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Update on Denosumab Treatment in Postmenopausal Women with Osteoporosis

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Denosumab, a fully human recombinant monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL), blocks binding of RANKL to the RANK receptor, found on the surface of osteoclasts and osteoclast precursors, resulting in decreased bone resorption. Subcutaneous denosumab administration once every 6 months increases bone mineral density at the lumbar spine, total hip, and/or femoral neck, and reduces markers of bone turnover significantly in postmenopausal women with osteoporosis. Relative to placebo, denosumab treatment reduces the risk of vertebral, nonvertebral, and hip fractures significantly. The benefits of denosumab treatment are generally obvious after the first dose and were continued for up to 8 years of treatment in an extension study. The tolerability profile of denosumab during this extension phase was consistent with that observed during the initial 3-year FREEDOM trial. Postmarketing safety surveillance has not shown any unexpected findings. Ongoing safety surveillance will more fully define the long-term safety of denosumab. The benefits of denosumab would seem to be greater than its risks. Denosumab is an important choice in the treatment of postmenopausal women with osteoporosis at increased risk of fractures, including older patients who have difficulty with oral bisphosphonate intake and patients who are intolerant of, or unresponsive to, other therapies.

Keywords: Denosumab; Osteoporosis; Fracture

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone density and deterioration of the bone microarchitecture, resulting in a loss of bone strength, increased bone fragility, and an increased risk of fractures. Data from the 2008 to 2009 Korean National Health and Nutrition Examination Survey (KNHANES) estimated that 35.5% of women 50 years of age or older have osteoporosis [1]. The 2010 KNHANES survey results indicated that 37.7% of Korean menopausal women 50 years of age or older were at high risk of osteoporotic fracture [2]. The proportion of women with high fracture risk was shown to increase with age: 49.3% of those 55 years and older compared with 67.7% of those 65 years and older. The hip fracture incidence in Korea was reported to be 20,432 in 2008 [3]. Despite this major public health issue, diagnosis and treatment rates remain low, 29.9% and 14.4%, respectively [1].

Antiresorptive agents are an important pharmacological option for the treatment of osteoporosis. They include bisphosphonates, selective estrogen receptor modulators, estrogen, and

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denosumab. Denosumab, formerly known as AMG 162, is a novel antiresorptive treatment. Denosumab is a fully human recombinant monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL), a member of the tumor necrosis factor family, and blocks binding of RANKL (an essential factor in the terminal differentiation and activation of osteoclasts) to the RANK receptor found on the surface of osteoclasts and osteoclast precursors. Denosumab inhibits osteoclast differentiation, activity, and survival, and consequently, results in decreased bone resorption [4,5]. This article reviews the clinical effect of denosumab in the treatment of postmenopausal women with osteoporosis.

PHARMACOLOGICAL CONSIDERATIONS

The pharmacokinetics of subcutaneously administrated denosumab in healthy postmenopausal women were nonlinear with dose. The serum profiles are characterized by three distinct phases: a prolonged absorption phase, a prolonged β-phase, and a more rapid terminal elimination phase. Maximum serum concentrations were observed between 5 and 21 days after administration. A prolonged β-phase was characterized by half-lives that increased with dose to a maximum of 32 days. The more rapid terminal phase had a half-life that increased from 5 to 10 days as dose increased from 0.01 to 3.0 mg/kg. Because of the nonlinear pharmacokinetics, the mean serum residence time increased with dose, from 12 to 46 days [6]. A single subcutaneous dose of denosumab resulted in a dose-dependent, rapid (within 12 hours), profound (up to 84%), and sustained (up to 6 months) decrease in urinary N-telopeptide (NTX), a marker of bone resorption, demonstrating rapid inhibition of bone resorption and a sustained, but reversible, effect [6].

Treatment efficacy of denosumab did not differ with kidney function. Denosumab was not associated with an increase in adverse events among patients with impaired kidney function [7].

THERAPEUTIC EFFICACY

Effects on bone turnover markers

In a study to evaluate the efficacy and safety of subcutaneously administered denosumab over a period of 12 months in postmenopausal women (n=412) with low bone mineral density (BMD), denosumab groups showed decreases in levels of serum C-telopeptide (CTX), compared with the placebo group (P<0.001), as early as 3 days after treatment, which was the first scheduled time point after baseline [8]. The maximum mean percentage reduction in levels of serum CTX was 88% among the denosumab groups compared with 6% in the placebo group. The results of the urinary NTX/creatinine ratio were similar to those for serum CTX. There was a 1 month delay in the decrease in serum bone-specific alkaline phosphatase levels in subjects receiving denosumab (P<0.001) [8].

During the second year of treatment, denosumab maintained statistically significant reductions from baseline in serum CTX and urine NTX/creatinine versus the placebo (P< 0.001). Reductions in bone-specific alkaline phosphatase levels during the second year of denosumab treatment remained consistent, compared with the first year of treatment, and statistically greater than the placebo group (P≤0.002) [9].

In the Determining Efficacy: Comparison of Initiating Denosumab vs. alEndronate trial (DECIDE; n=1,189), which compared the efficacy and safety of denosumab with oral alendronate 70 mg once weekly in postmenopausal women with low bone mass, serum CTX reduction in denosumab-treated subjects was rapid, with maximal median decreases from baseline observed at month 1 (–89%) and was significantly greater than that observed for alendronate-treated subjects (–61%, P< 0.0001). Similarly, at month 3, median decreases were greater in the denosumab group than the alendronate group (–89% vs. –66%, P<0.0001). At month 6, the end of the dosing interval for denosumab, the median serum CTX reduction approached that of the alendronate group (–77% vs. –73%), although the treatment difference remained significant (P=0.0001). At month 12, the median decreases in serum CTX were similar in both treatment groups (–74% denosumab, –76% alendronate; P=0.52). Decreases in the bone formation marker N-terminal propeptide of type 1 procollagen (P1NP) were noted in both treatment groups. Denosumab-treated subjects had significantly greater decreases in serum concentrations of P1NP than alendronate-treated subjects at each time point assessed (P< 0.0001). Denosumab treatment resulted in significantly greater reduction of bone turnover markers than alendronate therapy [10].

In the multinational, phase 3 Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 months (FREEDOM) trial in postmenopausal women with osteoporosis (n=7,868), denosumab decreased serum CTX levels by 86% at 1 month, by 72% before treatment was administered at 6 months, and by 72% at 36 months. Levels of P1NP were 18%, 50%, and 76% below those in the placebo group at the same time points, compared with the placebo [11]. In the 2-year extension study of FREEDOM, women from the FREEDOM denosumab group

had 2 more years of denosumab treatment (n=2,343; long-term group) and those from the FREEDOM placebo group had 2 years of denosumab exposure (n=2,207; cross-over group). After the seventh dose of denosumab (the first 'extension' dose), reductions in CTX during the first 4 months and P1NP at 6 months were consistent with those observed after the first dose of denosumab during the core trial [12].

In the off-treatment extension of a randomized, double-blind study (n=256), after denosumab discontinuation, BTM increased above baseline within 3 months (serum CTX) or 6 months (P1NP) and returned to baseline by month 48 [13].

In a phase 3, randomized, double-blind, placebo-controlled, parallel-group 6-month study with a 6-month open-label extension in Korean patients with postmenopausal osteoporosis, denosumab reduced serum CTX and serum P1NP at months 1, 3, and 6. At month 6, denosumab demonstrated a treatment difference compared with placebo for median percent change in serum BTM levels, serum CTX (–52.1%, P<0.0001) and serum P1NP (–48.2%, P<0.0001) [14].

Effects on bone mineral density

In a phase 2 trial of postmenopausal women with low BMD (n=412), denosumab treatment for 12 months resulted in an increase in BMD at the lumbar spine of 3.0% to 6.7%, at the total hip of 1.9% to 3.6%, and at the 1/3 radius of 0.4% to 1.3%. In this trial, it appeared that doses of 30 mg of denosumab every 3 months and 60 mg every 6 months provided maximal biological effects at a minimum exposure dose [8]. In a 2-year extension treatment with denosumab, lumbar spine BMD increases with denosumab ranged from 4.1% to 8.9% [9]. At 24 months, alendronate treatment also increased BMD significantly compared with placebo at the lumbar spine, total hip, distal 1/3 radius, and total body. BMD changes with denosumab ≥60 mg every 6 months were similar to, or in some cases, greater than with oral alendronate 70 mg once weekly. Treatment with denosumab was associated with sustained increases in BMD, compared with placebo [9].

In the DECIDE trial (n=1,189), BMD changes at the total hip, femoral neck, trochanter, lumbar spine, and 1/3 radius at 6 and 12 months were assessed. At the total hip, denosumab increased BMD significantly, compared with alendronate, at month 12 (3.5% vs. 2.6%, P<0.0001). Furthermore, significantly greater increases in BMD were observed with denosumab treatment at all measured skeletal sites [10].

From the overall study of 7,808 women and from a substudy of 441 participants, significant BMD improvements were observed as early as 1 month in the lumbar spine, total hip, and trochanter (all P<0.005 vs. placebo and baseline). BMD increased progressively at the lumbar spine, total hip, femoral neck, trochanter, 1/3 radius, and total body, from baseline to months 12, 24, and 36 (all P<0.005 vs. placebo and baseline). BMD gains above the least significant change of >3% at 36 months were observed in 90% of denosumab-treated subjects at the lumbar spine and 74% at the total hip, and gains of more than 6% occurred in 77% and 38%, respectively [15].

In the 2-year extension study of FREEDOM, there were further significant gains in BMD during the 4th and 5th years of denosumab treatment at the lumbar spine (1.9% and 1.6%, respectively), total hip (0.8% and 0.6%, respectively), and femoral neck (0.9% and 0.4%, respectively). Increases in BMD over 5 years of continued denosumab treatment reached 13.7% (lumbar spine), 7.0% (total hip), 6.1% (femoral neck), and 2.3% (1/3 radius; all P<0.0001) [12].

In the off-treatment extension study (n=256), discontinuation of denosumab resulted in a decline in BMD at all sites assessed over 24 months, with most of the decline occurring during the first 12 months after treatment discontinuation [13]. However, the previously treated denosumab group maintained higher BMD than the previously treated placebo group at these sites (P≤0.05).

For the subjects who received 8 years of continued denosumab treatment in a phase 2 study, BMD at the lumbar spine (n=88) and total hip (n=87) increased by 16.5% and 6.8%, respectively, compared with the parent study baseline, and by 5.7% and 1.8%, respectively, compared with the extension study baseline [16].

In a phase 3 study with Korean women with postmenopausal osteoporosis, a treatment difference of 3.2% (P<0.0001) was seen between the denosumab and placebo groups at month 6. At month 6, denosumab demonstrated a treatment difference, compared with placebo in the mean percentage change in BMD for the total hip (1.7%, P<0.0001) and femoral neck (1.4%, P=0.0042). In subjects who received denosumab for the whole 12 months, the mean percent change in lumbar spine BMD from baseline to month 12 was 5.6% [14].

Effects on fractures

In the FREEDOM trial (n=7,868), compared with the placebo, denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group versus 7.2% in the placebo group (risk ratio, 0.32; P< 0.001). During months 0 to 12, >12 to 24, and >24 to 36, there

was a significant (P<0.001) reduction in the risk of new vertebral fractures, with 61%, 78%, and 65% reductions in the risk of new vertebral fractures, respectively [11].

Denosumab also reduced the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group versus 1.2% in the placebo group (hazard ratio, 0.60; P=0.04). Denosumab reduced the risk of non-vertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, versus 8.0% in the placebo group (hazard ratio, 0.80; P=0.01) [11]. However, the effect of denosumab on nonvertebral fracture risk differed by femoral neck BMD, body mass index, and prevalent vertebral fracture at baseline. This risk reduction was statistically significant in women with a baseline femoral neck BMD T score ≤–2.5, in those with a body mass index <25 kg/m^2, and in those without, but not with, a prevalent vertebral fracture [17].

In the 2-year extension study of FREEDOM, yearly fracture incidences for both long-term and cross-over groups were below the rates observed in the FREEDOM placebo group. Specifically, 2.8% (n=59) of the women in the long-term denosumab group experienced ≥1 new vertebral fracture through year 2 of the extension (annualized rate of 1.4% for the 4th and 5th years of denosumab treatment). Fourteen women had a clinical vertebral fracture. Additionally, 1.4% and 1.1% of women in the long-term denosumab group experienced a nonvertebral fracture during the 4th and 5th years of denosumab exposure [12]. Eight-year denosumab treatment of women with postmenopausal osteoporosis was associated with low fracture rates and a favorable risk/benefit profile [18].

After treatment cessation with denosumab, there was no apparent increase in the risk of fracture in women who discontinued treatment during the FREEDOM study compared with placebo (mean duration off-treatment of 0.8 years; n=327 in denosumab and n=470 in placebo groups). Following discontinuation, similar percentages of subjects in both groups sustained a new fracture (9% placebo, 7% denosumab) [19].

Denosumab reduced the incidence of new vertebral and hip fractures in postmenopausal women with osteoporosis at a higher risk for fracture in subgroup analyses in the FREEDOM trial. Compared with placebo, denosumab treatment (n=359) was associated with a significantly greater reduction in the incidence of new vertebral fractures over 36 months than placebo (7.5% denosumab vs. 16.6% placebo, P<0.001; n=343 in the placebo group). Similar reductions in the risk of new hip fractures with denosumab treatment occurred in subjects aged 75 year or older (2.3% placebo vs. 0.9% denosumab, P<0.01) or with a baseline femoral neck BMD T-score of –2.5 or less (2.8% placebo vs. 1.4% denosumab, P=0.02) [20].

Effects on bone microarchitecture, mineralization, and strength

In the FREEDOM trial, qualitative evaluation of iliac crest bone biopsies collected after 24 and/or 36 months of denosumab (n=47) or placebo (n=45) treatment showed normal lamellar bone, normal mineralization, and the absence of marrow fibrosis in all subjects [21]. Median eroded surface was reduced by more than 80% and osteoclasts were absent from more than 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. The median bone-formation rate was reduced by 97%. At 24 months, denosumab biopsies showed reduced cortical porosity and increased volumetric BMD in cortical bone [21]. Denosumab treatment, through 5 years, resulted in normal bone quality with reduced bone turnover [22].

In another subset analysis of FREEDOM, hip and spine strength, estimated using the finite element analysis of hip and spine quantitative computed tomography scans, the finite element estimates of hip strength increased from 12 months (5.3%, P<0.0001) and through 36 months (8.6%, P<0.0001) in the denosumab group, compared with baseline. Similar changes were observed in the spine: strength increased by 18.2% at 36 months for the denosumab group (P<0.0001) and decreased by –4.2% for the placebo group (P=0.002). At 36 months, hip and spine strength increased for the denosumab group, compared with the placebo group, by 14.3% (P<0.0001) and 22.4% (P<0.0001), respectively. Further analysis of the finite element models indicated that strength associated with the trabecular bone was lost at the hip and spine in the placebo group, whereas strength associated with both the trabecular and cortical bone improved in the denosumab group [23].

Comparison with bisphosphonates

The Study of Transitioning from AleNdronate to Denosumab (STAND) evaluated switching from alendronate to denosumab therapy [24]. Subjects received open-label alendronate 70 mg once weekly for 1 month and then were assigned randomly to either continued weekly alendronate therapy or subcutaneous denosumab 60 mg every 6 months and were followed for 12 months. In subjects transitioning to denosumab, total hip BMD increased, by 1.90% at month 12, compared with a 1.05% increase in subjects continuing on alendronate (P<0.0001). Significantly greater BMD gains with denosumab versus alendro-

nate were also achieved at 12 months at the lumbar spine, femoral neck, and 1/3 radius (all $P<0.0125$). Median serum CTX levels remained near baseline in the alendronate group, and with denosumab were decreased significantly versus alendronate ($P<0.0001$) at all time points.

In the DECIDE trial, comparing efficacy with alendronate, significantly greater increases in BMD were observed with denosumab treatment at all measured skeletal sites (12-month treatment differences: 0.6%, femoral neck; 1.0%, trochanter; 1.1%, lumbar spine; 0.6%, 1/3 radius; $P\leq0.0002$ at all sites) [10].

Comparison with teriparatide

Combined teriparatide and denosumab increased BMD more than either agent alone. In an open-label, randomized, controlled study, patients were assigned in a 1:1:1 ratio to receive 20 μg teriparatide daily, 60 mg denosumab every 6 months, or both. BMD was measured at 0, 3, 6, and 12 months. At 12 months, lumbar spine BMD increased more in the combination group (9.1%) than in the teriparatide (6.2%, $P=0.0139$) or denosumab (5.5%, $P=0.0005$) groups. Femoral-neck BMD also increased more in the combination group (4.2%) than in the teriparatide (0.8%, $P=0.0007$) and denosumab (2.1%, $P=0.0238$) groups, as did total-hip BMD (combination, 4.9%; teriparatide, 0.7%, $P<0.0001$; denosumab 2.5%, $P=0.0011$). Combination treatment might, thus, be useful in treating patients at high risk of fractures [25].

SAFETY AND ADVERSE EVENTS

In the 3-year FREEDOM trial, there was no significant between-group difference in the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events [11]. Adverse events occurring in at least 2% of subjects in the denosumab or placebo group were infection (52.9% vs. 54.4%), cancer (4.8% vs. 4.3%), cardiovascular events (4.8% vs. 4.6%), falls (4.5% vs. 5.7%, $P=0.02$; excluding falls that occurred on the same day as a fracture), and eczema (3.0% vs. 1.7%, $P<0.001$). No woman developed hypocalcemia in the denosumab group in the FREEDOM trial. No woman developed neutralizing antibodies to denosumab. Twelve subjects (0.3%) in the denosumab group reported the serious adverse event of cellulitis, compared with one subject (<0.1%) in the placebo group ($P=0.002$). There was no significant difference in the overall incidence of the adverse events of cellulitis, with 47 (1.2%) in the denosumab group and 36 (0.9%) in the placebo group.

In post-marketing reports (as of September 2013, estimated exposure with denosumab was 1,252,566 patient-years) for assessment of atypical femoral fracture (AFF), osteonecrosis of the jaw (ONJ), severe symptomatic hypocalcemia (SSH), and anaphylaxis [26], four reports had been adjudicated as consistent with the American Society for Bone and Mineral Research definition of AFF. All patients had prior bisphosphonate use. For ONJ, 32 reports were adjudicated as consistent with the American Association of Oral and Maxillofacial Surgeons definition of ONJ. Eight reports of SSH included symptoms of seizures and/or tetany; seven of the eight patients had chronic kidney disease, a risk factor for hypocalcemia. Most SSH events occurred within 30 days of denosumab administration and resolved with calcium and vitamin D treatment. For anaphylaxis, five reports included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and/or urticaria. Most events occurred within 1 day of the first denosumab dose; emergency room treatments included antihistamines and steroids and there was no fatal outcome [26].

In the FREEDOM trial, denosumab at a dose of 60 mg every 6 months did not seem to delay fracture-healing [27]. Delayed healing was reported in seven subjects (two in the denosumab group and five in the placebo group), including one with subsequent nonunion (in the placebo group).

Denosumab treatment had no effect on progression of aortic calcification (AC) or the incidence of cardiovascular adverse events versus placebo. Postmenopausal women with osteoporosis (1,142 placebo, 1,221 denosumab) were selected from the FREEDOM trial who were at high risk of cardiovascular events according to modified Raloxifene Use for the Heart (RUTH) criteria. Frequency of AC progression over 3 years did not differ between women in the placebo (22%) and denosumab (22%) groups ($P=0.98$). The frequency of cardiovascular adverse events did not differ between the placebo (40%) and denosumab (38%) groups ($P=0.26$) [28].

CONCLUSIONS

Denosumab is a fully human recombinant monoclonal antibody to the RANKL and blocks binding of RANKL to the RANK receptor. Subcutaneous denosumab administration once every 6 months decreases osteoclastogenesis and increases BMD at the lumbar spine, total hip, and/or femoral neck and significantly reduces markers of bone turnover in postmenopausal women with osteoporosis. Denosumab treatment significantly reduces the incidence of new vertebral, nonvertebral,

and hip fractures in postmenopausal women. Postmarketing safety surveillance has not shown any unexpected findings. Continued safety surveillance will define the long-term safety of denosumab. The benefits of denosumab are greater than its risks. Denosumab is an important choice for the treatment of postmenopausal women with osteoporosis at increased risk of fractures, including older patients who have difficulty with intake of oral bisphosphonates and patients who are intolerant of, or unresponsive to, other therapies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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