Bone 58 (2014) 48–54

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: Efficacy and safety results from a randomized open-label study

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ARTICLE INFO

Article history:
Received 30 May 2013
Revised 16 September 2013
Accepted 9 October 2013
Available online 17 October 2013

Edited by: R. Baron

Keywords:
Denosumab
Postmenopausal osteoporosis
Risedronate
Bone mineral density
Bone turnover markers

ABSTRACT

Denosumab has been shown to reduce new vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis. In subjects who were treatment-naïve or previously treated with alendronate, denosumab was associated with greater gains in bone mineral density (BMD) and decreases in bone turnover markers when compared with alendronate-treated subjects. This trial was designed to compare the efficacy and safety of denosumab with risedronate over 12 months in postmenopausal women who transitioned from daily or weekly alendronate treatment and were considered to be suboptimally adherent to therapy.

In this randomized, open-label study, postmenopausal women aged ≥55 years received denosumab 60 mg subcutaneously every 6 months or risedronate 150 mg orally every month for 12 months. Endpoints included percentage change from baseline in total hip BMD (primary endpoint), femoral neck, and lumbar spine BMD at month 12, and percentage change from baseline in sCTX-1 at months 1 and 6. Safety was also assessed.

A total of 870 subjects were randomized (435, risedronate; 435, denosumab) who had a mean (SD) age of 67.7 (6.9) years, mean (SD) BMD T-scores of −1.6 (0.9), −1.9 (0.7), and −2.2 (1.2) at the total hip, femoral neck, and lumbar spine, respectively, and median sCTX-1 of 0.3 ng/mL at baseline. At month 12, denosumab significantly increased BMD compared with risedronate at the total hip (2.0% vs 0.5%), femoral neck (1.4% vs 0%), and lumbar spine (3.4% vs 1.1%; $p < 0.0001$ at all sites). Denosumab significantly decreased sCTX-1 compared with risedronate at month 1 (median change from baseline of −78% vs −17%; $p < 0.0001$) and month 6 (−61% vs −23%; $p < 0.0001$). Overall and serious adverse events were similar between groups.

In postmenopausal women who were suboptimally adherent to alendronate therapy, transitioning to denosumab was well tolerated and more effective than risedronate in increasing BMD and reducing bone turnover.

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8756-3282
http://dx.doi.org/10.1016/j.bone.2013.10.006

Introduction

Osteoporosis is defined as a systemic skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [1–3]. Sustained benefit of a therapeutic agent for a chronic condition such as osteoporosis generally requires continued treatment. While bisphosphonates are the most commonly used treatment for postmenopausal osteoporosis, difficult dosing regimens and multiple side effects may limit drug adherence [4]. This poor adherence to bisphosphonate therapy in osteoporosis is both common and associated with unfavorable outcomes and increased treatment costs [5,6]. In addition, if a patient sustains a low-trauma fracture or continues to have low bone mineral density (BMD) while on treatment, some clinicians may consider that a patient has failed therapy and may recommend transition to another medication. For subjects who are suboptimally treated with bisphosphonates under these circumstances, it is important to understand whether they are appropriate for, and would receive benefit from, transitioning to a new therapy, such as one with a different mechanism of action than bisphosphonates.

Denosumab has been approved in many countries for the treatment of postmenopausal women with osteoporosis at increased or high risk for fracture. Denosumab is a fully human monoclonal antibody against RANKL, a cytokine that is an essential mediator for osteoclast formation, function, and survival [7]. In postmenopausal women with osteoporosis, denosumab 60 mg administered subcutaneously every 6 months significantly reduced bone turnover markers, increased BMD, and reduced new vertebral, hip, and nonvertebral fractures compared with placebo in the pivotal 36-month fracture trial [8].

It has been shown that in subjects who were treatment-naïve or previously treated with alendronate, transitioning to denosumab treatment was associated with greater gains in BMD and decreases in bone turnover markers when compared with subjects continuing on alendronate treatment [9,10]. It is not known whether this observation would be similar with other bisphosphonates, which is an important consideration for women or their physicians who are considering a change in therapy due to unsatisfactory treatment effect.

The purpose of this randomized, open-label trial was to compare the safety and efficacy of transitioning to denosumab or the bisphosphonate risedronate for 12 months, in postmenopausal women who were previously treated with daily or weekly alendronate and were considered to be suboptimally adherent to their current therapy.

Methods

Study design

This 12-month, multicenter, international (82 centers in Europe, Australia, and Canada), randomized, open-label, parallel-group study was conducted in postmenopausal women who had previously been prescribed alendronate therapy, but had either stopped taking alendronate or were currently taking alendronate, but demonstrated suboptimal adherence to treatment.

Treatment

Subjects were randomized 1:1 to receive either denosumab 60 mg subcutaneously (SC) every 6 months (Q6M) or risedronate orally (PO) 150 mg once monthly (QM, one 75 mg tablet on each of 2 consecutive days) for 12 months. The protocol specified that all subjects were required to take daily supplements of ≥1000 mg elemental calcium and ≥800 IU vitamin D during the study.

Participants

Ambulatory, postmenopausal women aged ≥55 years were eligible if they had been previously prescribed alendronate therapy, with the first daily or weekly alendronate prescription ≥1 month prior to screening, without limitation of alendronate treatment duration. All subjects provided signed informed consent prior to initiation of any study procedure.

With a 1:1 randomization ratio, a sample size of 362 evaluable subjects in each treatment group would give >90% power to detect a difference >1% at the total hip BMD at 12 months using a two-sided t-test at the 5% significance level, assuming a common standard deviation (SD) of 2.65%. Assuming a dropout rate of 10% in 12 months, the planned enrollment was 400 subjects in each treatment group, with a total sample size for the study of approximately 800 subjects.

To be eligible to participate in this study, the subject must have either stopped oral alendronate therapy before the screening visit, or was still taking oral alendronate therapy (no washout period) with low adherence, which was assessed by a score of <6 on the Osteoporosis Specific Morisky Medication Adherence Scale (OS-MMAS). The OS-MMAS is an osteoporosis-specific version of the MMAS, an 8-item questionnaire that has been evaluated for reliability and validity [11]. Each of the 8 items captures a specific medication-taking behavior. Scores from the OS-MMAS can range from 0 to 8 and have been categorized into 3 levels of adherence: high (score = 8), medium ($6 \leq$ score < 8), and low (score < 6). There was no inclusion criterion based on BMD.

Key exclusion criteria included any prior or current treatment with osteoporosis medication other than daily or weekly oral alendronate therapy, hormone replacement therapy, and calcium and vitamin D (use of raloxifene or calcitonin prior to initiation of alendronate therapy was allowed); use of the following medications within 3 months of screening: tibolone, anabolic steroids or testosterone, and glucocorticosteroids (≥5 mg prednisone equivalent per day for >10 days or a total cumulative dose of ≥50 mg); contraindicated or poorly tolerant of alendronate; significantly impaired renal function; previous participation in clinical trials with denosumab within the preceding 12 months regardless of treatment; reported malignancy within the last 5 years, except cervical carcinoma in situ or basal cell carcinoma; and any metabolic bone disease that had the potential to interfere with the interpretation of the findings. Vitamin D deficiency, defined as serum 25 (OH) vitamin D levels <20 ng/mL, was an exclusion criterion: repletion as confirmed by a serum vitamin D level ≥20 ng/mL was allowed and subjects were able to be re-screened only once.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines, and the study protocol was approved by an institutional review board for each study site.

Assessments

Bone mineral density

Dual-energy X-ray absorptiometry (DXA) scans were performed at the proximal femur and lumbar spine (L1 to L4) at baseline and month 12 or end-of-study visit using GE Lunar or Hologic series scanners. The same DXA machine was used for all study procedures for a particular subject. The left side was used for all study procedures of the proximal femur, unless prohibited (e.g., hip implant). If the right side was used at screening, then the same side was used consistently throughout the study. DXA scans were performed in duplicate, i.e., an initial scan and a repeat scan (after repositioning the patient on the table between measurements) at each visit, and analyzed by a central imaging vendor (Synarc, Portland, OR, USA).

Biochemical markers

Measurement of the biochemical marker of bone turnover, serum C-telopeptide of type I collagen (sCTX-1), was performed by Covance Laboratory (Indianapolis, IN, USA). sCTX-1 measurements were taken after an overnight fast and prior to the dose of investigational product in a subset of subjects who agreed to participate in the bone marker

substudy at day 1 (baseline) and at months 1 and 6 (152 subjects: 68 risedronate; 84 denosumab). All samples were shipped to the central laboratory for analysis and measured in multiple assays. Evaluation of anti-denosumab antibodies in a subset of subjects receiving denosumab was performed at day 1 and month 12 or at the end-of-study visit with a screening immunoassay; any binding antibodies were confirmed with a cell-based anti-denosumab binding antibody immunoassay for neutralizing antibodies (PPD, Richmond, VA, USA).

Statistical analysis

The primary endpoint was the mean percentage change from baseline in total hip BMD at month 12. The secondary endpoints were the mean percentage change in femoral neck and lumbar spine BMD at month 12 and the median percentage change from baseline in sCTX-1 at month 1. An exploratory endpoint was the median percentage change from baseline in sCTX-1 at month 6. Safety was assessed over the 12-month study through incidence of adverse events (AEs) and serious adverse events (SAEs) that were collected throughout the study.

The full analysis set included all randomized subjects and was used to analyze all BMD endpoints. The mean percentage change from baseline for each of the BMD skeletal sites at month 12 was analyzed using an analysis of covariance (ANCOVA) model including treatment and adjusting for study day of BMD assessment, treatment by BMD-assessment-day interaction, baseline BMD value, DXA machine type, and baseline BMD value by DXA-machine-type interaction. Summary statistics for the results included least-squares means point estimates of the mean percentage change from baseline for each treatment group at month 12. The 95% two-sided confidence intervals (CIs) and associated p-values were provided for the treatment difference between the least-squares means at month 12 for denosumab and risedronate for each skeletal site.

The pre-specified primary analytical approach for BMD endpoints employed an imputation for missing baseline and post-baseline BMD. For each anatomical site, missing baseline BMD values were imputed with the mean of all non-missing baseline BMD data from the same corresponding machine type (Hologic or Lunar). Missing post-baseline BMD values were imputed with the predicted values from the regression model based on baseline covariates of each individual subject. Other sensitivity analyses and an additional post-hoc analysis based on subjects with complete data were also performed. Since none of these analyses changed the overall conclusions of the findings, this manuscript will focus on findings from the pre-specified primary analysis.

The primary ANCOVA analysis mentioned above was repeated controlling for pre-specified covariates (baseline age, prior alendronate treatment [duration, time since initiation, time since discontinuation, and branded or generic alendronate], previous osteoporotic fractures, and baseline sCTX-1), individually and simultaneously. Moreover, all BMD endpoints were analyzed by each covariate subgroup, and the treatment-by-subgroup interaction term was further assessed in the ANCOVA model. If the p-value of an interaction term was ≥ 0.05, the quantitative treatment-by-subgroup interaction was considered not significant. If the quantitative interaction was significant, the Gail and Simon test [12] was used to assess the qualitative interaction at the 5% significance level.

The least significant change (LSC) in BMD measurements for the total hip, femoral neck, and lumbar spine was calculated from the duplicate DXA scans. The proportions of subjects with a BMD change at month 12 < LSC and ≥LSC at each skeletal site were evaluated between treatment groups. The LSC is an important determinant in evaluating BMD changes because it reflects the smallest change in BMD that, when equaled or exceeded, allows the physician to conclude whether or not there has been a statistically significant change in the measurement.

An additional post-hoc subgroup analysis was conducted in subjects at higher risk vs the remaining at-risk subjects. Higher-risk subjects met any 1 of the following:

1) Baseline BMD T-score ≤ -2.5 at the total hip or femoral neck,
2) Baseline BMD T-score ≤ -1.0 at the total hip or femoral neck and prior osteoporotic fracture, or
3) Baseline sCTX-1 > 0.9 ng/mL (upper limit of premenopausal reference range) and BMD T-scores ≤ -2.0 at the total hip or femoral neck.

Treatment comparisons of median percentage change from baseline in sCTX-1 at each time point were analyzed using a Wilcoxon rank-sum test.

The safety analysis set included all randomized subjects who received ≥1 dose of investigational product. Incident fractures were reported as AEs. Two adjudication committees evaluated potential safety events of atypical femoral fractures and osteonecrosis of the jaw (ONJ). All subtrochanteric, mid-shaft, and distal femur fractures were evaluated to determine consistency with the definition of atypical femoral fracture [13]; AEs potentially associated with ONJ were identified based on a pre-defined list of terms in the Medical Dictionary for Regulatory Activities (MedDRA) and adjudicated.

Results

Subjects

Among 1431 screened subjects, a total of 870 (435 risedronate, 435 denosumab) subjects were enrolled and randomized into the study; 824 (94.7%) subjects (402 risedronate, 422 denosumab) completed the study, and 46 (5.3%) subjects (33 risedronate, 13 denosumab) discontinued the study (Fig. 1). The most frequent reasons for study discontinuation were consent withdrawn (15 risedronate, 7 denosumab) and AEs (13 risedronate, 3 denosumab). Although enrolled subjects were considered suboptimally adherent to alendronate therapy at study entry, as expected in the conduct of a clinical trial, compliance with study medication was satisfactory, with 369 (85.8%) subjects in the risedronate group who received ≥24 tablets through month 12, and 415 (96.7%) subjects in the denosumab group who received the 2 scheduled injections.

Baseline demographics and key characteristics among enrolled subjects are shown in Table 1. The mean (SD) age was 67.7 (6.9) years, most subjects were white or Caucasian (97.6%), and the mean (SD) baseline total hip, femoral neck, and lumbar spine BMD T-scores were −1.6 (0.9), −1.9 (0.7), and −2.2 (1.2), respectively. Based on subject-reported fracture history, the number of subjects with a history of any fracture was 431 (49.5%); with an osteoporotic fracture (all fractures excluding skull, facial bones, fingers, and toes and not associated with known high-trauma severity or pathological fractures) was 301 (34.6%); and with a vertebral fracture was 82 (9.4%). Sixty-one (7.0%) subjects had a recent osteoporotic fracture <1 year prior to the study.

The median (interquartile range [IQR]) durations of prior alendronate use were 27.2 (8.9, 64.0) months for risedronate-treated subjects and 20.0 (5.7, 52.5) months for denosumab-treated subjects (Table 1). The majority of subjects had used alendronate for ≥12 months (69.2% of risedronate and 63.9% of denosumab subjects), and most had discontinued therapy for <12 months (86.7% of risedronate and 85.3% of denosumab subjects; Table 1). There were 126 (29.0%) risedronate-treated subjects and 133 (30.6%) denosumab-treated subjects who were still receiving alendronate at study entry. Consistent with low adherence to previous alendronate therapy, the median baseline serum levels of sCTX-1 were 0.32 and 0.33 ng/mL in the risedronate- and denosumab-treated groups, respectively.

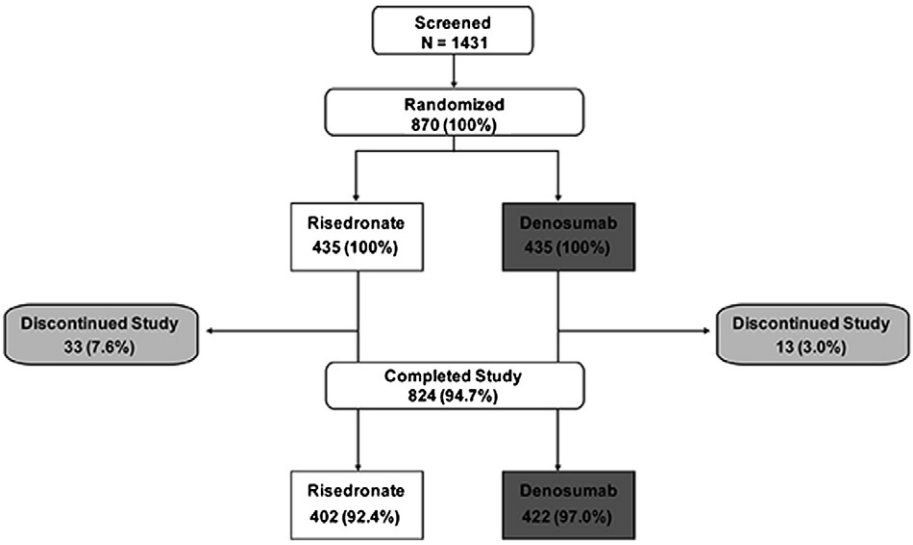

Fig. 1. Subject disposition.

Outcomes

Bone mineral density

Denosumab significantly increased BMD at the total hip at month 12 with a mean percentage change from baseline of 2.0% (95% CI: 1.8%, 2.3%); the difference in mean percentage change from risedronate was 1.6% (95% CI: 1.2%, 2.0%; $p < 0.0001$). Denosumab also significantly increased BMD at the femoral neck and lumbar spine at month 12 with a mean percentage change from baseline of 1.4% (95% CI: 1.0%, 1.7%) and 3.4% (95% CI: 3.1%, 3.8%), respectively, and compared with risedronate, a difference in mean percentage change between the treatment groups of 1.4% (95% CI: 0.9%, 1.8%; $p < 0.0001$) and 2.3% (95% CI: 1.8%, 2.8%; $p < 0.0001$), respectively (Fig. 2).

Since DXA measurements were performed in duplicate, the LSC in the BMD measurements was able to be calculated to further characterize the BMD changes at month 12 with denosumab or risedronate treatment. The calculated LSCs were 1.89% at the total hip, 3.14% at the femoral neck, and 2.16% at the lumbar spine. At month 12, a significantly greater percentage of denosumab-treated subjects as compared with risedronate-treated subjects had BMD gains that were ≥LSC at the total hip (49% vs 20%, $p < 0.0001$), femoral neck (24% vs 14%, $p < 0.0001$), and lumbar spine (64% vs 32%, $p < 0.0001$; Fig. 3).

After controlling for additional covariates (baseline age, prior alendronate treatment [duration, time since initiation, time since discontinuation, and branded or generic alendronate], previous osteoporotic fractures, and baseline sCTX-1), individually and simultaneously in the primary ANCOVA model, the effect of denosumab treatment remained consistent and significant ($p < 0.0001$ in each covariate analysis) at all 3 skeletal sites.

When primary and secondary endpoints were analyzed by subgroups—including by age, prior alendronate treatment (duration, time since initiation, time since discontinuation, and branded or generic alendronate), previous osteoporotic fractures, at-risk/higher-risk subjects, and baseline sCTX-1 tertile—the results demonstrated that increases in total hip, femoral neck, and lumbar spine BMD were numerically greater in the denosumab group than in the risedronate group at month 12 in all subgroups.

Table 1
Baseline demographics and clinical characteristics.

	Risedronate (N = 435)	Denosumab (N = 435)
Age, years	67.7 (6.8)	67.8 (7.0)
Years since menopause	20.1 (8.8)	20.2 (8.9)
History of osteoporotic fracture, n (%)[a]	150 (34.5)	151 (34.7)
Total hip BMD T-score	−1.6 (0.8)	−1.6 (0.9)
Femoral neck BMD T-score	−1.9 (0.7)	−1.9 (0.8)
Lumbar spine BMD T-score	−2.3 (1.1)	−2.2 (1.2)
Serum 25-hydroxyvitamin D, ng/mL	34.9 (13.5)	34.4 (13.2)
Duration of prior alendronate use, months		
Median (IQR)	27.2 (8.9, 64.0)	20.0 (5.7, 52.5)
0 to <12 months, n (%)	133 (30.6)	157 (36.1)
≥12 months, n (%)	301 (69.2)	278 (63.9)
Time since prior alendronate use, n (%)		
0 to <12 months	377 (86.7)	371 (85.3)
≥12 months	45 (10.3)	46 (10.6)
Never took alendronate	12 (2.8)	18 (4.1)
Still taking alendronate at study entry, n (%)	126 (29.0)	133 (30.6)
Serum CTX-1, ng/mL, median (IQR)		
Lower tertile: <0.23	0.16 (0.12, 0.19)	0.16 (0.12, 0.19)
Middle tertile: ≥0.23 to <0.37	0.29 (0.26, 0.33)	0.29 (0.25, 0.33)
Upper tertile: ≥0.37	0.53 (0.45. 0.63)	0.52 (0.44, 0.68)

Values are means (standard deviations) unless otherwise indicated. N = number of subjects randomized. IQR = interquartile range.

[a] Any fracture not including skull, facial bones, fingers, and toes, and not associated with known high-trauma severity or pathological fractures.

sCTX-1

There was a significant decrease in sCTX-1 from baseline in both treatment groups at month 1 and a significantly greater reduction was

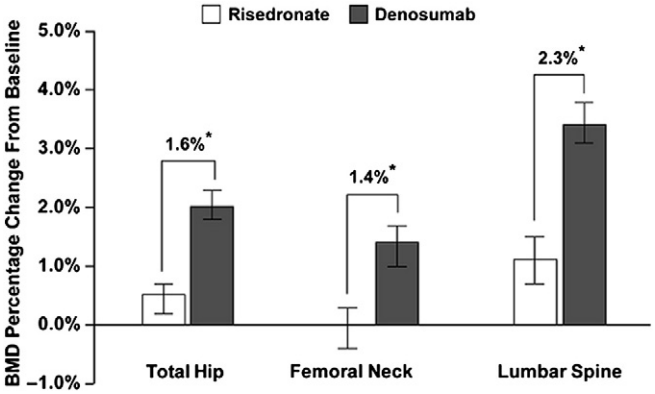

Fig. 2. Percentage change in BMD from baseline at month 12. Data are least-squares means and 95% confidence intervals. *$p < 0.0001$ denosumab vs risedronate.

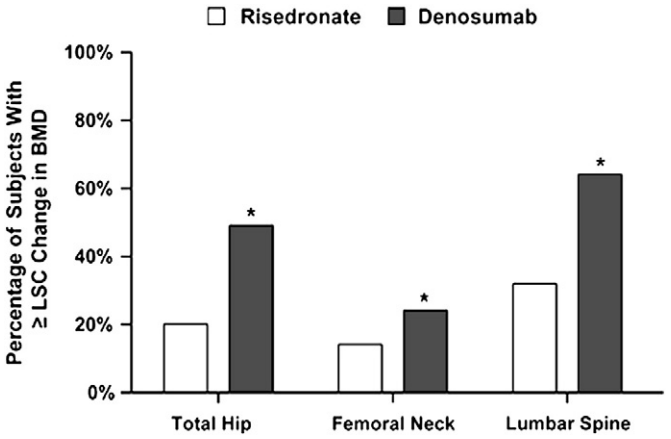

Fig. 3. Percentage of subjects with ≥least significant change (LSC) in BMD at month 12. *p < 0.0001 denosumab vs risedronate.

observed with denosumab treatment compared with risedronate treatment: median (IQR) percentage change of −77.7% (−85.9%, −67.6%) for denosumab and −17.0% (−36.8%, −1.6%) for risedronate (p < 0.0001; Fig. 4). Median reductions in sCTX-1 at month 6 were also greater in the denosumab group compared with the risedronate group: median (IQR) percentage change of −60.6% (−77.0%, −48.8%) for denosumab and –22.5% (−41.9%, 11.4%) for risedronate (p < 0.0001).

BMD/sCTX-1 associations and determinants of response

The BMD mean percentage changes from baseline at month 12 by tertiles (<0.23, ≥0.23 to <0.37, and ≥0.37 ng/mL) of baseline sCTX-1 for each skeletal site are reported in Fig. 5. This additional analysis showed that subjects treated with denosumab, compared with risedronate, demonstrated significantly greater gains in lumbar spine BMD at month 12 at each tertile of baseline sCTX-1 (p < 0.01; Fig. 5). Significantly greater gains in total hip and femoral neck BMD were also observed among subjects in the middle and highest tertiles of baseline sCTX-1 (p < 0.01). At all sites the magnitude of the BMD gain was significantly more pronounced in the middle and highest sCTX-1 tertiles (treatment-by-sCTX-1 tertile interaction p-values < 0.01).

The post-hoc analysis showed that nearly half of the enrolled population was at higher risk for fracture: 46.4% and 45.5% of risedronate- and denosumab-treated subjects, respectively. These higher-risk subjects demonstrated BMD gains that were consistent with findings in the overall population (Fig. 6).

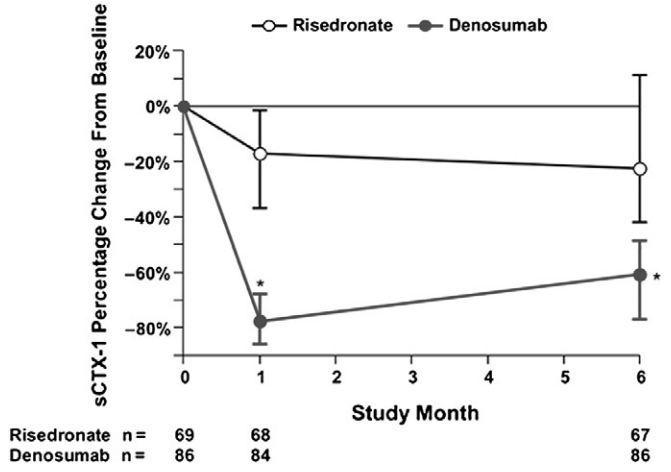

Fig. 4. Percentage change in sCTX-1 from baseline. Data are medians and interquartile range (IQR). n = number of subjects with values at baseline and at the time point of interest. *p < 0.0001 denosumab vs risedronate.

Safety

Overall, the subject incidences of AEs were 293 subjects (68.3%) in the risedronate group and 269 subjects (62.7%) in the denosumab group, with the most frequently experienced AEs (≥4% in either treatment group [risedronate, denosumab]) being hypertension (2.6%, 4.2%), arthralgia (4.4%, 4.0%), nasopharyngitis (4.2%, 3.5%), and constipation (5.1%, 3.3%). Most of the AEs in both groups were categorized as being either mild or moderate in severity (Table 2). SAEs were reported for 8.2% of risedronate-treated subjects and 7.7% of denosumab-treated subjects. There was no evidence of clustering of SAEs within any given system organ class or high-level group term in either treatment group. SAEs reported for ≥2 denosumab-treated subjects were osteoarthritis, radius fracture, cerebral ischemia, cerebrovascular accident, arthralgia, and atrial fibrillation; these SAEs were each experienced by 2 (0.5%) denosumab-treated subjects. In the risedronate treatment group, the most frequently reported SAEs (2 [0.5%] subjects each) were breast cancer and coronary artery stenosis; all other SAEs were experienced at an incidence of 1 subject each. One death due to cardiac arrest was reported in a risedronate-treated subject. No deaths were reported in the denosumab group.

This study was not designed with adequate statistical power to compare the incidence of fractures between treatment groups; descriptive results are reported here. Fractures reported as AEs regardless of trauma severity occurred in 4.0% (17) of subjects in the risedronate treatment group and in 5.4% (23) of subjects in the denosumab treatment group. The incidence of clinical fractures was similar between treatment groups (15 subjects [3.5%] in the risedronate group, 19 subjects [4.4%] in the denosumab group), with the anatomical distribution of fractures generally being typical for postmenopausal women with low bone mass. Of the subjects who had a clinical fracture on study, 10 (66.7%) subjects in the risedronate group and 6 (31.6%) subjects in the denosumab group had a medical history of osteoporotic fracture.

The independent adjudication committee for atypical femoral fracture evaluated the 2 diaphyseal femoral fractures; one occurred after a trauma described as severe by the investigator while the other was characterized by cortical thickening without a cortical break. Both fractures were adjudicated as not consistent with the ASBMR definition of atypical femoral fracture [13]. There were no adjudicated cases of ONJ. No case of fracture healing complication was reported. No subject tested positive for anti-denosumab binding antibodies at month 12. No subject was reported to have hypocalcemia or other clinically significant laboratory findings.

Discussion

This open-label, phase 3 study shows that in postmenopausal women who were previously suboptimally adherent to alendronate therapy, transitioning to denosumab was more effective than transitioning to risedronate as measured by BMD and sCTX-1. While BMD and bone turnover are not the sole predictors of fracture risk, they are important considerations in the overall management and monitoring of osteoporosis treatment. In the denosumab group, we observed a significant increase in BMD, higher than in the risedronate group, at all measured skeletal sites. In addition, duplicate DXA measurements at baseline and at the end of the study permitted assessment of LSC, and more subjects treated with denosumab compared with risedronate showed gains ≥LSC at each anatomical site measured. Of note, this study was not powered to assess the relationship between these changes in BMD with denosumab vs risedronate and the anti-fracture effect. Denosumab also significantly reduced sCTX-1 during the 6-month dosing interval compared with risedronate. With denosumab, maximal reduction of sCTX-1 was rapidly achieved following administration, with levels of sCTX-1 indicating release of inhibition at the end of the dosing interval, an observation that has been seen in

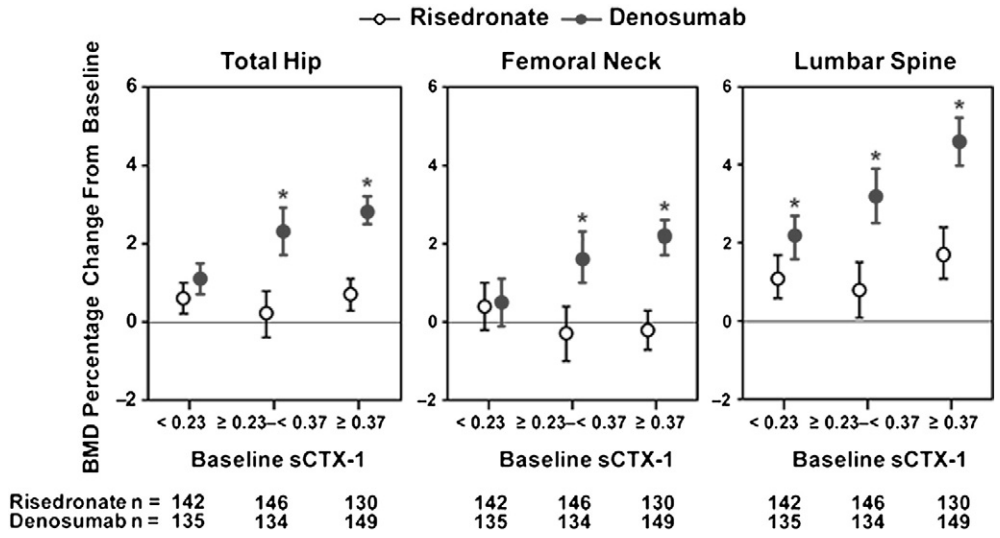

Fig. 5. Percentage change in BMD from baseline at month 12 by baseline sCTX-1. Data are least-squares means and 95% confidence intervals. n = number of subjects with data. *p < 0.01 denosumab vs risedronate. Treatment-by-subgroup interaction p-value is >0.05.

other clinical trials with denosumab [14–16]. This observation contrasts with sCTX-1 reduction for the risedronate group, which remained relatively stable after reaching a nadir by month 1.

These results confirm the data obtained in another switching study [10] conducted in osteoporotic subjects (T-score = −2.6 at the lumbar spine vs T-score = −2.2 in the current study). In contrast, in subjects transitioning from alendronate to a single infusion of zoledronic acid, BMD values remained unchanged at 12 months in those who transitioned to zoledronic acid at 12 months [17]. While the difference in BMD outcomes may be related to suboptimal adherence to previous alendronate treatment in our study, sCTX-1 at study entry was reduced in both treatment groups (<0.3 ng/mL).

Bisphosphonates are currently the most commonly utilized treatment for osteoporosis, and alendronate is generally prescribed as a first-line therapy. Transitioning therapies may occur due to difficult dosing regimens, side effects, or perceived treatment failure, but the incidence is not known. The practice of cycling patients from oral alendronate through multiple, other oral bisphosphonates occurs despite a lack of evidence demonstrating additional benefits in BMD, bone turnover markers, or overall adherence and effectiveness. Thus, studies such as this one can be used not only to assess the pharmacological effects of the drugs, but also to help physicians choose the best therapeutic strategy. Of particular interest is the observation that subjects with the highest level of remodeling at baseline achieved the greatest gains in BMD, something that was not observed in subjects who were treated with risedronate. Greater reductions in sCTX-1 and greater gains in BMD associated with denosumab treatment have similarly been observed when compared with alendronate in subjects who were treatment-naïve [9] or pre-treated with alendronate [10], and when compared with ibandronate in subjects pre-treated with an oral bisphosphonate [18].

Low BMD is an important and modifiable risk factor for fracture in postmenopausal women, and with denosumab, which has a unique mechanism of action, a strong relationship between BMD increases and anti-fracture efficacy has been shown [19]. The gains in BMD observed in the current study are statistically significant as reflected in the proportion of individuals who had BMD gains ≥LSC.

In this study, there was no BMD-based inclusion criterion, and it was the investigator's responsibility to assess the appropriateness of the potential study subject to receive prolonged osteoporosis therapy. To better define characteristics of the study population, we developed a higher-risk subgroup by BMD threshold, BMD threshold plus fracture, or baseline sCTX-1 upper limit to identify within the study population a group that would be expected to receive highest priority for prolonged therapy. We found that one-third of this subgroup had prior osteoporosis-related fractures. Interestingly, this subgroup showed BMD responses that were consistent with the overall study cohort, demonstrating consistency of effect of denosumab independently of prevalent fractures.

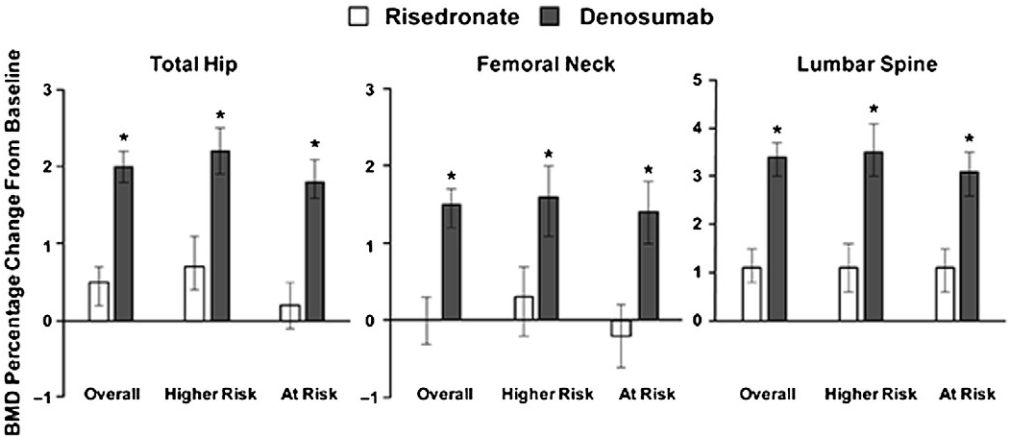

Fig. 6. Percentage change in BMD from baseline at month 12 in higher-risk subjects. Data are least-squares means and 95% confidence intervals. *p < 0.0001 denosumab vs risedronate. Treatment-by-subgroup interaction p-value is >0.05. A higher-risk subject is defined as subject with baseline BMD T-score ≤ −2.5 at total hip or femoral neck, or baseline BMD T-score ≤ −1.0 at total hip or femoral neck and prior fracture, or sCTX-1 > 0.9 ng/mL and BMD T-scores ≤ −2.0 at total hip or femoral neck.

Table 2
Summary of subject incidence of adverse events.

Event, n (%)	Risedronate (N = 429)	Denosumab (N = 429)
Adverse events regardless of relationship to treatment		
All	293 (68.3)	269 (62.7)
Serious	35 (8.2)	33 (7.7)
Fatal	1 (0.2)	0
Leading to IP discontinuation	19 (4.4)	10 (2.3)
Selected serious adverse events		
Infections	5 (1.2)	5 (1.2)
Pancreatitis	1 (0.2)	1 (0.2)
Cellulitis	1 (0.2)	0
Selected adverse events of interest		
Eczema	5 (1.2)	4 (0.9)
Fracture	17 (4.0)	23 (5.4)
Hypersensitivity	15 (3.5)	8 (1.9)
Malignancy	8 (1.9)	6 (1.4)

N = all subjects who received ≥1 dose of IP; n = number of subjects reporting ≥1 event.
IP = investigational product.

No new safety risks were identified in this open-label study, and the safety profile of denosumab was consistent with that previously observed for denosumab in clinical trials with the same 60 mg Q6M dosage. Bone safety is a key issue of prolonged treatment, in particular in the context of prior alendronate therapy, because of the long-term bone retention of this drug. The subject incidences of AEs and SAEs were similar between the treatment groups. This study was not designed with adequate statistical power to evaluate anti-fracture efficacy of denosumab and risedronate. Similar numbers of clinical fractures were reported by investigators for risedronate- and denosumab-treated subjects, and location of incident fractures was not unusual. Many of these subjects who sustained a fracture on-study had a history of prevalent fractures at study entry, increasing their risk for future fracture.

Conclusion

In conclusion, in postmenopausal women who were previously taking alendronate with suboptimal adherence, transitioning to denosumab was well tolerated and more effective to increase BMD and lower bone turnover than switching to risedronate.

Role of funding source

This study was funded by Amgen Inc.

Author disclosures

C Roux: Research grants and/or consulting or speaking fees from Amgen Inc., Bongrain, Lilly, MSD, Novartis, Roche, and Servier.

LC Hofbauer: Research grants and/or consulting fees from Amgen Inc., Merck, and Novartis, and the osteoporosis program is supported by DFG Forschergruppe-1586 (SKELMET).

PR Ho, I Ferreira, S Siddhanti, and RB Wagman: Employees of Amgen Inc. and may own stock and/or stock options in Amgen Inc.

JD Wark: Research grants and/or consulting or speaking fees from Amgen Inc., Eli Lilly, Merck, Novartis, Servier, Sanofi, and UCB.

MC Zillikens: Consulting and/or speaking fees from Amgen Inc., Eli Lilly, Merck, Novartis, and Servier.

A Fahrleitner-Pammer: Research grants and/or consulting or speaking fees from Amgen Inc., Eli Lilly, Novartis, Roche, Sanofi, Servier, and Takeda.

F Hawkins: Nothing to disclose.

M Micaelo: Nothing to disclose.

S Minisola: Consulting and/or speaking fees from Abiogen, Amgen Inc., Bruno Farmaceutici, Eli Lilly, GSK, Medtronic, Merck Sharp & Dohme, Nycomed, Neopharmed, Novartis, Pfizer, Roche, Sigma Tau, Stroder, and Warner Chilcott.

N Papaioannou: Research grants and/or consulting or speaking fees from Amgen Inc., Eli Lilly, and Servier.

M Stone: Research grants and/or consulting or speaking fees from Amgen Inc., Eli Lilly, Merck, and Servier.

JP Brown: Research grants and/or consulting or speaking fees from Amgen Inc., Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Sanofi, Servier, Takeda, and Warner-Chilcott.

Acknowledgments

The authors would like to thank the trial investigators and participants. Erica Rockabrand, PhD, of Amgen Inc. provided medical writing support. CR, LCH, JDW, MCZ, AFP, FH, MM, SM, NP, MS, IF, SS, and JPB contributed to the conception and design of the study, the acquisition of data, and the analysis and interpretation of the data. PRH and RBW contributed to the acquisition of data, and the analysis and interpretation of the data. All authors participated in drafting or revising the manuscript and all authors approved the final version of the manuscript for submission.

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