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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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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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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