or the underlying condition for which glucocorticoids were prescribed. This suggests that our results may be applicable to the overall population of patients who may be receiving longterm glucocorticoid therapy.

ALN OW administration was generally well tolerated and exhibited a similar incidence of clinical AE, including UGI AE, as documented in the placebo group. Although our study was not powered to detect a difference in fracture incidence between active treatment and placebo, fracture events were reported as AE. Six ALN and no placebo patients experienced a clinical fracture. This was not statistically significant.

We report that for a lower-risk population of patients taking glucocorticoids, 12 months of concomitant treatment with ALN OW resulted in significant increases in lumbar spine, hip trochanter, total hip, and total body BMD relative to baseline. A significant treatment difference versus placebo was observed at 12 months for the mean percentage change from baseline for lumbar spine, trochanter, and total hip BMD. No significant treatment difference versus placebo was observed at 12 months for the mean percentage change from baseline for femoral neck and total body BMD. There were no differences between treatment groups with respect to AE, and the safety profile was consistent with previous trials with ALN. This study highlights the benefits of a once-weekly bisphosphonate therapy for preventing glucocorticoid-induced bone loss even in lower-risk patient populations.

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