ORIGINAL RESEARCH

Randomized Trial of Alendronate Plus Vitamin D$_3$ Versus Standard Care in Osteoporotic Postmenopausal Women with Vitamin D Insufficiency

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Abstract Vitamin D insufficiency is common in patients with osteoporosis. We conducted a randomized trial comparing alendronate 70 mg combined with vitamin D$_3$ 5,600 IU in a single tablet (ALN/D5600, $n = 257$) with standard care chosen by the patients' personal physicians ($n = 258$) in patients with postmenopausal osteoporosis (BMD T score ≤ 2.5 or ≤ 1.5 and a prior fragility fracture) who had vitamin D insufficiency (serum 25[OH]D values 8–20 ng/ml) and who were at risk of falls. Virtually all patients randomized to standard care received bisphosphonate therapy, and in approximately 70% of cases this was combined with vitamin D supplements. However, only 24% took ≥ 800 IU/day of supplemental vitamin D. At 6 months the proportion of patients with vitamin D insufficiency was 8.6% in the ALN/D5600 group compared with 31.0% in the standard care group ($P < 0.001$). Those in the ALN/D5600 group also had a greater reduction in urinary NTX/creatinine ratio (-57% vs. -46%, $P < 0.001$) and bone-specific alkaline phosphatase (-47% vs. -40%, $P < 0.001$). In the ALN/5600 group, by 12 months the increase in BMD was greater at the lumbar spine (4.9% vs. 3.9%, $P = 0.047$) and the total hip (2.2% vs. 1.4%, $P = 0.035$), significantly fewer patients were vitamin D—insufficient (11.3% vs. 36.9%, $P < 0.001$), and bone turnover marker (BTM) results were similar to those at 6 months. There was no difference between groups in those who experienced falls or fractures, and adverse events were similar. Based on the finding that ALN/D5600 was more effective than standard care at correcting vitamin D insufficiency, increasing BMD, and reducing BTMs in this patient group, greater attention needs to be directed toward optimizing the treatment of osteoporosis and correcting vitamin D deficiency in postmenopausal women.

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Vitamin D deficiency and insufficiency are prevalent worldwide, especially among osteoporotic women [1]. Although there is continued debate as to what constitutes an optimal serum concentration of 25-hydroxyvitamin D (25[OH]D), vitamin D deficiency is often defined as a value <8 ng/ml (20 nmol/l). There is a consensus that serum 25(OH)D concentrations should be >20 ng/ml (50 nmol/l) for optimal bone health [2], whereas some have suggested that values of 30 ng/ml (75 nmol/l) may be preferable [3]. At the present time, however, patients whose serum 25(OH)D concentrations are above the limit for deficiency (8 ng/ml) but below the level for optimal bone health (20 ng/ml) are termed to have "vitamin D insufficiency."

One multinational study has shown that the average concentration of 25(OH)D in postmenopausal women is 12 ng/ml [4]. Another study reported that about 50% of women receiving therapy for osteoporosis had 25(OH)D concentrations lower than 30 ng/ml but that 25% had levels lower than 20 ng/ml [5]. The risk factors for vitamin D deficiency include low dietary vitamin D, older age, obesity, and low sun exposure [1, 5], but epidemiologic studies have revealed that there is only a weak correlation between serum 25(OH)D and latitude in osteoporotic subjects [6]. Furthermore, vitamin D deficiency and insufficiency can occur among individuals who have apparently had abundant sunlight exposure [7]. Previous studies have shown that serum 25(OH)D levels correlate inversely with PTH and bone turnover markers (BTMs) but positively with bone mineral density (BMD) [6, 8–12]. In one study, concentrations of 25(OH)D at or below 12 ng/ml were also associated with an increased risk for osteoporotic fracture in older individuals [13]. There is ample evidence to demonstrate that vitamin D supplementation, with or without calcium, leads to a decrease in PTH [8, 14, 15], suppression of BTMs [15, 16], and an increase in BMD [10, 14]. In addition, vitamin D supplementation prevents falls in older adults [17]. There is also evidence to suggest that vitamin D reduces fracture risk, with antifracture efficacy best documented in older individuals receiving vitamin D_3 supplementation at 700–800 international units (IU) per day [18].

Calcium and vitamin D supplements are widely prescribed as an adjunct to other osteoporosis treatments. Unfortunately, adherence to these supplements is poor [19–21], despite the fact that coadministration of vitamin D with antiosteoporosis therapy enhances the therapeutic response [10, 22]. In addition, the doses prescribed are often lower than current recommendations. A combination tablet of alendronate 70 mg plus vitamin D_3 5,600 IU (ALN/D5600) for weekly administration was formulated in order to address this issue and improve vitamin D status in patients receiving alendronate therapy. In this study we evaluated the efficacy and safety of ALN/D5600 in women

with osteoporosis who had vitamin D insufficiency (serum 25[OH]D values 8–20 ng/ml) and who were at increased risk of falls. This was done within the context of a randomized controlled trial in which one group of patients received ALN/D5600 and the other received "standard care" for osteoporosis using a similar design to that used previously in the treatment of hypertension [23]. In the context of this study, patients in the standard-care group were referred to primary-care physicians or other specialists for treatment that could include any appropriate and locally available option. These physicians decided on treatment independently of the investigators without knowledge about the trial design and study end points.

Methods

Study Design

This was a multicenter, international, randomized trial using referred care as active control. Participants were randomized—using a computer-generated allocation schedule generated by the study sponsor—to treatment with the weekly ALN/D5600 combination tablet under the care of a study investigator or referral to a primary-care physician or specialist, who was not an investigator, for usual care of osteoporosis and low vitamin D. In countries where osteoporosis treatment was not reimbursed, the study sponsor provided financial aid. All participants visited investigator sites periodically for assessments of efficacy and safety. The study was conducted over a 12-month period. Due to the referred-care nature of the trial, it was an open-label design. However, participants, investigators, site staff, and the sponsor's clinical team were blinded to postbaseline concentrations of serum 25(OH)D and BTMs. An exception to this was serum 25(OH)D <6 ng/ml, identified by the central laboratory. When this occurred, "rescue" vitamin D was administered and study treatment was discontinued.

Participants

Women who participated in this trial were ≥65 years of age with BMD T scores ≤−2.5 at the lumbar spine, total hip, or femoral neck or a T score of ≤−1.5 plus a previous fragility fracture of the hip, spine, wrist, humerus, or clavicle. All participants were postmenopausal, defined as ≥1 year without menses, ≥6 months without menses with serum FSH levels >40 mIU/ml, or ≥6 months without menses following bilateral oophorectomy. Participants also had vitamin D insufficiency (serum 25[OH]D concentrations 8–20 ng/ml) and were at increased risk of falls defined by the fact that they had suffered one or more falls

within 12 months before study initiation and had reduced lower extremity physical function (score 4–9 on the Short Physical Performance Battery [SPPB]) [24, 25]. Among exclusion criteria were use of active hormonal vitamin D analogs within 2 months, oral bisphosphonates for ≥2 months within the previous 2 years, IV pamidronate or ibandronate within the previous year, fluoride treatment at >1 mg/day for over 2 weeks within the past 3 months, strontium-containing products for more than 2 weeks within the past 6 months, parathyroid hormone for more than 2 weeks within the past 3 months, anabolic steroids within the past 12 months, systemic glucocorticoids (≥5 mg/day prednisone or equivalent) for more than 2 weeks within the past 6 months, any use of IV zoledronate, current use of chemotherapy or heparin, need for assistance walking or standing up, abnormal laboratory safety screening tests or electrocardiogram, malignancy within the previous 5 years, malabsorption syndrome, or uncontrolled upper gastrointestinal disorders, cardiovascular disorders, primary or secondary hyperparathyroidism, thyroid disease, or renal disease. All participants provided written informed consent. The study was conducted in accordance with the principles of good clinical practice and approved by the appropriate institutional review boards and regulatory agencies.

Assessments

Biochemical Assessments

Blood and urine samples were collected at screening, baseline, and months 3, 6, and 12 and analyzed at Quest Diagnostics (Valencia, CA). Serum 25(OH)D samples were analyzed by a high-performance liquid chromatography/tandem mass spectrometry assay. It should be noted that the assay was recalibrated after recruitment of participants. However, baseline and on-treatment 25(OH)D measurements were all performed with the second, recalibrated assay, with calibration verified by comparison to National Institute of Standards Technology 25(OH)D standards. BTMs were also analyzed by Quest Diagnostics. Urinary N-telopeptides of type I collagen (NTX) concentration was determined using a competitive immunoassay technique, and serum bone-specific alkaline phosphate (BSAP) concentration was determined using an immunoenzymatic assay technique.

BMD

BMD was measured at screening and month 12 using dual-energy X-ray absorptiometry (DXA). The same DXA scanner was used for each participant's measurements.

Falls

Participants were asked to record falls on a study calendar and to notify the study site of falls by telephone or pre-stamped postcard. After notification, study-site personnel telephoned women reporting falls to obtain details about the event, including a description of the fall, the location, contributing factors (e.g., tripping, poor vision), the immediate aftermath, longer-term consequences, and the medical attention that was required. All participants were also routinely contacted on a monthly basis to survey fall incidences (except when an office visit was scheduled in the same month, where fall events were reviewed). Falls were adjudicated by an independent committee, blinded to treatment allocation. During the study a *fall* was defined as "coming to rest unintentionally on the ground or other lower level from a standing or sitting position, not due to major intrinsic or extrinsic event."

Adverse Experiences

Reports of clinical and laboratory adverse events (AEs) were collected at physician visits at months 3, 6, and 12. Participants could report an AE at any time throughout the trial.

Statistical Methods

The primary end point of the trial was the proportion of patients with serum 25(OH)D <20 ng/ml after 6 months of treatment. Secondary end points were the proportion of patients with 25(OH)D <20 ng/ml at 12 months, percent changes in the BTMs NTX (expressed as a ratio to urinary creatinine) and BSAP at 6 and 12 months, and percent changes in lumbar spine and total-hip BMD at 12 months. Exploratory end points included the incidence of falls during 12 months of treatment and change from baseline in 25(OH)D. Data were analyzed by a modified intent-to-treat approach: Women who took at least one dose of ALN/D5600 or were assigned to receive usual care and had data reported at least once postrandomization were included in the efficacy and safety analyses. For analysis of the fall-related end points, all randomized patients were included. A per-protocol analysis was performed for BTMs, to describe changes observed during the actual use of specific drugs and nutrients. Between-group differences in the primary end point were assessed using a logistic regression model, entering treatment, baseline 25(OH)D stratum (≤15 ng/ml or >15 ng/ml), baseline age stratum (≤75 or >75 years), and region (North America and Europe or the rest of the world) into the model. A log transformation was applied to NTX and BSAP before the calculation of percent change from baseline using a longitudinal data-analysis

method [26], including terms for treatment, time, interaction of time by treatment, as well as adjustment for baseline 25(OH)D stratum, region, and age stratum. A similar method was used for calculating change from baseline in 25(OH)D. For percent change from baseline in lumbar spine and total-hip BMD at 12 months, a traditional longitudinal data-analysis model was applied with terms for treatment, baseline 25(OH)D stratum, region, and age stratum. Intake of vitamin D supplements was calculated, using concomitant medicine reports, by summing the intake of all vitamin D analogs for each participant and dividing the amount consumed by the days on therapy to calculate units per day of the 1-year study. The effect on falls was evaluated using a Cox proportional hazards model for time to first or second fall. Missing data were not imputed. Safety and tolerability were assessed in all patients as treated, and the analysis is descriptive.

Results

Participants and Treatment

The disposition of the participants in the trial is shown in Fig. 1. Women were recruited from 77 centers in 24 countries throughout the world between July 2008 and July 2010, and most participants (88.5%) completed the 1 year of treatment. The treatment groups were well matched at baseline (Table 1). The average age of participants was 73 years, and 72% were Caucasian. All women had 25(OH)D <20 ng/ml at screening, and the average 25(OH)D was 14.9 ng/ml; but at baseline approximately 84% of women had 25(OH)D concentrations <20 ng/ml. Among the referred-care patients, almost all were prescribed treatments for osteoporosis (Table 2A). Treatments

included bisphosphonates (alendronate, risedronate, ibandronate, or zoledronate), strontium, hormonal vitamin D, raloxifene, or supplements alone. Approximately 71% of the women who received active drugs also received instructions to take calcium and/or vitamin D supplementation. The estimated vitamin D intake in the referred-care group is summarized in Table 2B. Only 24.1% of the women in referred care took ≥800 IU vitamin D/day.

Serum 25(OH)D

Over three times as many women in the referred-care treatment group compared with the ALN/D5600 treatment group had 25(OH)D concentrations <20 ng/ml. At 6 months 8.6% of participants in the ALN/D5600 group and 31.0% in the referred-care group had concentrations of 25(OH)D <20 ng/ml ($P < 0.001$) (Fig. 2a). Similar findings were observed at 12 months (11.3 and 36.9% for ALN/D5600 and referred care, respectively, $P < 0001$). The proportions of participants with 25(OH)D concentrations below various threshold levels at 12 months is shown in Fig. 2b. At 12 months, the mean (95% confidence interval [CI]) serum 25(OH)D concentrations in the ALN/D5600 group had risen by 12.7 (11.4–14.0) ng/ml compared with 8.4 (7.1–9.7) ng/ml in the referred-care group. The treatment difference was 4.3 (2.5–6.1) ng/ml (Fig. 3a). Figure 3b, c illustrate the distribution of 25(OH)D values in each treatment group.

BTMs

BTMs were measured at 6 and 12 months. Concentrations of both markers decreased in each treatment group (Fig. 4a, b), and the reduction was significantly greater in the ALN/D5600 group ($P < 0.001$ for both markers).
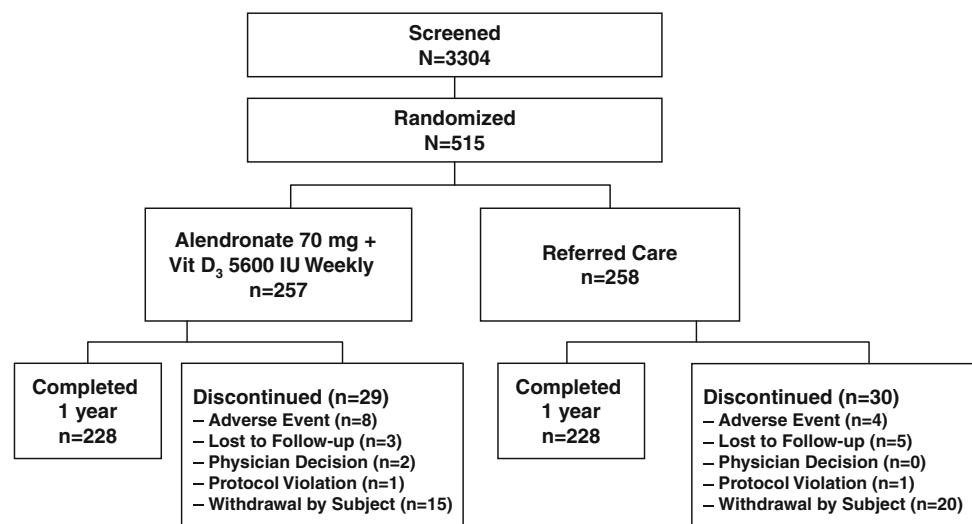
Fig. 1 Patient disposition

Table 1 Baseline characteristics

Treatment	ALN/D5600 (n = 257)	Referred care (n = 258)
Characteristic		
Age (years), mean (SD)	72.9 (5.3)	72.9 (5.9)
Age >75 years, n (%)	77 (30)	82 (32)
BMI (kg/m^2), mean (SD)[a]	27.3 (4.6)	27.5 (5.4)
Race, n (%)		
American Indian or Alaska Native	37 (14.4)	31 (12.0)
Asian	17 (6.6)	17 (6.6)
Black or African American	2 (0.8)	1 (0.4)
Multiracial	20 (7.8)	20 (7.7)
White	181 (70.4)	189 (73.3)
Region, n (%)		
Europe	98 (38)	97 (38)
Rest of world	159 (62)	161 (62.4)
25(OH)D (ng/ml), mean (SD)[a]	14.8 (5.5)	14.8 (5.4)
25(OH)D stratum, n (%)		
≤15 ng/ml	142 (55)	144 (56)
>15 ng/ml	115 (45)	114 (44)
Serum calcium (mg/dl), mean (SD)	9.4 (0.4)	9.4 (0.4)
Calcium intake from food and beverage (mg), mean (SD)	775 (386)	835 (446)
Serum phosphate (mg/dl), mean (SD)	3.6 (0.5)	3.7 (0.4)
BMD (g/cm^2), mean (SD)		
Lumbar spine	0.82 (0.15)	0.79 (0.14)
Total hip	0.74 (0.10)	0.75 (0.11)
Bone turnover markers		
BSAP (mg/l),[a] mean (SD), mean (SD)	16.2 (6.0)	16.9 (7.2)
NTX/creatinine (nmolBCE/mmol creatinine), mean (SD)[a]	47.4 (25.7)	49.3 (32.7)
Falls[b] in year before study start, n (%)		
1	220 (86)	231 (90)
≥2	36 (14)	27 (10)
Unknown	1 (<1)	0 (0)
SPPB score (0–12 ordered scale), mean (SD)	7.3 (1.4)	7.3 (1.4)

[a] These parameters had 1–14 fewer patients for the mean calculation

[b] *Fall* defined as coming to rest unintentionally on the ground or other lower level from a standing or sitting position, not due to major intrinsic or extrinsic event

BMD

At the end of 1 year, BMD was also measured. Again, both treatment groups showed significant improvement in BMD, and the increases at the spine and hip were significantly greater in the ALN/D5600 group than the referred-care group ($P = 0.047$ at the lumbar spine, $P = 0.035$ at the total hip, Fig. 4c).

Falls

There was no significant difference between treatment groups in the number of women who had at least one or at least two falls during the 12 months of the trial (Fig. 5). The hazard ratios (95% CI) of ALN/D5600 compared with referred care were 0.82 (0.59–1.15) for time to first fall and 0.93 (0.55–1.59) for time to second fall. Analysis using zero-inflated Poisson regression of fall rates gave similar results.

Safety and Tolerability

There were no differences in tolerability between the two treatment groups (Table 3). The incidences of specific AEs, including fractures, dental disorders, and upper respiratory disturbances, were similar between groups.

Discussion

This study has shown that administration of ALN/D5600 is more effective than standard care at elevating serum

Table 2 Treatment distribution among women receiving referred care

(A) Treatments in referred-care group

	n (%)
Drugs[a]	
Bisphosphonates	219 (84.9)
Alendronate	133 (51.6)
Risedronate	53 (20.5)
Ibandronate	43 (16.7)
Zoledronate	9 (3.5)
Strontium ranelate	15 (5.8)
Active vitamin D (calcitriol or α-calcidol)	9 (3.5)
Raloxifene	2 (0.8)
Supplements alone	
Calcium alone	17 (6.6)
Vitamin D alone	12 (4.7)
Calcium + vitamin D	5 (1.9)
None	6 (2.3)

(B) Average daily vitamin D intake from supplements

Vitamin D intake (IU/day)	n	%	Mean	SD	Median	Range
Any level	203	–	751	1502	245	0–13,968
<200	95	46.3	52	79	0	0–200
≥200 and <400	29	14.3	318	75	333	200–399
≥ 400 and < 600	13	6.4	496	64	488	400–595
≥ 600 and < 800	17	8.4	755	38	761	700–799
≥ 800	49	24.1	2429	2346	1591	819–13,968

[a] Of women receiving drugs, 12.1% also received vitamin D alone, 12.5% also received calcium alone, and 61.5% also received calcium plus vitamin D. Some women received more than one drug during the study and have been counted more than once in the table

Fig. 2 Proportions of women with 25(OH)D below specific thresholds. **a** Primary end point: Proportion of patients with 25(OH)D <20 ng/ml. **b** Proportion of patients with 25(OH)D below various thresholds at 12 months. *P < 0.001 between treatment groups

25(OH)D values, reducing BTMs, and increasing lumbar spine and total hip BMD. Significantly fewer women in the ALN/D5600 group had 25(OH)D levels <20 ng/ml compared with the standard-care group (8.6% vs. 31.0%). Similarly, the reduction in BTMs was significantly greater in the ALN/D5600 group and the responses of lumbar spine and total-hip BMD were superior, even though most of the women in the referred-care group were prescribed bisphosphonates (predominantly alendronate), along with calcium and vitamin D.

The greater efficacy in the ALN/D5600 group is likely to be the result of several factors. While 51% of the referred-care group were prescribed alendronate, a substantial proportion were prescribed risedronate, which is a less potent antiresorptive than alendronate [27]. 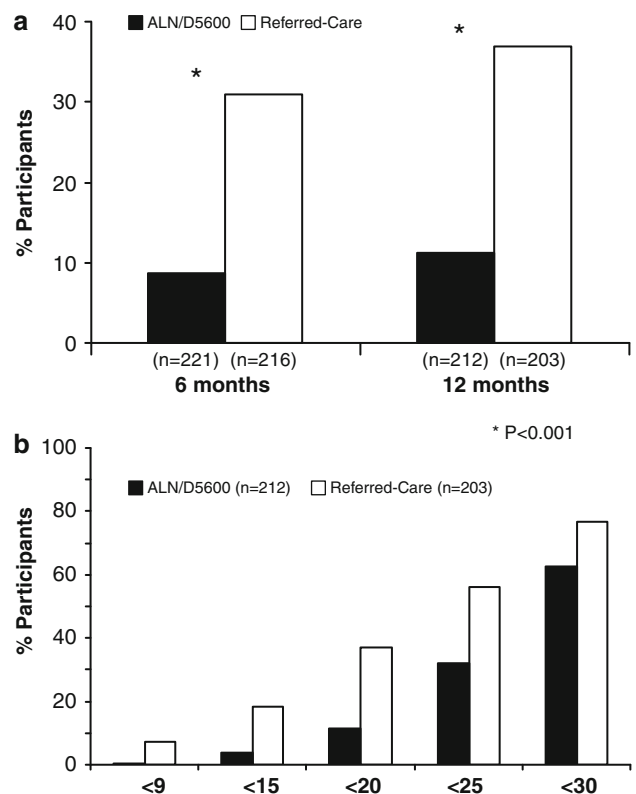Smaller numbers of patients received strontium ranelate and raloxifene, which are relatively weak antiresorptives; and a few patients received calcium and vitamin D supplements alone. Although most patients in the standard-care group were prescribed calcium and vitamin D supplements, the estimated vitamin D intake was lower than that in the ALN/D5600 group. Although we did not collect data on adherence to calcium and vitamin D supplements in the standard-care group, previous studies have shown that many patients prescribed calcium and vitamin D supplements do not adhere to this medication [19–21]. Despite the fact that the biochemical markers and BMD responses were better in the ALN/D5600 group, we did not observe a difference in the incidence of falls or fractures between the treatment groups, although the study had insufficient power to detect effects on falls or fractures.

In summary, the present study has demonstrated that treatment of postmenopausal osteoporotic women with a combination of alendronate and vitamin D_3 5600 IU is more effective than standard care at correcting vitamin D insufficiency, most probably because the vitamin D is given at the same time as the antiresorptive therapy,
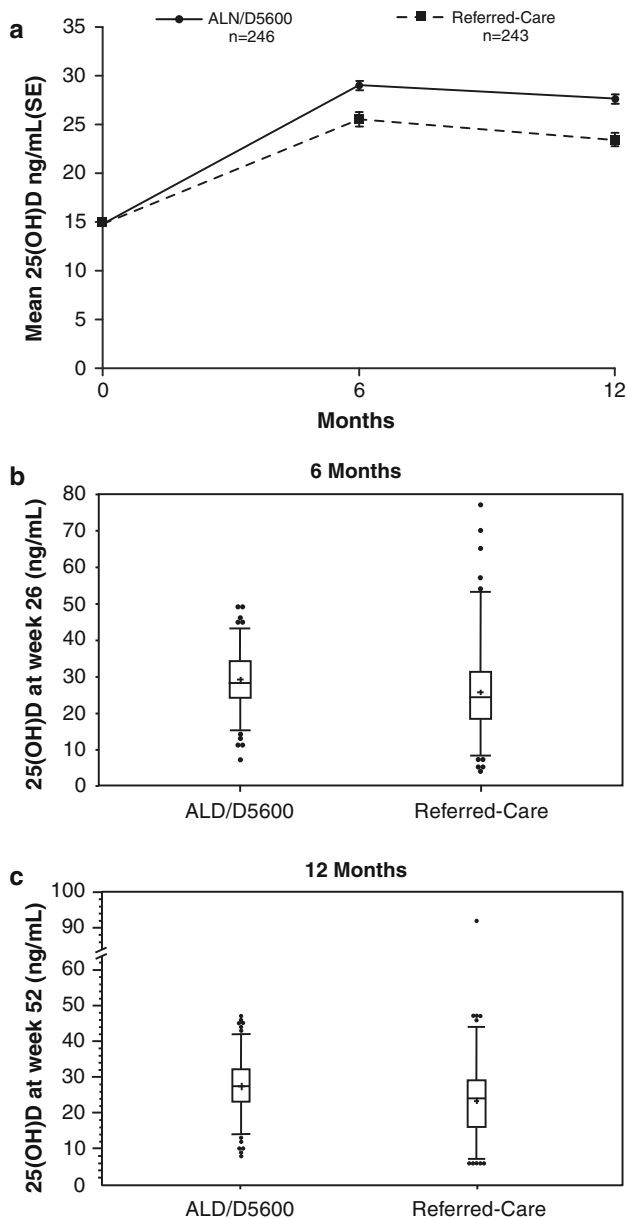
Fig. 3 Concentrations of serum 25(OH)D. **a** Changes from baseline in 25(OH)D. **b, c** Distribution of 25(OH)D concentrations after treatment with ALN/D5600 or referred care at 6 and 12 months. *Boxes* represent the borders of the 25th and 75th percentiles. *Center lines in boxes* designate the median and *points in boxes*, the mean. *Lines* at the tops and bottoms ("whiskers") represent the 2.5th and 97.5th percentiles

Fig. 4 Change from baseline in BTMs and BMD. **a** NTX/Cr. **b** BSAP. **c** BMD at 12 months. *$P < 0.001$, **$P < 0.047$, ***$P < 0.035$ between treatment groups

without the need for an additional prescription. It is important to note that in these patients with vitamin D insufficiency, even in the ALN/D5600 group, approximately two-thirds of patients did not attain serum 25(OH)D levels >30 ng/ml. This indicates that vitamin D_3 doses in excess of 800 IU daily may be required to ensure that higher levels of 25(OH)D advocated by some are achieved
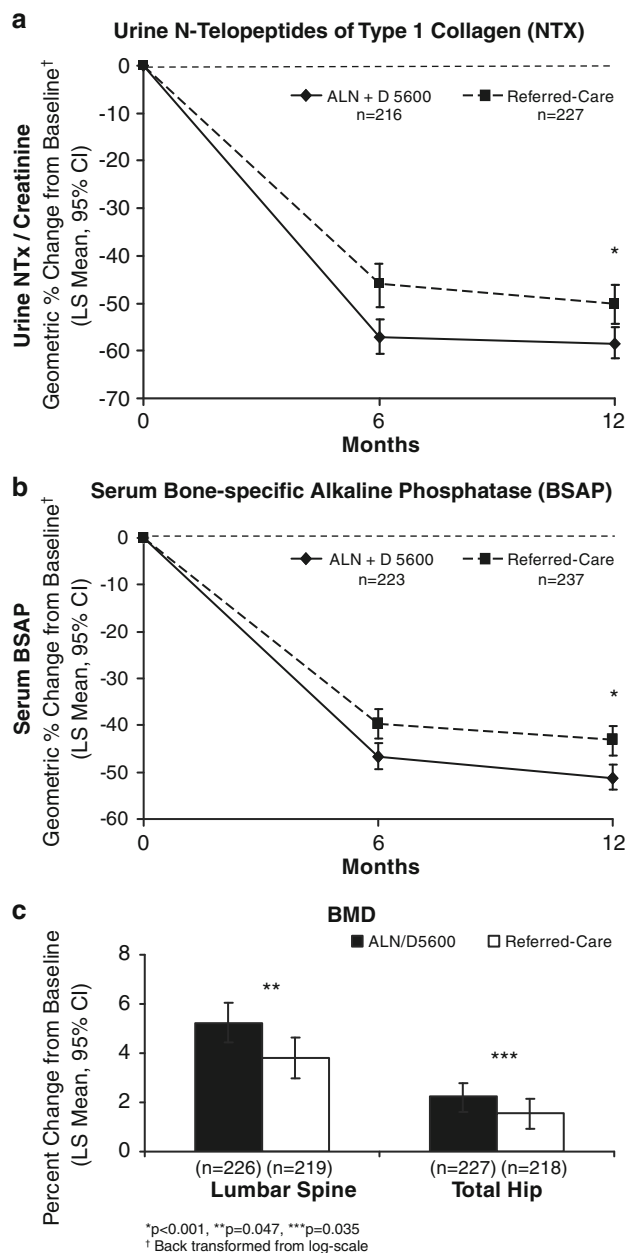
in this population. In view of the fact that adherence remains an important issue with calcium and vitamin D supplements, it is possible that combinations of specific antiosteoporotic agents with vitamin D, such as that described here, might give improved 25(OH)D status as well as BTMs and BMD in osteoporotic patients at risk of vitamin D deficiency. Furthermore, this study suggests there is room for improvement in the usual care of postmenopausal women with osteoporosis.
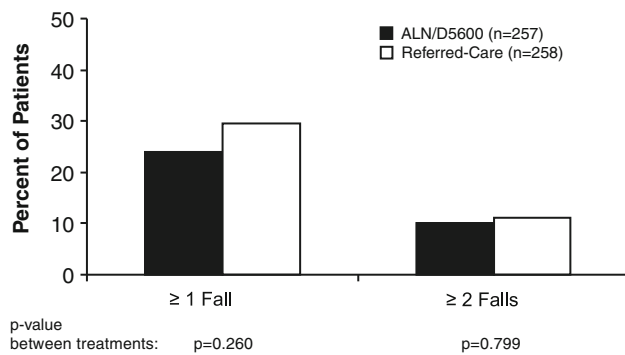
Fig. 5 Participant falls at 12 months

Table 3 Adverse experiences

Adverse experience	ALN/D5600 ($n = 257$)		Referred care ($n = 258$)	
	n	%	n	%
≥1 AE	157	61.8	167	64.7
With drug-related AEs	26	10.2	19	7.4
With serious AEs	25	9.8	29	11.2
With serious drug-related AEs	2	0.8	1	0.4
Diarrhea	1	0.4	–	–
Paroxysmal atrial fibrillation	–	–	1	0.4
Pyloric ulcer	1	0.4	–	–
Died	2	0.8	1	0.4
Discontinued due to an AE	10	3.9	8	3.1
Discontinued due to a drug-related AE	4	1.6	3	1.2
Discontinued due to a serious AE	4	1.6	3	1.2

Drug-related AEs were determined by the investigator to be related to the drug. Discontinued = study medication withdrawn

Appendix: FOCUS-D Investigators

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