Clinical Medicine Reviews in Women's Health

REVIEW

Emerging Options for the Treatment of Postmenopausal Osteoporosis: Focus on Denosumab

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Abstract

Objective: Denosumab, a fully human monoclonal antibody, is an antiresorptive drug in a late-stage of clinical development that neutralizes receptor activator of nuclear factor κB ligand (RANKL), thereby inhibiting osteoclast-mediated bone resorption. The purpose of this paper was to discuss the antifracture efficacy and safety of the subcutaneous administration of denosumab for the treatment of postmenopausal osteoporosis.

Methods: PubMed was searched and strictly conducted randomized controlled trials (RCTs) regarding the effect of denosumab on skeletal health in postmenopausal women were identified.

Results: The results of RCTs showed that a single subcutaneous dose of denosumab rapidly and profoundly reduced bone resorption and sustained (up to 6 months) this effect in postmenopausal women. Denosumab (60 mg, every 6 months) resulted in a sustained decrease in bone turnover, a rapid increase in bone mineral density (BMD), and an improvement of geometric parameters associated with bending and axial strength and cortical stability at purely cortical and mixed cortical/trabecular sites of the proximal femur in postmenopausal women with a low BMD. Denosumab (60 mg every 6 months) reduced the 3-year incidence of vertebral, nonvertebral, and hip fractures (Hazard ratios: 0.32, 0.80, and 0.60, respectively) in postmenopausal women with osteoporosis. Denosumab was well tolerated, and no related severe adverse events were observed.

Conclusions: The subcutaneous administration of denosumab every six months effectively decreased bone resorption, increased the BMD, and reduced the risk of vertebral, nonvertebral, and hip fractures in postmenopausal women. Denosumab offers an emerging option for the treatment of postmenopausal osteoporosis.

Keywords: denosumab, alendronate, RANKL, postmenopausal osteoporosis, vertebral fracture, hip fracture

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Introduction

Osteoporosis most commonly affects postmenopausal women because estrogen deficiency after menopause increases bone turnover and induces rapid bone loss. Since vertebral and hip fractures are associated with a particularly high morbidity and mortality,[1] the management of osteoporosis is extremely important. Strategies have been established to prevent fractures in patients with postmenopausal osteoporosis. Table 1 lists the antifracture efficacies of currently available drugs for postmenopausal osteoporosis.[2–4] Antiresorptive drugs are the predominant therapeutic category for the prevention of fractures in patients with postmenopausal osteoporosis, and nitrogen-containing bisphosphonates are the most commonly used. In particular, alendronate has been chosen as a representative of its class. This drug reduces bone turnover by binding to the mineralized surface of bone and inhibiting the bone-resorbing activity of mature osteoclasts.[5] This results in an increase in bone mineral density (BMD) and a reduction in the risk of vertebral, nonvertebral, hip, and wrist fractures.[6]

In clinical practice, however, at least 50% of patients stop taking oral bisphosphonates within one year after receiving a prescription.[7] Conversely, potential adverse events associated with long-term bisphosphonate use, including osteonecrosis of the jaw (ONJ) and atypical subtrochanteric or diaphyseal femur fracture,[8–10] have attracted recent attention. Although these complications are rare, there is concern that the increasing use of bisphosphonates may lead to a growing number of affected patients. Clinical administration of newer drugs at relatively infrequent intervals, such as once or twice a year, might improve treatment adherence. Patients who showed poor responses of BMD and bone turnover markers to bisphosphonate treatment may benefit from switching to newer treatments other than bisphosphonates.

Denosumab, a fully human monoclonal antibody, is an antiresorptive drug in a late-stage of clinical development that inhibits osteoclast-mediated bone resorption. This drug is administered to patients subcutaneously every 6 months, which is a convenient dosing regimen. The purpose of this paper was to discuss the actions of denosumab on bone resorption, the effects of denosumab or transitioning from alendronate to denosumab on BMD and bone turnover markers, the patient satisfaction with denosumab, and the antifracture efficacy and safety of denosumab in postmenopausal women by reviewing the literature. PubMed was searched for strictly conducted randomized controlled trials (RCTs) regarding the effect of denosumab on skeletal health in postmenopausal women using key words "denosumab" and "postmenopausal women". As to the skeletal effects of denosumab in postmenopausal women, English articles published between 2004 and 2010 were used for this review.

Table 1. Antifracture efficacies of currently available drugs against vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis: Results of randomized controlled trials.[2–4]

	Vertebral	Nonvertebral	Hip
Antiresorptive			
Raloxifene	O	–	–
Alendronate	O	O	O
Risedronate	O	O	O
Ibandronate	O	–	–
Zoledronate	O	O	O
Estrogen	O	O	O
Calcitonin	–	–	–
Anabolic			
Teriparatide	O	O	–

O: Positive evidence, –: Efficacy not established

Actions of Denosumab on Bone Resorption

The RANK/RANKL/OPG system plays an important role in regulating bone metabolism and osteoclastogenesis.[11] Receptor activator of nuclear factor κB (RANK) belongs to the tumor necrosis factor superfamily and is present in osteoclasts. RANK binds to RANK ligand (RANKL), which is produced by osteoblasts and other stromal cells so that this binding allows prefusion osteoclasts to combine and mature into the multinucleated macrophages that continue functional osteoclasts. Osteoprotegerin (OPG) acts as a decoy receptor by binding to RANKL and preventing RANK signaling. Thus, OPG is the key endogenous regulator of the RANKL-RANK pathway.

Denosumab (known as AMG 162) is a fully human monoclonal antibody that binds to RANKL with high affinity and specificity and inhibits RANKL action in a manner similar to that of OPG. A fully human monoclonal antibody is not a modified mouse protein but rather, a human protein developed

from a hybridoma generated form a mouse that has essentially been given a human immune system. Denosumab is a key mediator of osteoclastogenesis and bone resorption but works through a different pathway from that of bisphosphonates. Denosumab neutralizes RANKL, thereby inhibiting osteoclast-mediated bone resorption. The mechanism of action for this antibody involves a blocking mechanism, where the antibody's binding to RANKL inhibits the interaction of RANKL and its receptor (RANK). Inhibition of the RANK-RANKL interaction prevents receptor activation and clustering and the downstream signaling from the receptor. RANKL-induced RANK signaling is essential for the formation, function, and survival of mature osteoclasts, which are responsible for bone resorption. Because postmenopausal osteoporosis results, in part, from an increase in osteoclastic bone resorption through a mechanism driven by RANKL,[12,13] the inhibition of RANKL activation by denosumab may help to manage postmenopausal osteoporosis.

Clinical Pharmacokinetics of Denosumab[14]

Denosumab showed dose-dependent, nonlinear pharmacokinetic (PK) profile (Fig. 1).[15] However, approximately dose-proportional increases in exposure were observed for doses ≥60 mg (in the range of fixed doses of 60 to 210 mg). Following a 60 mg single subcutaneous dose, maximum serum denosumab concentrations (Cmax) are typically observed 1 to 4 weeks post-dose; after Cmax, serum denosumab levels decline over a period of 4 to 5 months with a mean half-life of approximately 25 to 30 days. No accumulation in serum denosumab concentrations was observed with repeated doses of 60 mg once every 6 month, and denosumab PK did not appear to change with time (up to 4 years exposure).

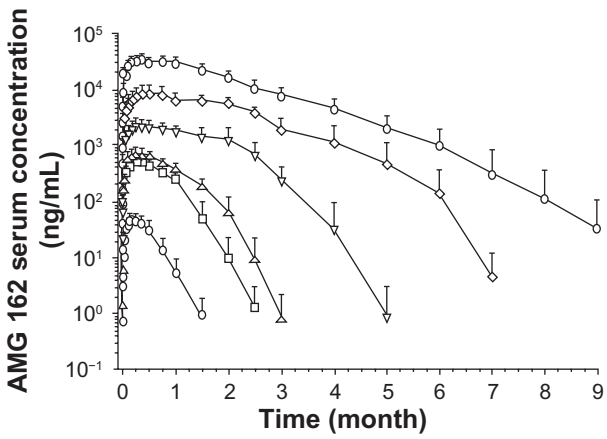

Figure 1. Serum concentration profile of denosumab.[15]
Data are presented as mean ± standard error.
No symbol: placebo, ○: 0.001 mg/kg, □: 0.03 mg/kg, Δ: 0.1 mg/kg, ∇: 0.3 mg/kg, ◊: 1.0 mg/kg, *: 3.0 mg/kg.
Denosumab had a long plasma-circulation time after a single subcutaneous injection (0.01, 0.03, 0.1, 0.3, 1.0, or 3.0 mg per kg).

Antiresorptive Activity of Denosumab in Postmenopausal Women: Phase 1 Dose Escalation Study[15]

The antiresorptive activity of denosumab was evaluated in 49 postmenopausal women in a randomized, double-blind, placebo-controlled, single-dose, dose escalation study. A single subcutaneous dose of denosumab (0.01, 0.03, 0.1, 0.3, 1.0, or 3.0 mg per kg) resulted in a dose-dependent, rapid (within 12 hours), profound (up to 84%), and sustained (up to 6 months) decrease in urinary cross-linked N-terminal telopeptide of type I collagen (NTX) (Fig. 2). Denosumab had a long plasma-circulation time after a single subcutaneous injection (Fig. 1), but the effect was reversible, as indicated by a return of the NTX levels when denosumab was cleared from the circulation.

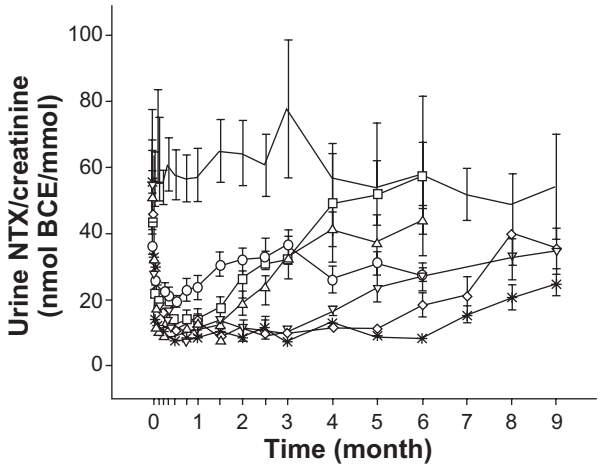

Figure 2. Effect of denosumab on bone resorption as reflected by changes in urinary NTX.[15]
Data are presented as mean ± standard error.
No symbol: placebo, ○: 0.001 mg/kg, □: 0.03 mg/kg, Δ: 0.1 mg/kg, ∇: 0.3 mg/kg, ◊: 1.0 mg/kg, *: 3.0 mg/kg.
A single subcutaneous dose of denosumab (0.01, 0.03, 0.1, 0.3, 1.0, or 3.0 mg per kg) resulted in a dose-dependent, rapid (within 12 hours), profound (up to 84%), and sustained (up to 6 months) decrease in urinary NTX.
NTX: Cross-linked N-terminal telopeptide of type 1 collagen.

Effect of Denosumab on Bone Resorption and BMD in Postmenopausal Women with a Low BMD: Phase 2 Study

Twelve-month results[16]

The phase 2 study was a prospectively designed 4-year trial with lumbar spine BMD as the primary endpoint. The efficacy of subcutaneously administered denosumab was evaluated over a period of 12 months in 412 postmenopausal women with a low BMD (T score between −1.8 and −4.0 at the lumbar spine or between −1.8 and −3.5 at the total hip or femoral neck) in a randomized, placebo-controlled, dose-ranging study. Subjects were randomly assigned to receive denosumab either every 3 months (at a dose of 6, 14, or 30 mg) or every 6 months (at a dose of 14, 60, 100, or 210 mg), open-label oral weekly alendronate (at a dose of 70 mg), or a placebo. Denosumab increased the BMD, compared with the placebo, at sites rich in trabecular bone (lumbar spine) and cortical bone (femoral neck, total hip, distal third of the radius, and total body) (Table 2). The increased BMD at the distal radius, which is composed mainly of cortical bone, differentiated the response to denosumab from the response to alendronate. This study further demonstrated near-maximal reductions in the mean levels of serum cross-linked C-terminal telopeptide of type I collagen (CTX), evident 3 days after the administration of denosumab. The reduction in bone turnover was sustained for approximately 6 months or more after single denosumab doses of 60 mg or more. This effect was reversible, as indicated by the return of the serum CTX levels toward baseline by the end of the 6 month treatment period at lower doses. Denosumab (30 mg every 3 months and 60 mg every 6 months) provided a maximal biologic effect at the minimum exposure dose.

Twenty-four-month results[17]

Denosumab increased the BMD at all the measured skeletal sites and decreased bone turnover markers, compared with the placebo, at 24 months. The denosumab-induced increases in the BMD at the lumbar spine ranged from 4.13% to 8.89%, compared with a −1.18% change in the placebo group. All 3-month doses of denosumab and all 6-month doses of 60 mg or more were associated with similar or greater increases in BMD, compared with open-label oral weekly alendronate. The release in the suppression of bone turnover markers that occurred at the end of each dosing interval with lower doses of denosumab suggests that the effect of denosumab on osteoclasts and their precursors is reversible.

Forty-eight-month results[18]

After 24 months of treatment, patients receiving denosumab either continued treatment at 60 mg every 6 months for an additional 24 months, discontinued treatment, or discontinued treatment for 12 months then re-initiated denosumab (60 mg every 6 months) for 12 months. Figure 3 shows that continuous denosumab treatment maintained the suppression of bone turnover and increased the BMD at the lumbar spine (9.4%–11.8%) and total hip (4.0%–6.1%). Twelve months of the discontinuation of denosumab decreased the BMD at the lumbar spine (6.6%) and total hip (5.3%), and retreatment with denosumab increased the BMD at the lumbar spine (9.0% from original baseline) (data not shown). The bone turnover markers increased upon discontinuation and decreased with retreatment (data not shown), suggesting that the effects of denosumab on bone turnover were fully reversible with discontinuation and were restored with subsequent retreatment.

Table 2. Percent changes in BMD by one-year treatment with placebo, denosumab, or alendronate.[16]

	Skeletal sites			
	Lumbar spine	**Total hip**	**One-third radius**	**Total body**
Placebo	–0.8%	–0.6%	–2.0%	–0.2%
Denosumab	3.0%–6.7%	1.9%–3.6%	0.4%–1.3%	0.6%–2.8%
Alendronate	4.6%	2.1%	–0.5%	About 1.5%

The BMD increases at the lumbar spine, total hip, one-third radius, and total body in the denosumab group were significantly greater than those in the placebo group (**$P < 0.0001$, $P < 0.0001$, $P < 0.001$ and $P < 0.001$, respectively). The BMD increases in the denosumab group were at least as great as those in the alendronate group. The BMD changes were greater at the one-third radius and total hip with denosumab at doses of 30 mg every 3 months and 60 mg every 6 months.

Abbreviation: BMD, bone mineral density.

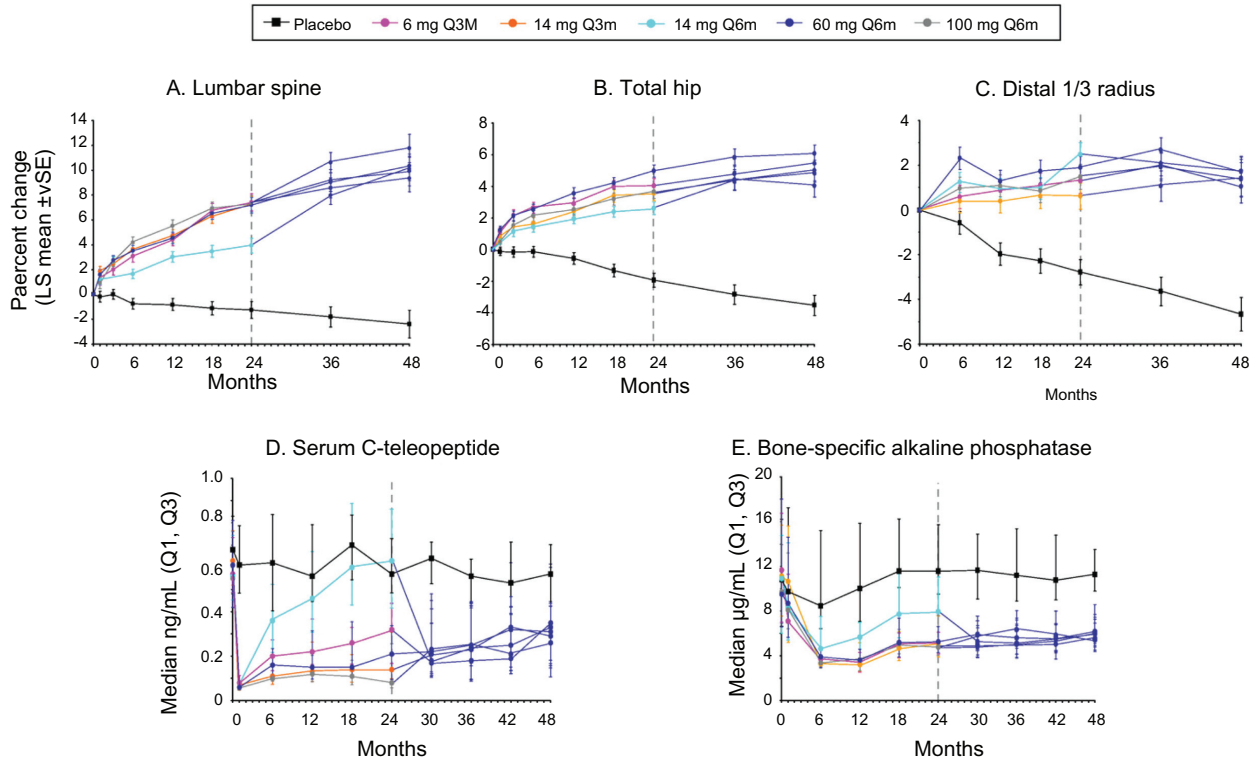

Figure 3. Percent changes in BMD and bone turnover markers by four-year treatment with placebo or denosumab.[18]
BMD values (A, B, and C) are shown as percent change from baseline (least square mean ± standard error), while bone turnover marker levels (D and E) are shown as absolute values (median with interquartile range) at the end of each dosing cycle. The dashed line at months 24 indicates the time at which patients were reallocated to the 60 mg Q6M dose. Continuous denosumab treatment maintained the suppression of bone turnover and increased the BMD at the lumbar spine (9.4%–11.8%) and total hip (4.0%–6.1%).
Abbreviations: Q3M, every 3 months; Q6M, every 6 months; BMD, bone mineral density.

Effect of Denosumab on Geometry of the Proximal Femur in Postmenopausal Women with a Low BMD: A Post-hoc Analysis of a Phase 2 Study[19]

A post-hoc analysis was performed for subjects treated for up to 24 months with denosumab (60 mg every 6 months, n = 39), a placebo (n = 39), or open-label alendronate (70 mg weekly, n = 38) in a phase 2 study. Hip scans were performed using dual-energy X-ray absorptiometry at baseline and at 12 and 24 months and were analyzed using hip structural analysis (HSA) software to evaluate the cross-sectional geometry parameters at the narrowest segment of the femoral neck, the intertrochanter and the proximal shaft. Geometric parameters and the derived strength indices included the bone cross-sectional area, section modulus, and buckling ratio. At 12 and 24 months, denosumab and alendronate improved these parameters, compared with the placebo. Denosumab improved the geometric parameters associated with bending and axial strength and cortical stability at purely cortical and mixed cortical/trabecular sites of the proximal femur. The effects of denosumab were greater than those of alendronate at the intertrochanteric and shaft sites (Fig. 4).

Effect of Denosumab on Geometry and BMD of the Distal Radius and Tibia in Postmenopausal Women with a Low BMD: A Phase 2 Study[20]

The effects of denosumab on the cross-sectional geometry and the BMD of the distal radius and tibia were assessed in 249 postmenopausal women with a low BMD in a double-blind, pilot study. Postmenopausal women (50–70 years old) with a low BMD (T score between –2.0 and –3.0 at the lumbar spine or total hip) were randomized to denosumab (60 mg every 6 months, n = 83), alendronate (70 mg weekly, n = 82), or placebo (n = 82) for 12 months. The cross-sectional geometry and BMD were assessed using high-resolution peripheral quantitative computed tomography (pQCT) at the distal radius and distal tibia

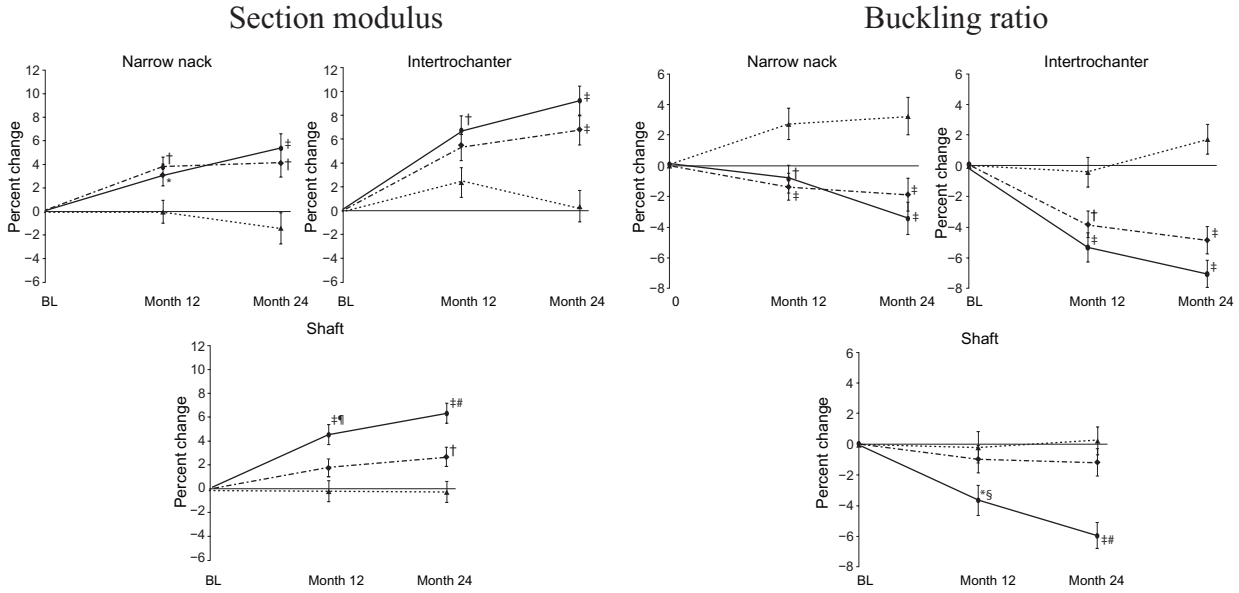

Figure 4. Percent change in section modulus and buckling ratio at the narrow neck, intertrochanter, and femoral shaft with denosumab, alendronate, or placebo.[19]
Data are presented as least square mean ± standard error.
●: denosumab, ♦: alendronate, ▲: placebo.
*: $P < 0.05$, †: $P < 0.01$, ‡: $P < 0.001$ vs. placebo, ¶: $P < 0.05$, §: $P < 0.01$, #: $P < 0.001$ vs. alendronate.
At 12 and 24 months, denosumab and alendronate improved section modulus and buckling ratio, compared with the placebo. The effects of denosumab were greater than those of alendronate at the intertrochanteric and shaft sites.

and QCT at the distal radius. In the placebo group, the total, cortical, and trabecular volumetric BMD and the cortical thickness decreased (–2.1% to –0.8%) at the distal radius after 12 months. Alendronate prevented a decline (–0.6% to 2.4%), while denosumab prevented a decline or improved these variables (0.3% to 3.4%). The changes in the total and cortical volumetric BMD were greater with denosumab than with alendronate. Similar changes in these parameters were observed at the tibia. The polar moment of inertia also increased more in the denosumab treatment group than in the alendronate or placebo treatment groups. Structural decay as a result of increased bone turnover and the progression of bone fragility might be more effectively prevented with denosumab.

Effect of Proposed Therapeutic Dose of Denosumab on Bone Resorption and BMD in Postmenopausal Women with a Low BMD: A Phase 3 Study

North American study[21]

A 2-year, randomized, double-blind, placebo-controlled study was conducted in North America to evaluate the ability of denosumab to increase the BMD and to decrease bone turnover markers in early and later postmenopausal women with a low BMD. The primary endpoint was lumbar spine BMD, and the additional endpoints were volumetric BMD of the distal radius, total hip, one-third radius and total body BMD, HSA parameters, and bone turnover markers. Three hundred thirty-two postmenopausal women with a low lumbar spine BMD (T score between –1.0 and –2.5) were randomly assigned to receive denosumab (60 mg every 6 months) or a placebo. Denosumab produced significant increases in BMD at the lumbar spine (6.5%), total hip (3.4%), one-third radius (1.4%), and total body (2.4%) compared with the placebo (–0.6%, –1.1%, –2.1%, and –1.4%, respectively); increased the distal radius volumetric BMD; improved the HSA parameters; and significantly suppressed serum CTX, tartrate-resistant acid phosphatase-5b (TRAP5b), and intact N-terminal propeptide of type 1 procollagen (P1NP). Denosumab (60 mg every 6 months) increased BMD and decreased the bone turnover markers in early and later postmenopausal women with a low BMD.

Multinational study[22]

A multicenter, randomized, double-blind study was designed to compare the efficacy of the proposed

therapeutic dose of denosumab with alendronate through 12 months of treatment in postmenopausal women with a low BMD. The primary hypothesis was that treatment with denosumab would be noninferior to treatment with alendronate with respect to the mean percent change in total hip BMD. The secondary hypotheses included superiority at the total hip and one-third radius and noninferiority at the trochanter, femoral neck, and lumbar spine with respect to the mean percent change in BMD. This study was called the Determining Efficacy: Comparison of Initiating Denosumab vs. Alendronate (DECIDE) trial. In total, 1189 postmenopausal women with a low BMD (T score ≤ -2.0 at the lumbar spine or total hip) in Western Europe, North and South America, and Australia were randomized to receive denosumab (60 mg) subcutaneously every 6 months plus a weekly oral placebo or a weekly oral alendronate (70 mg) plus a subcutaneous placebo every 6 months. Significantly greater increases in BMD were observed with denosumab at all the measured skeletal sites (5.3% vs. 4.2% at the lumbar spine, 3.5% vs. 2.6% at the total hip, 2.4% vs. 1.8% at the trochanter, and 1.1% vs. 0.6% at the one-third radius). Denosumab led to a significantly greater reduction in bone turnover markers compared with alendronate (Figs. 5 and 6).

Transitioning from Alendronate to Denosumab: A Phase 3 Study[23]

A multicenter, international, randomized, double-blind, double-dummy study was performed in 504 postmenopausal women $\geq$55 years old with a low BMD (T score between –2.0 and –4.0 at the lumbar spine or total hip) who had been treated with alendronate for at least 6 months to evaluate the effects of transitioning to denosumab on BMD and bone turnover in comparison with continued alendronate. The primary endpoint was total hip BMD, and the secondary endpoints included serum CTX and lumbar spine BMD. Other endpoints included femoral neck and one-third radius BMD. This study was called the Study of Transitioning from Alendronate to Denosumab (STAND) trial. Subjects received open-label alendronate (70 mg weekly for 1 month) and then were randomly assigned to either continued weekly alendronate or subcutaneous denosumab (60 mg every 6 months) and were followed for 12 months. The median period of prior alendronate treatment was 34.5 months in the alendronate group and 36.0 months in the denosumab group. Significantly greater BMD gains with denosumab treatment, compared with alendronate, were achieved at 12 months at the lumbar spine, total hip, femoral neck, and one-third radius. The median serum CTX levels remained near baseline in the alendronate group and were significantly decreased in the denosumab group, compared with alendronate, at all time points.

Patient Preference for and Satisfaction with Denosumab Treatment: A Phase 3 Study[24]

The patient preference for and satisfaction with denosumab or alendronate treatment were investigated in postmenopausal women with a low BMD who were enrolled in two separate randomized phase 3 double-blind, double-dummy studies and received denosumab (60 mg) subcutaneously every 6 months plus a weekly oral placebo or weekly alendronate tablet (70 mg) plus a subcutaneous placebo every 6 months (DECIDE and STAND).[22,23] In this investigation, 1100 women from DECIDE and 483 women from STAND were analyzed. After 12 months, patients completed the Preference and Satisfaction Questionnaire to rate their preference, satisfaction, and degree of bother with each regimen. Significantly more patients preferred, were more satisfied, and were less bothered by the injection every 6 months, compared with the weekly tablet.

Antifracture Efficacy of Denosumab in Postmenopausal Women with Osteoporosis[25]

An international, randomized, double-blind, placebo-controlled study was designed to compare the antifracture efficacy of denosumab through 36 months of treatment in postmenopausal women with osteoporosis. The primary endpoint was new vertebral fracture, and the secondary endpoints included nonvertebral and hip fractures. This study was called the Fracture Reduction Evaluation of Denosumab in Osteoporosis in Every 6 Months (FREEDOM) trial. The trial and consent were approved by the institutional review boards and ethics committees overseeing the study sites in the United State and other countries. In total, 7868 women (age range: 60–90 years) with

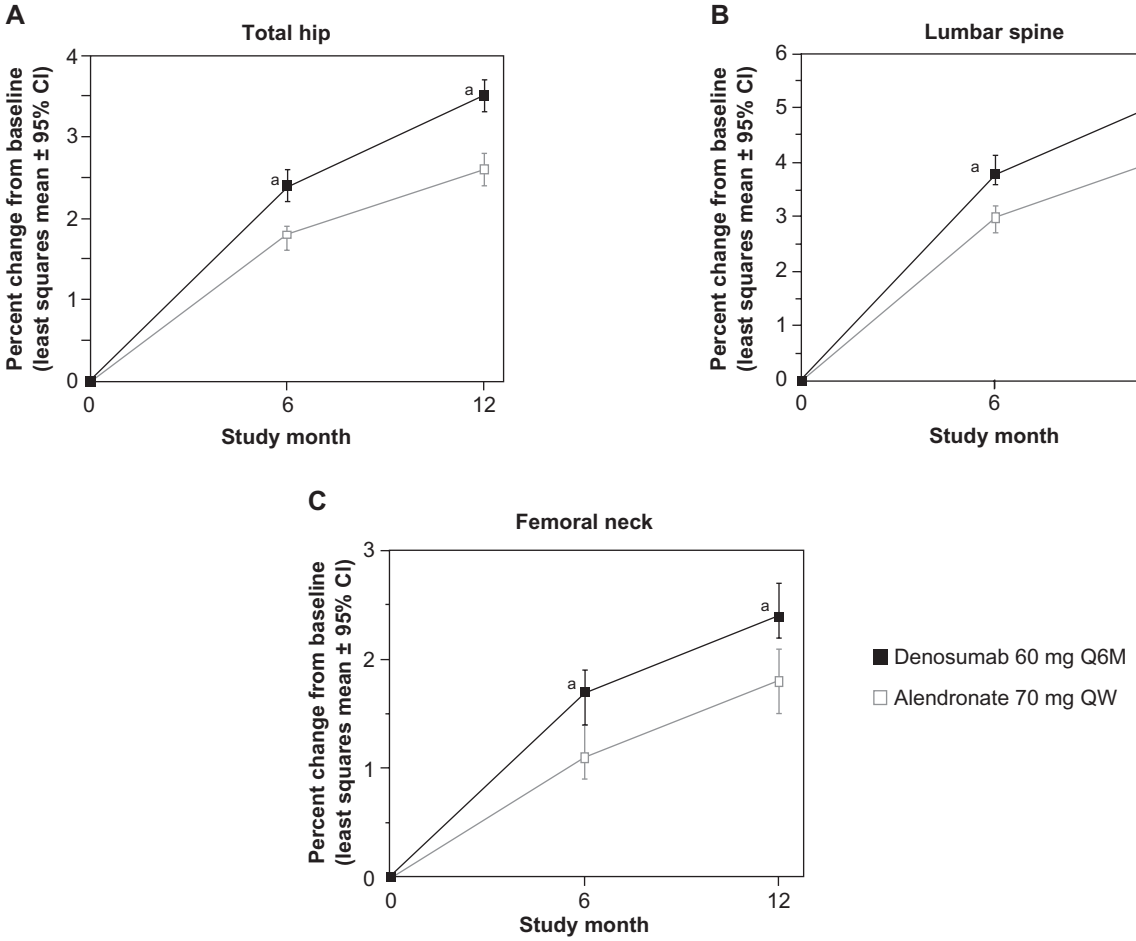

Figure 5. Percent changes in BMD at the total hip, lumbar spine, and femoral neck in denosumab and alendronate group.[22]
Data are presented as least square mean ± 95% confidence interval (CI).
a: significantly different from alendronate.
Significantly greater increases in BMD were observed with denosumab at all the measured skeletal sites (5.3% vs. 4.2% at the lumbar spine, 3.5% vs. 2.6% at the total hip, 2.4% vs. 1.8% at the trochanter, and 1.1% vs. 0.6% at the one-third radius).
Abbreviations: Q6M, every 6 months; QW, weekly; BMD, bone mineral density.

osteoporosis (BMD T score between –2.5 and –4.0 at the lumbar spine or total hip) were randomly assigned to receive either 60 mg of denosumab or a placebo subcutaneously every 6 months for 36 months. After 36 months, compared with the placebo, denosumab reduced the risk of new radiographic vertebral, nonvertebral, and hip fractures (Hazard ratios: 0.32, 0.80, and 0.60, respectively). BMD of the hip and lumbar spine was measured at baseline and at 1, 6, 12, 14, and 36 months in 441 subjects, and concentrations of two markers of bone turnover were measured in 160 subjects from fasting serum samples collected before the injection on day 1, at 1 month after the baseline injection, and before injections at 6, 12, 24, and 36 months. Denosumab was associated with a relative increase in the BMD of 9.2% at the lumbar spine and 6.0% at the total hip (Fig. 7). Compared with the placebo, denosumab decreased the serum CTX and P1NP levels by 86% and 18%, respectively, at 1 month and by 72% and 76%, respectively, at 36 months (Fig. 7).

Adverse Events Associated Long-term Use of Denosumab

Overall, denosumab was well tolerated, and no treatment-related serious adverse events were observed. No cases of ONJ or atypical subtrochanteric or diaphyseal femur fracture occurred with the subcutaneous administration of denosumab every 6 months in the 3 year FREEDOM trial.[25] Potentials concerns regarding the effects of denosumab on the immune system have been raised as RANKL is expressed

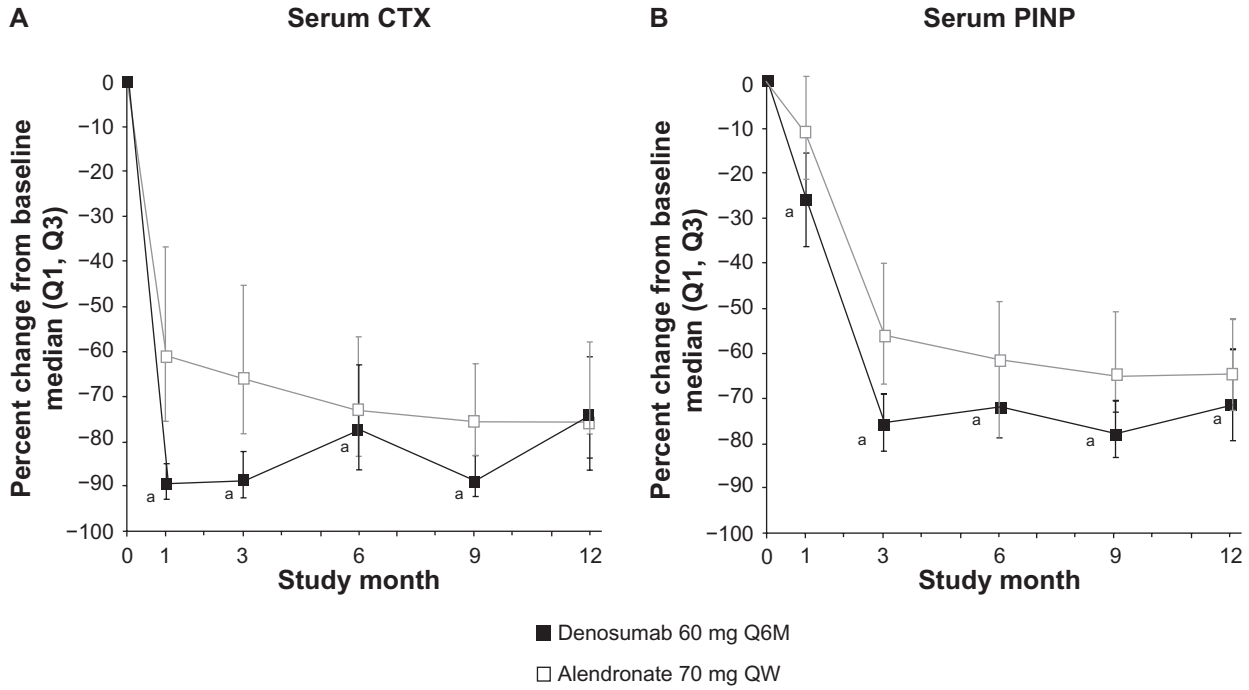

Figure 6. Percent changes in bone turnover markers serum CTX and P1NP through 12 months in denosumab and alendronate group.[22]
Data are presented as median (Q1, Q3).
A: significantly different from alendronate.
Denosumab led to a significantly greater reduction in bone turnover markers compared with alendronate.
Abbreviations: Q6M, Every 6 months; QW, weekly; CTX, cross-linked C-terminal telopeptide of type 1 collagen; P1NP, intact N-terminal propeptide of type 1 procollagen.

not just on bone cells but also on immune cells.[26] It had been speculated that the inhibition of RANKL might increase the risk of cancer or infection.[27] In the FREEDOM study,[25] however, the number of new malignancies was similar between densoumab and placebo treated patients and the overall the rate of infections and of serious infections was also balanced between denosumab and placebo. Serious adverse events of cellulitis, however were observed in 0.3% of the denosumab treated patients and in <0.1% of placebo patients ($P = 0.002$). An increase in adverse events of eczema was observed. However, the adverse events observed in clinical trials were not the sorts of cancers or infections commonly seen in immunosuppressed patients.

Contraindications of Denosumab

Because denosumab is not eliminated via hepatic metabolic mechanisms, hepatic impairment and drug interaction studies have therefore not been conducted. A renal impairment study was conducted in patients with normal, mild, moderate, severe, and end-stage renal disease.[14] No notable relationship was observed between denosumab PK and renal function and it was concluded that no dose adjustment is necessary in patients with renal impairment.[14]

The contraindications of denosumab are considered allergy for this drug and hypocalcemia. The safety for expectant mother and woman with a possibility of pregnancy has not been established.

Discussion

The antiresorptive activity is of importance for denosumab in the treatment of postmenopausal osteoporosis. Denosumab administration resulted in significant inhibition of bone resorption, as assessed by reductions in bone resorption markers. Ttreatment with 60 mg of denosumab resulted in rapid reduction in serum CTX within 6 hours of subcutaneous administration by approximately 70%,[21,25] with reductions of approximately 85% occurring by 3 days.[18] Serum CTX reductions appeared to be maintained throughout the dosing interval (6 months). At the end of the dosing cycle, some attenuation of bone resorption inhibition was observed, indicating that reduction of bone turnover associated with denosumab administration is

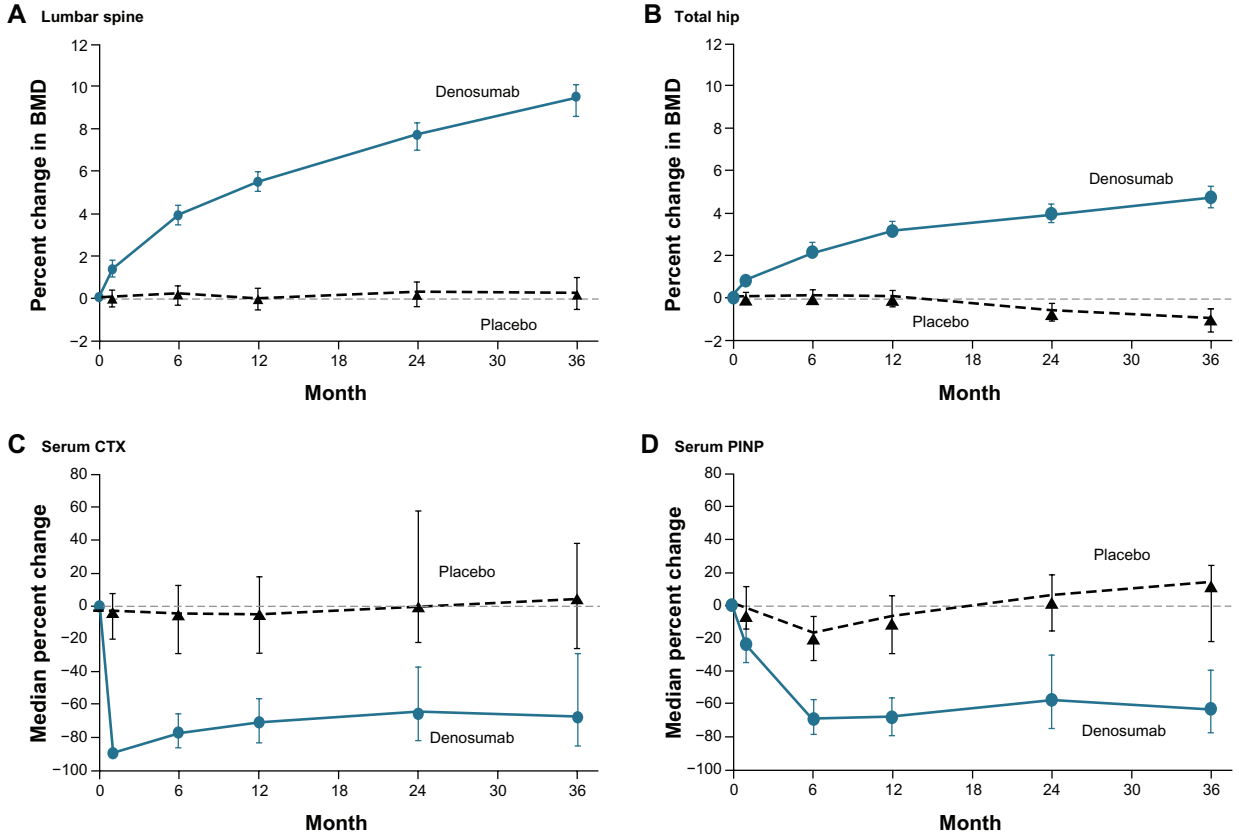

Figure 7. Percent changes in BMD and bone turnover markers by three-year treatment with placebo or denosumab.[25]
As compared with placebo, denosumab had a relative increase of 9.2% in BMD at the lumbar spine and 6.0% at the total hip. Compared with the placebo, denosumab decreased the serum CTX and P1NP levels by 86% and 18%, respectively, at 1 month and by 72% and 76%, respectively, at 36 months.
Abbreviations: BMD, bone mineral density; CTX, cross-linked C-terminal telopeptide of type 1 collagen; P1NP, intact N-terminal propeptide of type 1 procollagen.

reversible when serum concentrations of denosumab diminish.

The results of RCTs showed that a single subcutaneous dose of denosumab rapidly and profoundly reduced bone resorption and sustained this effect (for up to 6 months) in postmenopausal women. Denosumab (60 mg every 6 months) resulted in a sustained decrease in bone turnover, a rapid increase in BMD, and an improvement of the geometric parameters associated with bending and axial strength and cortical stability at purely cortical and mixed cortical/trabecular sites of the proximal femur in postmenopausal women with a low BMD. The 4-year beneficial effects of denosumab on BMD and bone turnover markers were also confirmed. An abstract showed that continuous treatment with denosumab resulted in a sustained reduction in bone turnover markers and further gains in the BMD over a period of up to 6 years.[28] Denosumab (60 mg every 6 months) reduced the 3-year incidence of vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis.

Compared with alendronate, denosumab (60 mg every 6 months) resulted in greater increases in BMD at the total hip, lumbar spine, femoral neck, trochanter, and one-third radius, greater decreases in bone turnover markers, and greater improvements in geometric parameters associated with bending and axial strength and cortical stability at the intertrochanteric and shaft sites of the proximal femur in postmenopausal women with a low BMD. These greater effects of denosumab can be explained by the different mechanisms of antiresorptive action between denosumab and alendronate. Alendronate binds with a high affinity to bone and is subsequently taken up by osteoclasts, leading to the disruption of the bone-resorbing capability and osteoclast apoptosis at a mature stage.[29] Denosumab inhibits RANKL,

subsequently reduces osteoclast formation, activity and survival, and targets osteoclasts at a more immature stage, preventing their maturation and activation before they adhere to the bone matrix.[30–34] Denosumab suppresses bone resorption more strongly and increases BMD to a greater extent than alendronate.

An increase in the one-third radius BMD is one of the reported advantages of denosumab over alendronate. Denosumab also improved the geometry of the femoral shaft (HSA), radius and tibia (pQCT and QCT). Thus, denosumab has a positive and distinctive effect on cortical bone sites. Denosumab might suppress bone resorption on the endocortical bone and Haversian canal surfaces strongly enough to improve the BMD and proximal femur geometry at cortical sites.

Patient adherence to therapy is another advantage of denosumab over oral bisphosphonates. A regimen comprised of dosing every 6 months may improve the adherence of patients (compliance and persistence) to the treatment. In clinical practice, the adherence to oral bisphosphonate treatment among osteoporotic women is poor.[35] Low compliance and persistence rates consistently resulted in increased rates of fractures.[35] Optimal antifracture efficacy is dependent upon adherence. New therapies for osteoporosis need to demonstrate compliance. The use of once-yearly intravenous zoledronic acid would also improve the compliance rates. Significantly more patients preferred, were more satisfied, and were less bothered with the subcutaneous injection of denosumab every 6 months, compared with the weekly alendronate tablet, suggesting the benefit of the subcutaneous administration of denosumab every 6 months in improving adherence to osteoporosis treatment.

The three-year treatment with denosumab reduced the risk of new radiographic vertebral, nonvertebral, and hip fractures by 68%, 20%, and 40%, respectively. The absence of head-to-head trials makes it difficult to compare the antifracture efficacy of denosumab and other drugs. However, the risk reduction rate of vertebral fractures with denosumab treatment (68%) was similar to that reported for intravenous zoledronate (70%) or teriparatide (65%)[4,36] and appears to be greater than the reductions reported for oral bisphosphonates.[5] Although the risk reduction rates of nonvertebral fractures were similar among these drugs,[5] the risk reduction rate of hip fractures with denosumab (40%) appears to be similar to that of zoledronate (41%),[4] but not greater than that of alendronate (55%) despite greater improvements in the BMD, geometry parameters, and bone turnover markers.[2,37,38] Denosumab seems to be at least as efficacious as currently approved drugs in preventing vertebral and nonvertebral fractures. Alendronate strongly suppresses bone turnover and subsequently increases the hip BMD, decreases cortical porosity, improves parameters of hip structure geometry (cortical thickness, cross-sectional area, section modulus, and buckling ratio), produces more uniform mineralization (increases the mean degree of mineralization of bone), and suppresses osteocyte apoptosis in cortical bone, thereby effectively preventing hip fractures.[37]

An abstract showed the effect of denosumab on the incidence of hip, new vertebral, and nonvertebral fractures over 3 years among postmenopausal women with higher fracture risk according to the results of a subgroup analysis from the FREEDOM study.[39] The prespecified criteria for an increased fracture risk were subjects with $\geq$2 of the 3 prespecified risk factors: (1) age $>$70 years, (2) baseline BMD T-score ≤ -3.0 at lumbar spine, total hip, or femoral neck, and (3) prevalent vertebral fracture at baseline. The risk reduction rates of hip, new vertebral, and nonvertebral fractures after denosumab treatment were 48%, 65%, and 12%, respectively. The antifracture efficacy of denosumab in the higher risk subgroups was consistent with the risk reductions for the overall population.

The effect zoledronate on mortality was reported in patients suffering a low-trauma hip fracture.[40,41] An annual fusion of zoledronate within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures (35%) and improved the rate of survival (28%).[40] Administration of zoledronate to patients suffering a low-trauma hip fracture 2 weeks or later after surgical repair induced reductions in the risk of subsequent clinical vertebral, nonvertebral, and hip fractures (53%, 34%, and 48%, respectively) and reduced mortality.[41] Thus, it is of interest to study the effect of denosumab on fracture incidence and mortality in patients who suffered from a low-trauma hip fracture.

The inhibition of RANKL might theoretically increase the risk of cancer or infection.[27] However,

no significant difference in the incidence of cancer or the overall incidence of infection has been reported in postmenopausal women treated with denosumab. Overall, denosumab was well tolerated, and no related serious adverse events were observed. However, a significant increase in the incidence of hospitalization for cellulitis has been reported, and this risk should be recognized in clinical practice when the drug is used in patients with coexisting illnesses.

Although no ONJ was reported in clinical trials for postmenopausal osteoporosis, ONJ occurred among patients treated with high-dose denosumab for breast cancer bone metastasis with similar incidence among those treated with high-dose zoledronate.[42] This suggests that a rare case would be expected at the lower, less frequent doses used for the treatment of osteoporosis. Thus, clinical risk factors of ONJ[8] might need to be assessed carefully prior to the use of denosumab for patients with osteoporosis.

In postmenopausal women with a low BMD who were previously taking weekly oral alendronate, transitioning to the subcutaneous administration of denosumab every 6 months was found to increase the BMD at all skeletal sites evaluated and to reduce the bone turnover markers to a greater extent than the continuation of alendronate treatment. Thus, postmenopausal women with a low BMD may be safely transitioned from alendronate to denosumab to achieve an incremental increase in BMD. This information is of importance because of the greater patients' preference and satisfaction with denosumab, compared with oral bisphosphonates, possibly leading to an improvement in patient adherence to treatment for osteoporosis. Furthermore, transitioning from oral bisphosphonates to denosumab may enable some of the potential adverse events associated with long-term bisphosphonate use to be avoided.[8–10]

Conclusions

The administration of denosumab every 6 months decreases bone resorption and increase the BMD by inhibiting RANKL and reduces the risk of vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis. The antifracture efficacy of denosumab against vertebral and nonvertebral fractures seems at least as efficacious as currently approved drugs. Denosumab might be useful for improving the adherence of patients to osteoporosis treatment. This review emphasizes the elegant nature of the activity of denosumab, mimicking the native modulator regulatory function of OPG in the RANK/RANKL system. Denosumab offers an emerging option for the treatment of postmenopausal osteoporosis.

Disclosures

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