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EXPERT REVIEW

Denosumab for the Treatment of Postmenopausal Women at Increased Risk of Osteoporotic Fractures

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Abstract: Denosumab is the first fully human monoclonal antibody that inhibits the formation, function and survival of osteoclasts by blocking the interaction of RANKL with its osteoclastic receptor RANK. Clinical studies have shown that the decreased bone resorption and increased bone mineral density resulting from the use of denosumab 60 mg twice yearly entail significant risk reduction of vertebral, hip and non-vertebral fractures in women with postmenopausal osteoporosis, with an acceptable rate of side effects so far. Denosumab offers a new choice for the treatment of postmenopausal osteoporosis in patients at high risk for fractures.

Keywords: denosumab, RANK-L, postmenopausal osteoporosis, osteoporosis treatment, bone mass, vertebral fractures

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Introduction

Osteoporosis is a skeletal disease associated with an imbalance in bone remodeling. Bone resorption exceeds bone formation resulting in bone loss and deterioration of the microarchitecture, leading to compromised bone strength and susceptibility to fractures.[1] Remodeling of bone is a continuous process in which old bone is removed by the osteoclast and replaced by new bone formed by the osteoblast. This process is regulated by systemic and local regulators of bone cell activity.[2] Systemic regulators of osteoblast differentiation and activity include vitamin D metabolites, parathyroid hormone, sex steroid hormones, interleukins and prostaglandins. The principal regulators of bone resorption, via osteoclast differentiation and activity, are the receptor activator of nuclear factor kappaB ligand (RANKL), receptor activator of nuclear factor kappaB (RANK) and osteoprotegerin (OPG). RANKL is an osteoblast-derived glycoprotein from the superfamily of the TNF (tumor necrosis factor) receptors.[3] Its receptor, RANK, is located on the cell membrane of osteoclast and pre-osteoclasts.[4] RANKL/RANK binding stimulate the differentiation, activity and survival of osteoclasts, resulting in increased bone resorption.[5] OPG is a glycoprotein receptor produced and secreted by the osteoblasts. The catabolic effects of the RANKL are prevented by OPG. By binding RANKL and preventing RANK/RANKL interaction, acting like a decoy receptor, OPG inhibits bone resorption and encourages bone formation.[6] Therefore, bone remodeling depends, at least in part, on the relative balance between RANKL and OPG expression. An increase of RANKL relative to OPG is associated with the development of postmenopausal osteoporosis and other skeletal diseases characterized by bone loss.[7] This piece of knowledge became the basis to develop new antiresorptive therapies for osteoporosis and other skeletal disorders associated with increased bone turnover. This is the case of denosumab (Prolia™, Amgen Inc; Thousand Oaks, CA, USA), a drug currently available for the treatment of postmenopausal women with osteoporosis at high risk of fracture, that has also been approved in some countries as a therapy for bone loss associated with hormone ablation therapy. This is a review of the clinical development of denosumab for postmenopausal osteoporosis.

Mechanism of Action, Metabolism and Pharmacokinetics

Denosumab is a fully human monoclonal antibody to RANKL that has been designed to imitate the inhibiting actions of OPG over RANKL.[8] Denosumab is an IgG2 with high affinity (Kd = 3 $\times 10^{-12}$ M) for RANKL.[8] By binding RANKL denosumab prevents RANKL and RANK interaction, in a similar way to OPG, and thus inhibiting formation, activation and survival of osteoclasts, decreasing bone resorption. In preclinical studies the inhibition of RAKL increased trabecular and cortical bone mass and strength.[9] Denosumab is highly specific to RANKL and does not bind to other members of the TNF family, including TNFα, TNFβ, TNF-related apoptosis-inducing ligand (TRAIL), or CD40 ligand.

Similar to other fully human monoclonal antibodies, the pharmacokinetics of denosumab are nonlinear with dose. Healthy postmenopausal women were given a subcutaneous dose of denosumab ranging from 0.01 to 3.0 mg/kg and followed for up to nine months.[10] Three phases were observed: (1) a prolonged absorption phase with maximum serum concentration (C_{max}) obtained at 5–21 days after dose, increasing as dose increased; (2) a prolonged beta phase, with a serum half-life up to 32 days for the maximum dose, and (3) a rapid terminal phase occurring when serum concentration dropped below 1000 ng/ml.

The absorption, bioavailability, distribution and elimination of denosumab are not well defined. Studies on other therapeutic monoclonal IgG antibodies given by subcutaneous injection suggest that absorption is probably by the lymphatic system, followed by drainage of lymph fluid into the vascular system.[11] Bioavailability is estimated to be in the range of 50%–100%, with a distribution about the same as the plasma volume,[11,12] and clearance is most probably by thereticulo-endothelial system.[11] Denosumab does not seem to be filtered or excreted by the kidneys.

Clinical Efficacy

Phase I study

A phase I study was conducted in 49 healthy postmenopause women who received a single subcutaneous dose of denosumab 0.01, 0.03, 0.1, 0.3, 1.0, 3.0 mg/kg or placebo. All cohorts were followed for six months and those receiving the three highest doses for nine months.[10]

The effects of denosumab on bone remodeling were assessed by measurement of urinary N-telopetide (NTX), a marker of bone resorption, and serum bone-specific alkaline phosphatase (BSAP), a marker of bone formation. Denosumab induced a rapid and profound reduction in NTX levels that was sustained for up to six months and reversible after discontinuation. A reduction in BSAP occurred later and was of lesser magnitude.

Phase II study

A phase II randomized, dose-finding study in postmenopausal women with low bone mass (lumbar spine T-score between −1.8 and −4 or total hip or femoral neck T-score −1.8 to −3.5) evaluated the efficacy and safety of denosumab compared with alendronate or placebo.[13–15] Patients were randomized to receive a subcutaneous injection of denosumab 6, 14 or 30 mg every three months, 14, 60, 100 or 210 mg every six months, open label alendronate 70 mg weekly or placebo for 24 months. The primary endpoint was the percentage change in lumbar spine bone mineral density (BMD) at twelve months compared with baseline. Other outcomes included assessment of bone turnover by measurement of serum C-telopeptide (CTX), urinary NTX and serum BASP and percentage change from baseline in BMD at total hip, femoral neck and distal one-third radius. At twelve months, denosumab treatment was associated with a significant increase in lumbar spine BMD of 3.0% to 6.7% compared with baseline. Smaller BMD increases were observed at the other skeletal sites evaluated, and similar to those induced by weekly alendronate. Denosumab treatment induced a dose-dependent decrease in bone turnover markers, which was rapid, sustained and reversible.[13] Results at 24 months confirmed and extended the twelve month data, with further increases in BMD and continuing suppression of bone turnover markers.[14]

At the 24-month time point, the dose chosen to continue the study was 60 mg subcutaneously every six months. Patients treated with denosumab were randomized to continue treatment for 24 months, completely discontinue treatment or switched to placebo for twelve months and resumed denosumab treatment for twelve months. The placebo group continued without changes and the alendronate-treated patients discontinued treatment and were followed. Continuous denosumab treatment for 48 months resulted in further increases in BMD at the lumbar spine (9.4% to 11.8%) and total hip (4.0% to 6.1%) while there was a loss of 2.4% and 3.5% with placebo at the spine and hip, respectively.[15] Bone turnover markers remained suppressed over the 48 months in the denosumab group. Discontinuation of denosumab resulted in a BMD decrease at both lumbar spine (6.6%) and total hip (5.3%) within the first twelve months after discontinuation. Reintroduction of denosumab resulted in a response in BMD and bone turnover markers similar to that obtained with the initial treatment, suggesting that there is no blunting of the effects of denosumab when treatment is restarted. Within twelve months of denosumab discontinuation, bone turnover markers increased above baseline values, but spontaneously returned to baseline values at month 24. The basic bone mechanism leading to this readjusting in bone turnover is unknown. However, considering the absence of bone retention for denosumab, it is unlikely related to the drug.

The original 4-year study was extended to an additional four years, with all patients switched to open label denosumab 60 mg every six months. The results of an interim analysis after two years of the extension study representing a total of six years exposure to denosumab, have been recently published. Lumbar spine BMD was increased by 13.3% compared with baseline, with sustained suppression of bone turnover markers.[16]

Phase III studies

The efficacy and safety of denosumab for the prevention of osteoporosis in postmenopausal women with low bone mass (osteopenia) was evaluated in a randomized, placebo controlled, phase III trial.[17] Postmenopausal women (n = 332) with a lumbar spine T-score between −1.5 and −2.5 were randomized to receive subcutaneous injections of 60 mg denosumab or placebo, every six months for two years. The primary efficacy outcome was the percentage change from baseline in lumbar spine BMD at 24 months, compared with placebo. Other outcomes included changes in bone turnover markers and total hip, distal one-third radius and total body BMD as measured by DXA and trabecular, cortical and integral volumetric

BMD at the distal radius by quantitative computed tomography (QCT). QCT scans were also used to determine the percentage change from baseline in volumetric bone mineral content (BMC), cortical thickness, volume, circumference, and density-weighted polar moment of inertia (PMI); a derived index of bone strength. For statistical analysis, patients were stratified by whether their time since menopause at enrollment was more or less than five years. Lumbar spine BMD significantly increased in the overall denosumab group in comparison with placebo at 24 months (6.5% vs. –0.6%, $P < 0.0001$). There was no difference between the early and later postmenopausal strata. Denosumab also significantly increased BMD at the total hip, distal radius and whole body, as compared with placebo for both strata and the strata combined. There was a significant decrease in bone turnover markers compared with placebo. The bone turnover markers suppression was held for the whole length of the treatment. The effect was similar between the different time-since-menopause strata.

The QCT scans showed that denosumab treatment significantly increased total volumetric BMD and BMC at the proximal, distal, and ultradistal regions of the radius. At 24 months, the ultradistal region had the greatest percentage increase in integral BMD (4.7% [95% CI, 3.6–5.7]; $P < 0.001$) and integral BMC (5.7% [95% CI, 4.8–6.6]; $P < 0.001$) over placebo. When cortical and trabecular bone at the proximal and distal regions were separately assessed, cortical bone had significant ($P < 0.001$) increases in BMD, BMC, and thickness, and trabecular bone had a significant increase in BMD relative to placebo ($P < 0.05$). Bone strength, estimated by density-weighted PMI, significantly increased compared with placebo after six months of treatment, with the largest percentage increase occurring at 24 months in the ultradistal region (6.6% [95% CI, 5.6–7.6]; $P < 0.0001$).[18]

The pivotal study showing the beneficial effect of denosumab on the risk of osteoporotic fractures was the FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every six Months) Phase III trial.[19] This study randomized 7868 postmenopausal women with osteoporosis into two arms: placebo or denosumab (60 mg) subcutaneously every six months. The primary endpoint was a reduction in incident morphometric vertebral fracture over a three year period. Secondary endpoints included reduction in hip and other non-vertebral fractures and changes in BMD and BTM. Study subjects had a baseline T-score at the lumbar spine or total hip $<$–2.5 to $\geq$–4.0, with approximately 23% having at least one prevalent vertebral fracture at the time of enrollment into the study. Treatment with denosumab induced a 68% reduction in the risk of new vertebral fractures compared with placebo (2.3% denosumab vs. 7.2% placebo; $P < 0.0001$), 40% reduction in the risk of hip fracture (0.7% denosumab vs. 1.2% placebo, $P = 0.04$) and 20% reduction in the risk of non-vertebral fractures (6.5% denosumab vs. 8.0% placebo, $P = 0.01$). Denosumab significantly increased BMD at all skeletal sites evaluated.

The study was extended for another two years beyond the initial three years, with all patients switched to open label denosumab 60 mg every six months. Subsequently, the study was extended for an additional five years, to complete ten years of denosumab exposure.

A head to head comparison of the effects of denosumab and alendronate on BMD and bone turnover markers was performed in a 1-year Phase III, double-blind, double-dummy non-inferiority study.[20] Postmenopausal women (n = 1189) with low bone mass (T-score $\leq$ –2 at lumbar spine or total hip) were randomized to receive 60 mg denosumab subcutaneously every six months plus weekly oral placebo or weekly oral alendronate (70 mg) plus subcutaneous placebo injections every six months. The primary endpoint was percentage change from baseline in total hip BMD at month twelve. Secondary endpoints included percentage change from baseline of BMD at femoral neck, trochanter, lumbar spine and one- third distal radius and changes in BTM. Compared with alendronate, denosumab-treated patients showed a significantly greater increase in BMD at the total hip (denosumab 3.5% vs. alendronate 2.6%; $P < 0.0001$) and all other skeletal sites measured. Denosumab induced a statistically greater reduction in BTM compared with alendronate.

The effects of transitioning from alendronate to denosumab on BMD and bone remodeling in comparison with continued alendronate therapy was evaluated in a 1-year, randomized, double-blind,

double-dummy, parallel-group, Phase III trial conducted in postmenopausal women previously treated with alendronate for at least six months.[21] After an 1-month run-in period during which all received open-label alendronate 70 mg once weekly, 504 postmenopausal women, with lumbar spine or total hip T-score of –2 to –4, were randomized to receive subcutaneous denosumab injections 60 mg once every six months or to continue receiving oral alendronate 70 mg weekly. The primary endpoint was percentage change from baseline in total hip BMD at month twelve for denosumab compared with alendronate. Results at twelve months showed a statistically significant greater increase in BMD in subjects transitioned to denosumab compared with those continuing on alendronate at total hip (denosumab 1.90% vs. alendronate 1.05%; $P < 0.0001$), lumbar spine and one-third radius.

Other clinical studies

The effects of denosumab on bone histology and histomorphometry were assessed on iliac crest bone biopsies collected at 24 and/or 36 months from osteoporotic postmenopausal women in the FREEDOM study (45 women receiving placebo and 47 denosumab), and at twelve months from postmenopausal women previously treated with alendronate in the trasitioning from alendronate study (21 continuing alendronate and fifteen changed to denosumab at trial entry).[22] Qualitative histological evaluation of biopsies showed normal lamellar bone, normal mineralization and absence of marrow fibrosis in all subjects. In the FREEDOM study, median eroded surface was reduced by >80% and osteoclasts were absent from >50% of biopsies in the denosumab group. Double labeling in trabecular bone was observed in 94% of placebo bones, and in 19% of those treated with denosumab. Median bone formation rate was reduced by 97%. Among denosumab-treated subjects, those with double labels and those with absent labels had similar levels of biochemical markers of bone turnover. In the transition trial, indices of bone turnover tended to be lower in the denosumab group, compared with alendronate. Double labeling in trabecular bone was seen in 20% of the denosumab biopsies and in 90% of alendronate samples, indicating that denosumab 60 mg every six months produces greater inhibition of turnover than occurs with alendronate 70 mg/week.

A double-blind; pilot study was conducted to compare the effects of denosumab and alendronate on cortical and trabecular microarchitecture at the radius and tibia in postmenopausal women using quantitative computed tomography (QCT) and high-resolution peripheral quantitative computed tomography (HRpQCT).[23] Postmenopausal women with a lumbar spine or total hip T-score between –2 and –3 were randomized to receive subcutaneous injection of denosumab 60 mg every six months (n = 83), oral alendronate 70 mg weekly (n = 82), or placebo (n = 82). HR-pQCT of the distal radius and distal tibia and QCT of the distal radius were done at baseline, month six, and month twelve. In the placebo arm, total, cortical, and trabecular BMD and cortical thickness decreased (–2.1% to –0.8%) at the distal radius after twelve months. Alendronate prevented the decline (–0.6% to 2.4%, $P = 0.051$ to <0.001 vs. placebo), while denosumab prevented the decline or improved these variables (0.3% to 3.4%, $P < 0.001$ vs. placebo). Changes in total and cortical BMD were greater with denosumab than with alendronate ($P \leq 0.024$). Similar changes in these parameters were observed at the tibia. The polar moment of inertia (an indicator of bone strength) also increased more in the denosumab than alendronate or placebo groups ($P < 0.001$).

Safety

In the phase I study of denosumab, no drug-related serious adverse events (SAEs) were reported[10] and no subjects were discontinued from the study due to an adverse event. The incidence of reported infectious events was similar across groups (33% in placebo and 38% in the denosumab groups combined). There were mild transient dose-depending decreases in albumin-adjusted serum calcium. The maximum mean decrease at any time point was 10%, but none of the subjects had values below 2 mmol/liter. No clinically significant changes in any other laboratory parameters were noted. Tests for anti-denosumab antibodies were negative.

The 4-year data for the phase II study reported a similar rate of AEs and SAEs among the denosumab, placebo and alendronate groups.[15] There was no

significant difference in the incidence of malignant neoplasms among groups. The overall incidence of infections was similar in all treatment groups. However, infections that required hospitalization occurred in 3.2% (10/314) of the patients treated with denosumab compared to none in the other groups. All infections were caused by ordinary germs of the community and solved with standard antibiotic treatment. The 6-year data showed that the safety profile of denosumab did not change over time.[16]

In FREEDOM, by far the largest clinical trial of denosumab, no differences were observed in the total incidence of AEs or SAEs between placebo and denosumab.[19] The incidence of serious infections was 3.4% (133/3876) in placebo and 4.1% (159/3886) in denosumab. The incidence of infections resulting in death was 0.2% in both groups. Endocarditis was reported in three patients receiving denosumab and none in the placebo group. Pancreatitis was reported in four patients (0.1%) in the placebo and eight patients (0.2%) in the denosumab groups. In all eight patients in the denosumab group, pancreatitis was a serious event, including one that resulted in death. No cases of osteonecrosis of the jaw were reported. There were no fractures of the femoral shaft in the denosumab-treated patients, compared with three such fractures in the placebo group. Eczema was reported in 3% (118/3886) of the patients in the denosumab group compared to 1.7% (65/3876) in placebo ($P < 0.001$). The overall incidence of cellulitis was similar in both groups. However, cellulitis as a SAE occurred in 0.3% (12/3886) in the denosumab-treated patients compared to less than 0.1% (1/3876) in the placebo group ($P = 0.002$).

Overall, the safety profile of denosumab is generally favorable, but possible adverse effects on the immune system and over-suppression of bone remodeling remain as safety concerns. A meta-analysis conducted with data from the three major studies of postmenopausal women found that the risk of serious infections with denosumab was statistically significant (Mantel-Haenzel risk ratio 1.26, 95% CI 1.01–1.57, $P = 0.04$).[24] This finding suggests the need of monitoring the infection risk in denosumab-treated patients. There is no evidence of clinical adverse consequences due to bone remodeling suppression induced by denosumab. Iliac crest biopsy data showed normal bone quality. However, the clinical significance of the absence of tetracycline label in patients receiving denosumab is uncertain. Denosumab is contraindicated in patients with hypocalcemia, therefore measurement of serum calcium levels prior to denosumab use is recommended.

Place of Denosumab in Osteoporosis Treatment

Although the evidence supports the use of denosumab as a first line treatment for postmenopausal osteoporosis, it is more likely that the less expensive oral bisphosphonates will still be the choice for initiation of treatment for most patients. However, denosumab might be used in patients with contraindications for oral bisphophonates, gastrointestinal intolerance, malabsorption and poor adherence or response to therapy, instead of IV bisphosphonates, the currently most common step-up for those patients. The subcutaneous administration of denosumab would offer an advantage over IV infusions. Also, the six months dosing interval might be attractive to patients who have difficulty with the sometimes-bothersome requirements for oral bisphophonate treatment. In a study on the adherence, preference and satisfaction of postmenopausal women taken denosumab (60 mg every six months) or alendronate (70 mg once weekly), subject ratings for necessity, preference and satisfaction were significantly greater for denosumab and ratings for treatment bother were significantly greater for alendronate.[25] In postmenopausal osteoporosis treatment, improved compliance and persistence could help to reduce healthcare costs and improve clinical outcomes. In a recent study[26] the cost-effectiveness of denosumab given for up to five years to a cohort of women aged 71 years, T-score $\leq -2,5$ and a prevalence of vertebral fractures of 34% was compared with that of generic alendronate, risedronate, strontium ranelate and no treatment. The results showed that denosumab is a cost-effective alternative to oral osteoporosis treatments, particularly for patients at high risk of fractures and low expected adherence to oral treatments.

Conclusion

Denosumab is a new option for the treatment of postmenopausal osteoporosis with a unique mechanism of action and dosing convenience. Denosumab reduces

the risk of vertebral, hip and non-vertebral fractures and increases BMD at all skeletal sites, notably at predominantly cortical sites, an effect not seen with other treatments for osteoporosis. The rate of increase in BMD is sustained over time. Compared with alendronate, denosumab induces a greater increase in BMD and in patients previously treated with alendronate, switching to denosumab is associated with greater increases in BMD than continuing with alendronate. However, no head to head comparison of the anti-fracture efficacy of denosumab with other treatments has been performed.

Denosumab is well tolerated, with a favorable safety profile and good compliance. The main safety concerns are the effects of a prolonged suppression of bone turnover and the potential adverse effects on the immune system that might increase the risk of infection or malignancy. Ongoing long term extension studies should provide more information on this topic. The role of denosumab in the treatment of other skeletal diseases associated with bone loss is under investigation.

Disclosures

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Conflict of Interest Statement

The author has no conflict of interest to disclose.

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