ORIGINAL ARTICLE

The comparison of alendronate and raloxifene after denosumab (CARD) study: A comparative efficacy trial

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Abstract

Summary Denosumab discontinuation results in accelerated bone remodeling, decreased bone mineral density (BMD), and an increased risk of multiple vertebral fractures. Bisphosphonates are at least partially effective at inhibiting these consequences but there have been no randomized clinical trials assessing the efficacy of alternative antiresorptives.

Purpose The aim of this study was to evaluate the comparative efficacy of alendronate and the SERM, raloxifene, in preventing the post-denosumab high-turnover bone loss.

Methods We conducted an open-label randomized controlled trial in which 51 postmenopausal women at increased risk of fracture were randomized with equal probability to receive 12-months of denosumab 60-mg 6-monthly followed by 12-months of either alendronate 70-mg weekly or raloxifene 60-mg daily. Serum bone remodeling markers were measured at 0,6,12,15,18, and 24 and areal BMD of the distal radius, spine, and hip were measured at 0,12,18 and 24 months.

Results After denosumab discontinuation, serum markers of bone remodeling remained suppressed when followed by alendronate, but gradually increased to baseline when followed by raloxifene. In the denosumab-to-alendronate group, denosumab-induced BMD gains were maintained at all sites whereas in the denosumab-to-raloxifene group, BMD decreased at the spine by 2.0% (95% CI -3.2 to -0.8, P = 0.003) and at the total hip by 1.2% (-2.1 to -0.4%, P = 0.008), but remained stable at the femoral neck and distal radius and above the original baseline at all sites. The decreases in spine and total hip BMD in the denosumab-to-raloxifene group (but not the femoral neck or distal radius) were significant when compared to the denosumab-to-alendronate group.

Conclusions These results suggest that after one year of denosumab, one year of alendronate is better able to maintain the inhibition of bone remodeling and BMD gains than raloxifene.

Keywords Denosumab · Raloxifene · Denosumab cessation · Osteoporosis

Introduction

Denosumab, a fully human monoclonal antibody that binds to and inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL), is a widely used osteoporosis medication that increases bone mineral density (BMD), improves

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bone microarchitecture, and significantly reduces the risk of vertebral, hip, and non-vertebral fracture [1–4].

Denosumab acts by blocking the binding of RANKL to its receptor on pre-osteoclasts and osteoclasts, the final common pathway leading to osteoclast activation and bone resorption [5, 6]. It produces almost complete and sustained suppression of bone remodeling to a greater degree than both intravenous and oral bisphosphonates [7, 8]. In iliac crest bone biopsy specimens taken from postmenopausal women with osteoporosis who had been taking denosumab for 24–36 months, there was an 80% reduction in eroded surface and complete absence of osteoclasts in more than 50% of the specimens [8]. Discontinuation of denosumab, however, results in a rapid reversal of its antiresorptive effects, a transitory overshoot of serum bone remodeling markers to above the pre-treatment baseline, and a progressive decrease in BMD [9–13]. This

reversal of the skeletal benefits achieved with denosumab appears to be lost even after a very short duration (12 months) of treatment with denosumab [14]. Of greater concern, post hoc analyses of the large phase 3 randomized controlled trial of denosumab (FREEDOM) reported that when denosumab is discontinued, there is an immediate loss in vertebral anti-fracture efficacy as well as a significant increase in the incidence of patients experiencing multiple vertebral fractures versus those originally assigned to placebo [15–17].

Given the above findings, determining the ideal sequence of therapy after denosumab is crucial. Clinical trials that have evaluated the efficacy of follow-up therapy with oral and parenteral bisphosphonates to maintain denosumab-induced BMD gains have reported preservation of BMD for at least 12 months after patients have transitioned from short-term denosumab to either oral alendronate or intravenous zoledronate [18–21]. However, in trials where patients have received a longer duration of denosumab (> 3 years), follow-up therapy with bisphosphonates have not been as effective in maintaining denosumab-induced BMD gains [22–25]. For patients who are unwilling or unable to tolerate bisphosphonate therapy, there have been no prospective trials assessing the efficacy of alternative antiresorptive drugs, such as selective estrogen receptor antagonists (SERMs). The aim of this study was to determine the comparative efficacy of the oral bisphosphonate, alendronate, and the SERM, raloxifene, when used in sequence with short-term denosumab. Specifically, we hypothesized that in postmenopausal women with osteoporosis who received denosumab for one year, alendronate would more effectively inhibit bone remodeling and maintain denosumab-induced gains in BMD compared to raloxifene.

Methods

Study design and participants

The Comparison of Alendronate or Raloxifene following Denosumab (CARD) study was a 24-month randomized, two-arm, open label study conducted at Massachusetts General Hospital, an academic hospital in Boston, Massachusetts.

From November 2018 to January 2020, women aged 45 years and older were recruited via targeted commercial mailings and referrals from an endocrine osteoporosis clinic. Eligible women were postmenopausal (defined as more than 36 months since last spontaneous menses or > 36 months since hysterectomy with bilateral oophorectomy plus serum FSH > 40 units / liter) and at increased risk of fracture defined as having at least one of the following three criteria: (i) spine or hip T-score < —2.5 SD; (ii) personal history of spine or hip fracture; or (iii) high fracture risk consistent with National Osteoporosis Foundation guidelines (spine or hip T-score between -1.0 and—2.5 SD and a 10-year hip fracture

probability ≥ 3% or a 10-year major osteoporosis-related fracture probability ≥ 20% based on the US-adapted fracture risk model, FRAX®). Hip fractures had to have occurred more than 12 months prior to enrollment. Women were excluded if they had current use or use in the past 12 months of oral bisphosphonates, teriparatide, abaloparatide or denosumab. Additionally, study participants were excluded if they had known congenital or acquired bone disease other than osteoporosis, a history of malignancy or radiation therapy, significant cardiopulmonary disease, major psychiatric disease, major alcohol and substance use, or any other condition that the investigator deemed may preclude the participant from participating safely or completing the protocol procedures.

The study protocol was approved by the Mass General Brigham Institutional Review Board and is registered with ClinicalTrials.gov, number NCT03623633. All study participants had to provide written informed consent before enrollment in the study.

Randomization and masking

Eligible participants were stratified by previous bisphosphonate use (previous use or none) and then randomly assigned within each stratum to one of the two treatment groups by computer-generated cards in a 1:1 ratio. Outcome assessors and the laboratory performing the laboratory tests were blinded to group assignment.

Study procedures

Study participants were randomized to receive denosumab 60-mg subcutaneously every 6 months for 12-months followed by 12-months of either alendronate 70-mg weekly or raloxifene 60-mg daily (Fig. 1). Adherence to alendronate and raloxifene were assessed by self-reported diary which was reviewed at each study visit. Average adherence rates were 98.7% for alendronate and 98.3% for raloxifene. All participants who reported a dietary intake of less than 1200 mg of calcium daily were given calcium supplementation (600 mg elemental calcium) to achieve an intake of 1200 mg of calcium daily. All participants received 400 IU of vitamin D. Study visits were conducted at 0, 6, 12, 15, 18, and 24 months. Blood collection was performed at each visit and bone density measurements by dual energy x-ray absorptiometry (DXA) were performed at 0, 12, 18, and 24 months. Vertebral Fracture Assessment (VFA) by DXA was completed at months 12 and 24. A semiquantitative method was used to determine the incidence of vertebral fractures between 12 and 24 months.

Fasting morning blood samples were collected and stored at -70 °C. Measurements of serum bone remodeling markers, serum cross-linked *C*-telopeptide of type I collagen (CTX) and procollagen *N*-propeptide of type
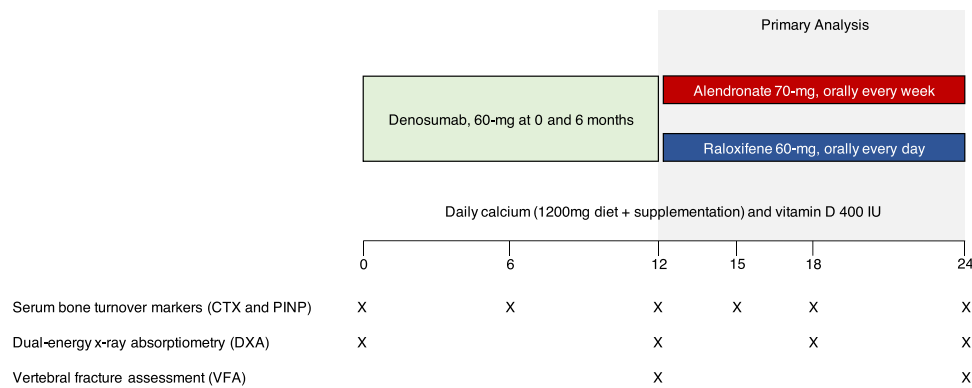
Fig. 1 Trial Schema of the 24-month open label randomized controlled trial. At baseline, all participants were randomized with equal probability to receive denosumab 60-mg at 0 and 6 months, followed by either alendronate 70-mg weekly or raloxifene 60-mg daily for 12-months. Serum bone turnover markers (CTX and PINP) were measured at each time point; bone mineral density was measured by DXA at the lumbar spine, hip, and distal one-third of the radius shaft at 0,12,18, and 24 months; VFA was conducted at 12 and 24 months

I collagen (PINP), were conducted as a batch analysis at the conclusion of the study by electrochemiluminescence (iSYS, Immunodiagnostic Systems, Scottsdale, AZ, USA). The inter- and intra-assay coefficients of variation (CVs) were 6.0% and 3.2% for CTX and 5.0% and 2.9% for PINP.

Areal bone mineral density (BMD) of the posterior-anterior lumbar spine (PA spine), total hip, femoral neck, and distal one-third of the radius shaft was measured by DXA using a Hologic densitometer (Hologic, Marlborough, MA). Vertebra with obvious deformities or focal sclerosis were excluded from all analyses (1 woman in each group). Based on our center's precision study, our short-term precision coefficient of variation (CV) for *in* vivo reproducibility is 0.54% for PA spine, 0.74% for total hip, 1.29% for femoral neck, and 3.17% for distal one-third radius, corresponding to a least significant change (LSC) of 0.014 g/cm^2, 0.018 g/cm^2, 0.025 g/cm^2, and 0.020 g/cm^2, respectively.

Adverse events including bone fractures were documented at each visit. Any serious adverse event that occurred during the study was reviewed by an independent data and safety monitoring board.

Outcomes

The outcome measures for this study were the between group differences in serum biochemical markers of bone remodeling (primary) as well as between group differences in DXA-derived spine and hip areal bone mineral density.

Statistical analysis

With a sample size of 20 participants per group, the study was powered to detect a between-group difference of 20% in serum

CTX between month 12 (6-months after the final denosumab injection) and month 18, based on a standard deviation of 22%, and with 80% power at a significance level of 5%. Statistical analysis of the time-specific treatment effects (0–24 months, 12–18 months, and 12–24 months) of the denosumab-to-alendronate group compared to the denosumab-to-raloxifene group were assessed by analysis of variance (ANOVA) based on a modified intention to treat principle, where all participants who completed at least one visit after month 12 (cessation of denosumab and randomization to alendronate or raloxifene) were included in the analysis set. A p value of 0·05 or less was considered to indicate statistical significance. Data are presented as mean (SD) for endpoints with a normal distribution and as median (IQR) for endpoints without a normal distribution. For illustration purposes, changes in bone density parameters are shown as percent change (95% confidence interval, CI) from baseline. Statistical analysis was done with SAS (version 9.2).

Role of the funding source

The funders had no role in the study design, data collection, analyses, nor interpretation of the study results, nor in the writing of this manuscript.

Results

Fifty-one women enrolled in the study and were randomly allocated, in a 1:1 ratio, to receive 12 months of either alendronate 70-mg weekly (n = 26) or raloxifene 60-mg daily (n = 25) after 12 months of denosumab treatment. Of the 51 women who enrolled in the study, 48 women (94%) completed at least one study visit after month 12 and were

included in the primary analysis. The demographic and baseline characteristics of the study participants are presented in Table 1. Study participants had an average age of 65.8 (5.2) years, 92% were white, 39% had a prevalent fragility fracture after the age of 45 years, and 33% had previously been treated with an oral bisphosphonate. Clinical characteristics were similar between groups apart from BMD at the femoral neck, which was significantly higher in the denosumab-to-raloxifene group (Fig. 2).

Changes in serum bone remodeling markers, CTX and PINP, are shown in Fig. 3. Treatment with denosumab decreased levels of CTX and PINP to a similar extent in both groups, and levels remained suppressed at all measured timepoints during the 12-month treatment period. After the transition, CTX and PINP levels remained suppressed at all time points in the denosumab-to-alendronate group. In the denosumab-to-raloxifene group, both CTX and PINP levels gradually increased and returned to baseline levels over 6 to 12 months. There was no overshoot in bone remodeling markers observed in either group.

Longitudinal changes in BMD at the PA spine, hip, and distal one-third of the radius shaft are shown in Fig. 4. Twelve months of denosumab increased BMD at the PA spine, total hip and femoral neck similarly in both groups. Conversely, BMD at the distal one-third of the radius shaft decreased in both groups. After the transition, denosumab-induced gains in BMD were maintained over 12 months at all measured sites in the denosumab-to-alendronate group. In the denosumab-to-raloxifene group, however, BMD decreased at the PA spine by 2.0% (95% CI -3.2 to -0.8, $P = 0.003$ for 12–24 month within group comparison) and at the total hip by 1.2% (95% CI -2.1 to -0.4%, $P = 0.008$ for 12–24 month within group comparison) but was maintained at the femoral neck and distal one-third of the radius shaft. From 12 to 24 months, the mean differences in BMD change in the denosumab-to-alendronate group compared to the denosumab-to-raloxifene group were 2.9% (95% CI 1.4 to 4.5%, $P < 0.001$) at the PA spine; 1.2% (95% CI 0.2 to 2.3%, $P = 0.02$) at the total hip; 0.6% (95% CI—1.8 to 3.0%, $P = 0.6$) at the femoral neck, and 0.3% (95% CI – 1.1 to 1.7%, $P = 0.6$) at the distal one-third of the radius shaft. In both groups, BMD remained above the pre-treatment baseline (0 months) at the PA spine and hip sites. Given the significant between group difference in femoral neck BMD at baseline, femoral neck outcomes were also re-analyzed after adjustment for baseline femoral neck BMD and showed similar results (data not shown).

Table 1 Demographics and Baseline Characteristics

Characteristic	Denosumab to Alendronate (n=26)	Denosumab to Raloxifene (n=25)
Age (yr)	66.0 (5.1)	65.4 (5.3)
Height (cm)	161.7 (5.4)	163.1 (6.3)
Body-mass index (kg/m^2)	23.2 (3.3)	24.6 (3.1)
White, non-Hispanic	23 (88%)	24 (96%)
History of fragility fracture	10 (38%)	10 (40%)
Previous oral bisphosphonate use	10 (38%)	7 (28%)
Duration of use, months	48 (36%)	32 (29%)
Time since discontinuation, months	73 (50%)	90 (67%)
Serum 25(OH)D (ng/mL)	36 (11.3)	35 (8.7)
PINP (ng/mL)	69.7 (56.6 – 84.2)	63.0 (53.8 – 78.4)
CTX (ng/mL)	0.65 (0.34 – 0.76)	0.46 (0.31 – 0.66)
Areal bone mineral density by DXA BMD (g/cm^2) *Baseline*		
Posterior-anterior lumbar spine	0.794 (0.085)	0.804 (0.072)
Femoral neck	0.585 (0.050)	0.628 (0.071)*
Total hip	0.707 (0.068)	0.736 (0.072)
Distal one-third of the radius shaft	0.564 (0.073)	0.584 (0.075)
Month 12 (after 12 months of denosumab)		
Posterior-anterior lumbar spine	0.843 (0.086)	0.831 (0.071)
Femoral neck	0.600 (0.047)	0.650 (0.068)*
Total hip	0.731 (0.067)	0.762 (0.075)
Distal one-third of the radius shaft	0.556 (0.073)	0.583 (0.074)

Data are presented as mean (SD), median (Q1 – Q3), or number (%). Abbreviations: 25(OH)D = 25-hydroxyvitamin D; DXA = dual x-ray absorptiometry; BMD = bone-mineral density. *$P < 0.05$

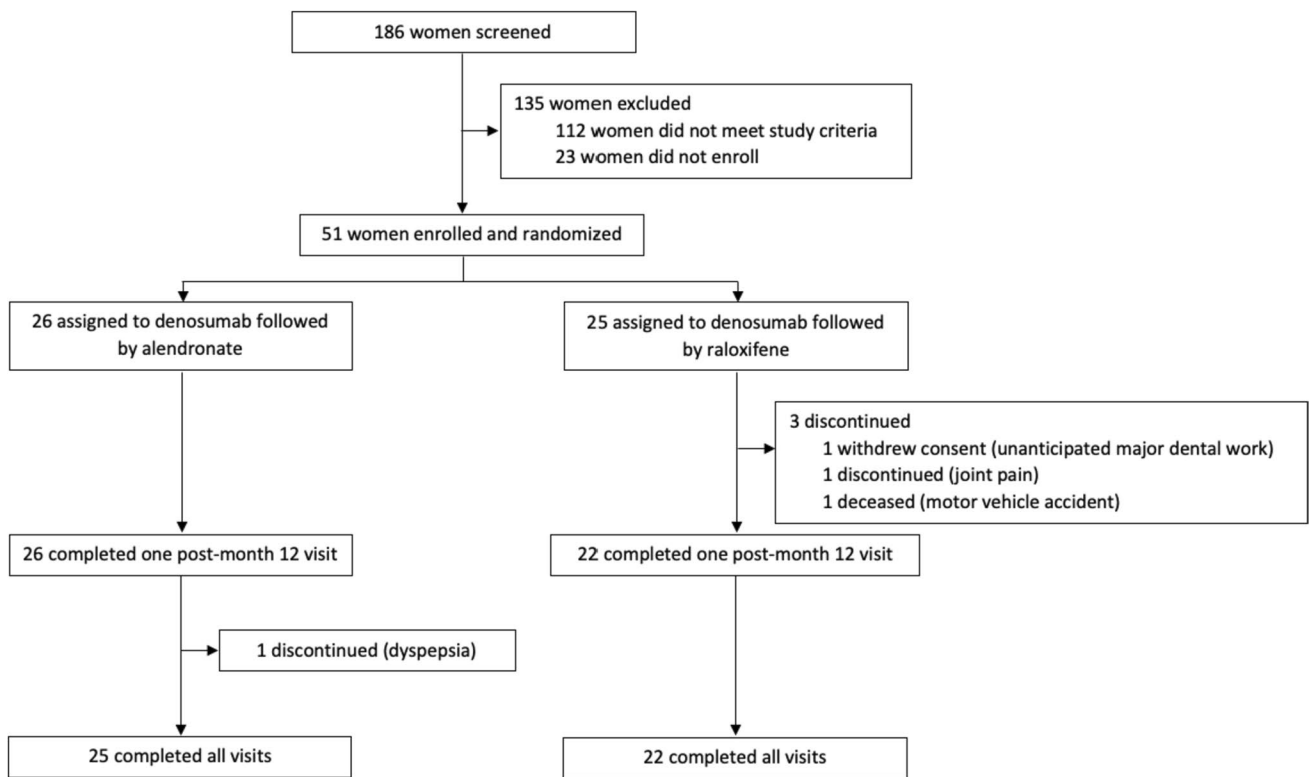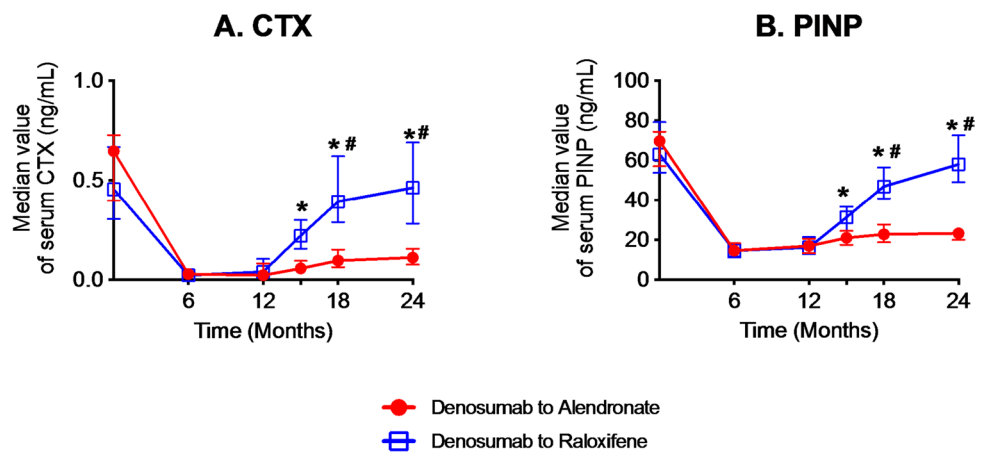**Fig. 2** Subject disposition

Fig. 3 Median value of serum bone remodeling markers, CTX (A) and PINP (B). Error bars show 95% CI. CTX = cross linked C-telopeptide of type I collagen; PINP = procollagen N-propeptide of type I collagen. *$P < 0.001$ for between-group comparison from month 0. #$P < 0.05$ for between-group comparison from month 12

An exploratory analysis of the percent of participants who had > 3% BMD loss at the PA spine, total hip, and femoral neck was calculated for all participants who completed baseline, month 12, and month 24 study visits. A 3% threshold was predetermined based on the widely accepted least significant change in DXA BMD measurements, which assumes a DXA precision error of 1% [26]. From 12 to 24 months, the number of participants with > 3% loss of BMD at the PA spine was 1 (4%) in the denosumab-to-alendronate group versus 6 (29%) in the denosumab-to-raloxifene group, $P = 0.04$. The number of participants with > 3% loss at the total hip was 0 in the denosumab-to-alendronate group compared to 5 (23%) in the denosumab-to-raloxifene group, $P = 0.02$. The number of participants with > 3% loss at the femoral neck was 1 (4%) in the denosumab-to-alendronate group compared to 5 (23%) in the denosumab-to-raloxifene group, $P = 0.08$.

The incidence rate of treatment related non-serious adverse events was 19 events in 12 women in the denosumab-to-alendronate group and 21 events in 15 women in the denosumab-to-raloxifene group (Table 2). All cases of constipation (n = 5) and gastro-esophageal reflux disease

Fig. 4 Mean percentage change in areal bone mineral density (aBMD) of the lumbar spine (A), distal one-third of the radius shaft (B), total hip (C), and femoral neck (D). Error bars show 95% CI. *P < 0.05, **P = 0.07, ***P = 0.09 for between-group comparison from month 0. #P < 0.05 for between-group comparison from month 12
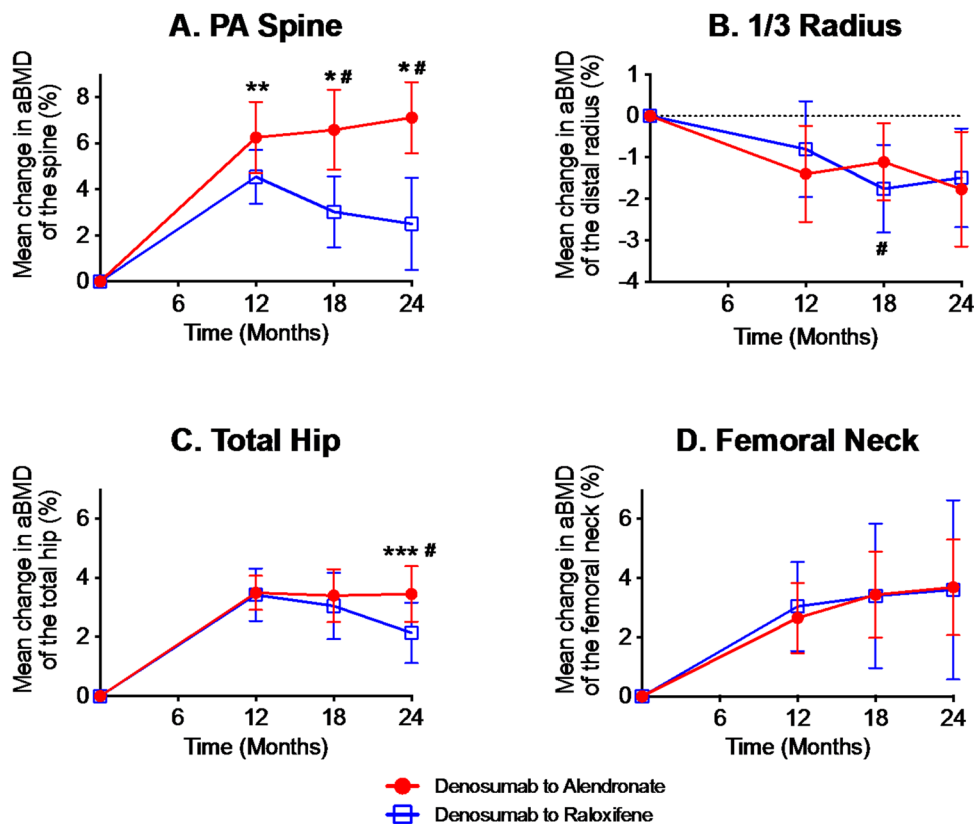
(n = 4) were reported in the denosumab-to-alendronate group, and all cases of hot flashes were reported in the denosumab-to-raloxifene group (n = 6). Serious adverse events, unrelated to the treatment intervention, occurred in 2 participants in the denosumab-to-alendronate group (one woman had diverticulitis with a bowel perforation and the other had palpitations and dyspnea associated with a known mitral valve prolapse) and 1 participant in the denosumab-to-raloxifene group (death after a motor vehicle accident). Between 0 to 12 months (denosumab phase), 2 participants in the denosumab-to-alendronate group had a humerus fracture and 1 participant in the denosumab-to-raloxifene group had simultaneous fractures of the femoral condyle and lateral tibial plateau. Between 12 to 24 months (transition phase), no clinical fractures were reported in either group. Study participants had a vertebral fracture

Table 2 Adverse Events

	Denosumab to Alendronate (n = 26)	Denosumab to Raloxifene (n = 25)
Treatment related non-serious adverse event	19 (73%)	21 (84%)
Abdominal pain	0 (0)	1 (4%)
Joint pain	5 (19%)	7 (28%)
Constipation	5 (19%)	0 (0)
Nausea	0 (0)	0 (0)
Urinary tract infection	1 (4%)	1 (4%)
Rash	1 (4%)	3 (12%)
Eczema	1 (4%)	1 (4%)
Gastro-esophageal reflux disease (GERD)	4 (15%)	0 (0)
Hot flashes	0 (0)	6 (24%)
Headaches	0 (0)	0 (0)
Muscle cramps/spasms	2 (8%)	2 (8%)
Any serious adverse event excluding death	2 (8%)	0 (0)
Study discontinuation due to adverse event	1 (4%)	1 (4%)
Deaths	0 (0)	1 (4%)

Data are n (%)

assessment (VFA) at 12 and 24 months. Only 1 participant in the denosumab-to-alendronate group had a new thoracic (T9) fracture assessed by VFA performed at 24 months. Formal comparisons of safety and fracture events between the denosumab-to-alendronate and denosumab-to-raloxifene groups are not possible because of the limited sample size.

Discussion

In this study, we report that in postmenopausal women with osteoporosis who discontinued denosumab after 12 months, alendronate was better able to suppress bone remodeling and maintain the denosumab-induced gains in BMD compared to raloxifene.

Discontinuation of denosumab, after 2 years of treatment, results in a transitory overshoot in serum bone remodeling markers to above pre-treatment baseline levels and an accompanying decrease in BMD [9]. The underlying molecular and cellular mechanisms responsible for this overshoot are not fully defined though reports from preclinical studies suggests that an increase in the osteoclast precursor pool [27], an increase in the RANKL:OPG ratio [28], and a decrease in the number of osteocytes and osteoblasts in the initial phase after denosumab discontinuation [29] may all play a role. The benefits observed with alendronate over raloxifene in our study are likely due to the greater suppression of bone remodeling achieved with alendronate compared to raloxifene [30, 31]. In our study, alendronate was able to maintain suppression of bone remodeling similar to what was achieved during treatment with denosumab. Raloxifene, however, was not able to maintain the same degree of bone remodeling suppression, and within 3 months of transitioning from denosumab to raloxifene, there was a significant increase in both CTX and PINP, with levels gradually increasing to baseline at 24 months. There was no overshoot in bone remodeling markers observed during treatment with raloxifene. However, as there was no placebo group in our study, it is not known whether the overshoot in bone remodeling occurs after 12 months of treatment with denosumab (as has been described with denosumab cessation after 24 months of treatment) [9]. This observation is in contrast to reports from two recently published retrospective studies, where raloxifene did not prevent the overshoot in bone remodeling in postmenopausal women with osteoporosis who transitioned to raloxifene 60-mg daily after an average of 12–18 months of denosumab [32, 33]. The reasons for this discrepancy are unclear but could be due to slightly different durations of denosumab treatment (women in these studies had up to 5 doses of denosumab whereas women in our study received 2 doses). In addition, given the retrospective nature of these studies, there may be confounding variables that have not been accounted for.

As expected, 12 months of denosumab resulted in BMD increases at the PA spine and hip. These gains in BMD are comparable to those reported in the landmark FREEDOM trial in postmenopausal women with osteoporosis who received denosumab 60-mg 6-monthly [4]. After the transition, consistent with the observed changes in serum bone remodeling markers, denosumab-induced BMD increases at the PA spine and total hip were better maintained in those who transitioned to alendronate compared to those who transitioned to raloxifene. At the end of the 24-month study period, PA spine and total hip BMD were significantly increased in the denosumab-to-alendronate group compared to the denosumab-to-raloxifene group. Overall BMD at the femoral neck and distal one-third of the radius shaft were similarly maintained in both groups, though there was a wide variation among individuals. Some of this variation is likely due to greater measurement error at the femoral neck and radius sites. Importantly, in both groups, after the transition from denosumab to either alendronate or raloxifene, BMD remained above the pre-treatment baseline at all sites. Our study results are similar to previously published reports from studies that have evaluated the efficacy of alendronate or raloxifene in maintaining BMD after cessation of denosumab. For example, in the multi-center Denosumab Adherence Preference Satisfaction (DAPS) study of 126 postmenopausal women [20], BMD gains at the spine and hip after 12 months of denosumab were maintained in the 115 women who transitioned to alendronate for 12 months. In a retrospective study of 66 postmenopausal women in Korea [33], after 1:1 propensity score matching, bone density loss at the lumbar spine was attenuated in those who transitioned from denosumab (1–4 doses) to raloxifene compared to those who did not receive any sequential treatment (2.8% versus 5.8%, $P = 0.01$), whereas BMD loss at the total hip did not differ between the two groups (1.4% versus 1.4%, $P = 1.0$) [33].

The ability of raloxifene to partially maintain BMD gains may be clinically significant. Many patients are unable to tolerate oral bisphosphonates, mainly due to upper gastrointestinal adverse effects such as nausea, dyspepsia, abdominal pain, and gastritis [34–36]. Intravenous bisphosphonates are also associated with an acute phase reaction (fever, headache, myalgia, and arthralgia) in approximately one-third of patients receiving their first infusion of zoledronic acid, though this incidence declines progressively with subsequent infusions [37]. Moreover, even in those without an absolute contraindication to bisphosphonate therapy, many patients often refuse to take these medications due to concerns of rare but serious side effects such as atypical femoral fractures and osteonecrosis of the jaw [38, 39]. It should be noted, however, that raloxifene may not be a suitable alternative for everyone, as there are off-target effects, such as an increased risk of venous thromboembolic events and hot flashes, that need to be

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