ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

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ABSTRACT

BACKGROUND

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Given its unique actions, denosumab may be useful in the treatment of osteoporosis.

METHODS

We enrolled 7868 women between the ages of 60 and 90 years who had a bone mineral density T score of less than −2.5 but not less than −4.0 at the lumbar spine or total hip. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary end point was new vertebral fracture. Secondary end points included nonvertebral and hip fractures.

RESULTS

As compared with 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; 95% confidence interval [CI], 0.26 to 0.41; P<0.001) — a relative decrease of 68%. Denosumab 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; 95% CI, 0.37 to 0.97; P=0.04) — a relative decrease of 40%. Denosumab also reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, versus 8.0% in the placebo group (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) — a relative decrease of 20%. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of denosumab.

CONCLUSIONS

Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis. (ClinicalTrials.gov number, NCT00089791.)

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FRACTURES ARE A MAJOR CAUSE OF DIS-ability and health care costs.[1,2] The use of denosumab is a novel approach to fracture prevention. It is a fully human monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL), a cytokine that is essential for the formation, function, and survival of osteoclasts.[3] By binding RANKL, denosumab prevents the interaction of RANKL with its receptor, RANK, on osteoclasts and osteoclast precursors and reversibly inhibits osteoclast-mediated bone resorption.[4]

In previous trials, the subcutaneous administration of 60 mg of denosumab every 6 months reduced bone turnover and increased bone mineral density.[5-8] We tested the effect of denosumab on the risk of fracture in postmenopausal women with osteoporosis.

METHODS

STUDY DESIGN

Our study, called Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM), was an international, randomized, placebo-controlled trial. Subjects were randomly assigned to receive subcutaneous injections of either 60 mg of denosumab or placebo at study sites every 6 months for 36 months. Randomization was stratified according to 5-year age groups.

SUBJECTS

Women between the ages of 60 and 90 years with a bone mineral density T score of less than −2.5 at the lumbar spine or total hip were eligible for inclusion. Women were excluded if they had conditions that influence bone metabolism or had taken oral bisphosphonates for more than 3 years. If they had taken bisphosphonates for less than 3 years, they were eligible after 12 months without treatment. Women were also excluded if they had used intravenous bisphosphonates, fluoride, or strontium for osteoporosis within the past 5 years; or parathyroid hormone or its derivatives, corticosteroids, systemic hormone-replacement therapy, selective estrogen-receptor modulators, or tibolone, calcitonin, or calcitriol within 6 weeks before study enrollment.

Although consensus conferences have not specified a permissible risk of fracture for placebo-controlled trials,[9,10] women were excluded if they had a bone mineral density T score of less than −4.0 at the lumbar spine or total hip or any severe

(or more than two moderate) prevalent vertebral fractures. As part of the consent process, potential subjects were informed about alternative treatments for osteoporosis. All women received daily supplements containing at least 1000 mg of calcium. Women were excluded if they had a serum 25-hydroxyvitamin D level of less than 12 ng per milliliter. Subjects with a baseline 25-hydroxyvitamin D level of 12 to 20 ng per milliliter were given at least 800 IU of vitamin D daily, and those with a baseline level above 20 ng per milliliter were given at least 400 IU daily. If total hip bone mineral density decreased by more than 7% during a 12-month period or by 10% or more during the study or if the T score dropped below −4.0, the subject was again counseled by the local study clinician about using alternative treatments in lieu of continuing to participate in the study. The trial and consent process were approved by the institutional review boards and ethics committees overseeing the study sites in the United States and other countries; 139 of 142 boards that reviewed the protocol approved it.

ASSESSMENTS OF EFFICACY

Lateral spine radiographs were taken annually and assessed for new vertebral fractures by a semiquantitative grading scale[11] at the central imaging center (Synarc). A prevalent fracture was defined as a vertebral body with a semiquantitative grade of 1 or more. A new vertebral fracture was defined as an increase of at least 1 grade in a vertebral body that was normal at baseline. Secondary end points were the time to the first nonvertebral fracture and the time to the first hip fracture. Fractures of the skull, face, mandible, metacarpals, fingers, or toes were excluded because they are not associated with decreased bone mineral density; pathologic fractures and those that were associated with severe trauma (defined as a fall from a height higher than a stool, chair, or first rung of a ladder or severe trauma other than a fall) were also excluded.[12] Clinical fractures were confirmed by diagnostic imaging or a radiologist's report.

Bone mineral density as evaluated on dual-energy x-ray absorptiometry was measured at baseline and then annually at the hip and after 36 months at the lumbar spine. Bone mineral density of both sites was measured at baseline and at 1, 6, 12, 24, and 36 months in 441 subjects. Concentrations of two markers of bone turnover were measured in 160 subjects from fasting serum samples collected before the injection on day 1, at

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Table 1. Baseline Characteristics of the Subjects.*

Variable	Denosumab (N = 3902)	Placebo (N = 3906)
Age		
Mean — yr	72.3±5.2	72.3±5.2
Group — no. (%)		
<70 yr	1030 (26.4)	1028 (26.3)
70–74 yr	1637 (42.0)	1642 (42.0)
≥75 yr	1235 (31.7)	1236 (31.6)
Body-mass index†	26.0±4.1	26.0±4.2
Region — no. (%)‡		
Western Europe	1761 (44.8)	1773 (45.1)
Eastern Europe	1374 (34.9)	1355 (34.4)
Latin America	472 (12.0)	462 (11.7)
North America	282 (7.2)	297 (7.5)
Australia and New Zealand	44 (1.1)	48 (1.2)
T score		
Lumbar spine	−2.82±0.70	−2.84±0.69
Total hip	−1.89±0.81	−1.91±0.81
Femoral neck	−2.15±0.72	−2.17±0.71
Prevalent vertebral fracture — no. (%)		
Yes	929 (23.8)	915 (23.4)
No	2864 (73.4)	2854 (73.1)
Unreadable or missing data	109 (2.8)	137 (3.5)
Serum 25-hydroxyvitamin D — ng/ml§	23.1±11.7	22.9±11.3

* Plus–minus values are means ±SD. A total of 60 subjects at one center (31 in the denosumab group and 29 in the placebo group) were excluded from all analyses because of issues with respect to study procedures and the reliability of data.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Percentages for region are based on all subjects enrolled in the study: 3933 in the denosumab group and 3935 in the placebo group.

§ Subjects with outlier values of more than 200 ng per milliliter were excluded from this analysis.

Dictionary for Regulatory Activities (MedDRA) system. All deaths and serious adverse events that were possibly related to cardiovascular disease were adjudicated by a committee of cardiologists using predefined criteria. A committee of experts reviewed reported events that met a broad range of MedDRA terms that might represent osteonecrosis of the jaw, defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after diagnosis.[13] Study investigators clinically assessed the healing of nonvertebral fractures within 6 months after their occurrence. A positive result on hypocalcemia testing was defined as an albumin-adjusted calcium level of less than 8.0 mg per deciliter (2.0 mmol per liter) in fasting specimens drawn just before injection of the study drug. Denosumab-specific antibodies were also assessed in those samples.

STUDY OVERSIGHT

A steering committee, consisting of a majority of investigators who were not employed by study sponsor Amgen, planned the analyses for the manuscript before the unblinding of data, and one member wrote the first draft of the manuscript. The committee members approved the manuscript for publication and vouch for the completeness and accuracy of the data. Analyses were performed by the sponsor and confirmed by an analyst at the San Francisco Coordinating Center. The authors received all analyses that they requested. The sponsor designed the protocol with advice from external investigators and was responsible for the management and quality control of data collected by the clinical sites. A data and safety monitoring committee reviewed unblinded data at least twice yearly.

STATISTICAL ANALYSIS

The study had a power of more than 99% to detect a 45% reduction in the incidence of new vertebral fractures and to detect a 40% reduction in the risk of any nonvertebral fracture and a power of 91% to detect a 40% reduction in the risk of hip fracture. These estimates were based on the assumption that the annual fracture rate in the placebo group over a 36-month period would be 4.0% for vertebral fractures, 3.3% for nonvertebral fractures, and 1.0% for hip fractures.

Analyses of efficacy were based on the intention-to-treat principle. To adjust for multiplicity and maintain the overall significance level at 0.05,

1 month after the baseline injection, and before injections at 6, 12, 24, and 36 months. Bone-turnover marker serum C-telopeptide of type I collagen was evaluated with the use of enzyme-linked immunosorbent assay (ELISA) (Nordic Bioscience Diagnostics A/S), and intact serum procollagen type I N-terminal propeptide (PINP) was evaluated with the use of radioimmunoassay (Orion Diagnostica Oy).

ADVERSE EVENTS

Physicians at study sites reported adverse events that were coded as preferred terms in the *Medical*

Table 2. Effect of Denosumab on the Risk of Fracture at 36 Months.*

Outcome	Denosumab	Placebo	Difference in Rates (95% CI)	Relative Risk or Hazard Ratio (95% CI)†	P Value
	no. (%)				
Primary end point					
New vertebral fracture	86 (2.3)	264 (7.2)	4.8 (3.9 to 5.8)	0.32 (0.26 to 0.41)	<0.001
Secondary end points					
Nonvertebral fracture‡	238 (6.5)	293 (8.0)	1.5 (0.3 to 2.7)	0.80 (0.67 to 0.95)	0.01
Hip fracture	26 (0.7)	43 (1.2)	0.3 (−0.1 to 0.7)	0.60 (0.37 to 0.97)	0.04
Other fracture end points					
New clinical vertebral fracture	29 (0.8)	92 (2.6)	1.7 (1.1 to 2.3)	0.31 (0.20 to 0.47)	<0.001
Multiple (≥2) new vertebral fractures	23 (0.6)	59 (1.6)	1.0 (0.5 to 1.5)	0.39 (0.24 to 0.63)	<0.001

* The percentages of new and multiple new vertebral fractures are calculated for 3702 subjects in the denosumab group and 3691 in the placebo group who underwent spinal radiography at baseline and during at least one visit after baseline. The percentages of nonvertebral, hip, and new clinical vertebral fractures are cumulative Kaplan–Meier estimates for 3902 subjects in the denosumab group and 3906 in the placebo group.
† Risk ratios are based on the Mantel–Haenszel method with adjustment for the age-stratification variable for vertebral fractures. Hazard ratios are based on the Cox proportional-hazards model with adjustment for the age-stratification variable for nonvertebral, hip, and clinical vertebral fractures.
‡ A total of 28 subjects (13 in the denosumab group and 15 in the placebo group) had nonvertebral fractures associated with severe trauma and were not included in the analysis.

the primary end point of new vertebral fracture was required to achieve significance before the next end points in the sequence (nonvertebral fracture and hip fracture) could be tested. Analyses regarding vertebral fractures included all subjects who had at least one follow-up radiograph.

The effect of treatment on the risk of new vertebral fracture was analyzed with the use of a logistic-regression model with adjustment for age strata. An age-stratified Cox proportional-hazards model was used to compare the two study groups for the secondary end points. Score tests were used to calculate P values in each model.[14,15] Subjects who were lost to follow-up or withdrew before having a fracture event had their last known fracture status carried forward. Radiographically defined vertebral fractures were analyzed by cumulative incidence and secondary end points by time-to-event analysis with the use of Kaplan–Meier methods. The absolute risk reduction between study groups was computed as the difference in incidence at 36 months for the primary end point and the difference in the Kaplan–Meier estimates at 36 months for the secondary end points with the use of a weighted average across the age strata. Analyses of changes in bone mineral density included all subjects who had at least

one follow-up measurement at or before the time point under consideration. Missing values were imputed by carrying forward the last observation.

Safety analyses included all subjects who received at least one dose of a study drug. Analyses of adverse and serious adverse events of cancer, infection, specific cardiovascular events, and potential adverse effects of potent antiresorptive therapies (including osteonecrosis of the jaw, delayed fracture healing, femoral-shaft fracture, hypocalcemia, and atrial fibrillation) were specified in advance. Preferred terms similar to eczema were combined as eczema, and erysipelas was included with cellulitis. To adjust for multiple comparisons for numerous reports of adverse events, we specified in advance to report MedDRA preferred terms of adverse events that occurred in at least 2% of subjects in either study group with a P value of 0.05 or less and serious adverse events that occurred in at least 0.1% of subjects in either group with a P value of 0.01 or less.

RESULTS

SUBJECTS

A total of 7868 women were enrolled in the study, 3933 in the denosumab group and 3935 in the pla-
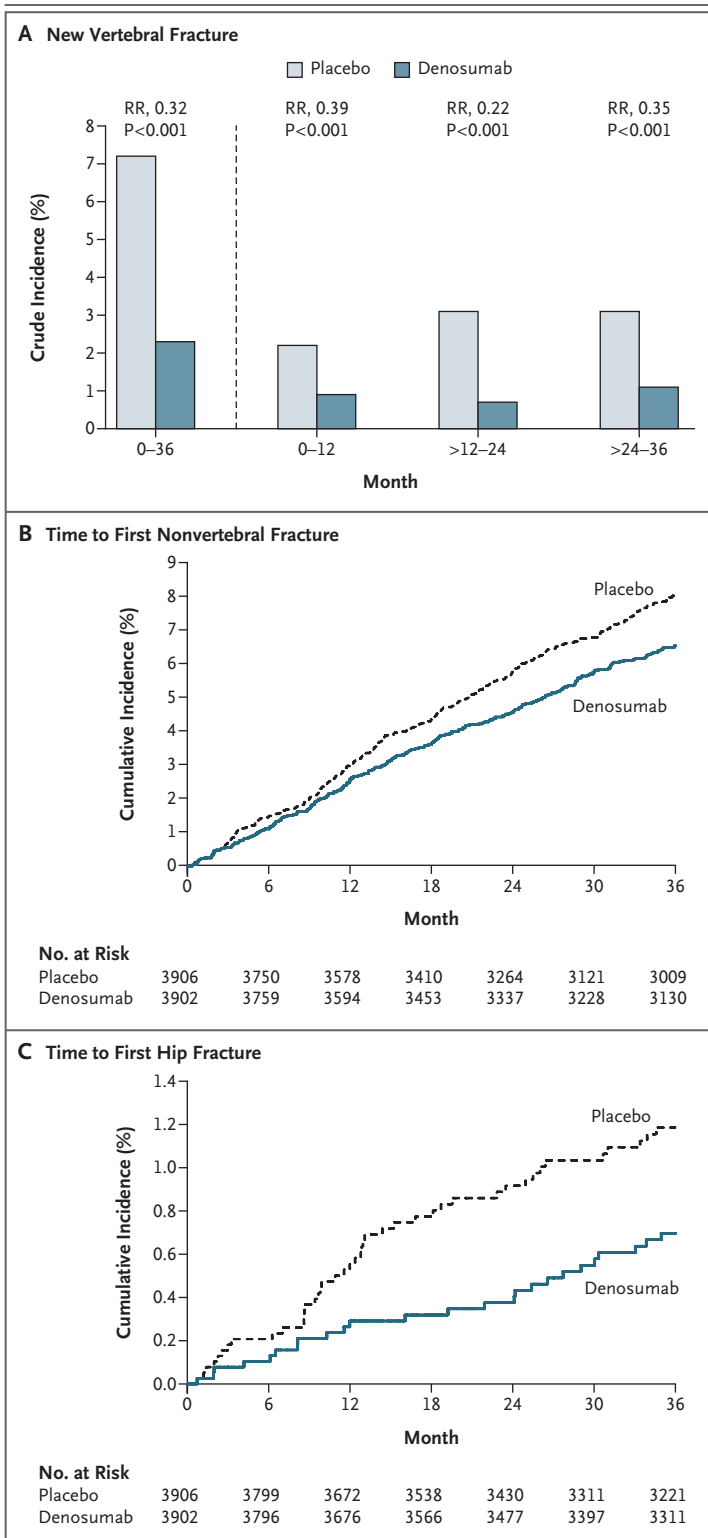
A New Vertebral Fracture

□ Placebo ■ Denosumab

RR, 0.32 RR, 0.39 RR, 0.22 RR, 0.35
P<0.001 P<0.001 P<0.001 P<0.001

Crude Incidence (%)

0–36 0–12 >12–24 >24–36
Month

B Time to First Nonvertebral Fracture

Cumulative Incidence (%)

Placebo

Denosumab

Month

No. at Risk

Placebo	3906	3750	3578	3410	3264	3121	3009
Denosumab	3902	3759	3594	3453	3337	3228	3130

C Time to First Hip Fracture

Cumulative Incidence (%)

Placebo

Denosumab

Month

No. at Risk

Placebo	3906	3799	3672	3538	3430	3311	3221
Denosumab	3902	3796	3676	3566	3477	3397	3311

Figure 1. Incidence of New Vertebral, Nonvertebral, and Hip Fractures.

The primary end point was the incidence of new vertebral fractures at 36 months (Panel A, left), which is shown for each study year (Panel A, right). Risk ratios (RRs) are for subjects in the group receiving denosumab, as compared with those receiving placebo. Kaplan–Meier curves of the time to the first nonvertebral fracture (Panel B) and the first hip fracture (Panel C) were determined on the basis of subjects who did not have a fracture or who did not leave the study before the time point of interest. The subjects at risk at 36 months included all those who completed end-of-study visits at or after the start of the window for the 36-month visit.
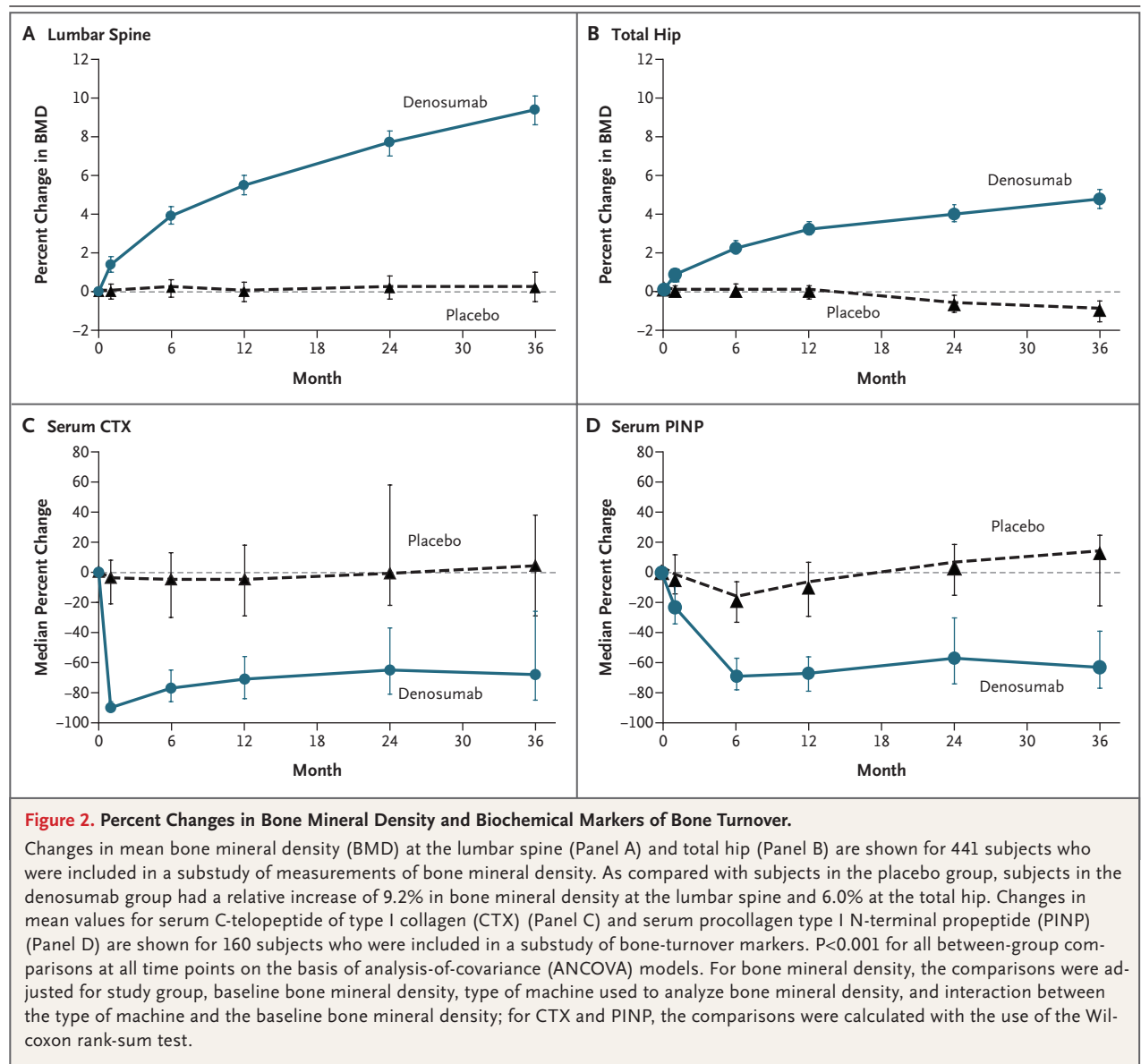
tion of their study center was halted owing to issues related to study procedures and the reliability of data. Baseline characteristics were similar between the two study groups (Table 1). The mean bone mineral density T scores were –2.8 at the lumbar spine, –1.9 at the total hip, and –2.2 at the femoral neck. About 24% of women had a vertebral fracture at baseline. Of 7868 subjects, 6478 (82%) completed 36 months of study and 5979 (76%) received all injections.

FRACTURES, BONE DENSITY, AND MARKERS OF BONE TURNOVER

The calculations of percentages of new and multiple new vertebral fractures were based on the number of subjects who underwent spinal radiography at baseline and during at least one visit after baseline. The 36-month incidence of new radiographic vertebral fracture was 2.3% (86 of 3702 subjects) in the denosumab group and 7.2% (264 of 3691 subjects) in the placebo group, representing a 68% reduction in relative risk (P<0.001) (Table 2). The reduction in risk was similar during each year of the trial (Fig. 1A). There were similar reductions in clinically diagnosed vertebral fractures (69%) and multiple new vertebral fractures (61%, P<0.001 for both comparisons) (Table 2).

The calculations of cumulative incidences of nonvertebral, hip, and new clinical vertebral fractures were based on Kaplan–Meier estimates of a 36-month cumulative incidence in 3902 subjects in the denosumab group and 3906 in the placebo group. Denosumab reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, as compared with 8.0% in the placebo group (hazard ratio, 0.80; 95% confidence interval [CI], 0.67 to 0.95; P=0.01) —

cebo group. Of these subjects, 60 (31 in the denosumab group and 29 in the placebo group) were excluded from all analyses because the participa-

Figure 2. Percent Changes in Bone Mineral Density and Biochemical Markers of Bone Turnover.

Changes in mean bone mineral density (BMD) at the lumbar spine (Panel A) and total hip (Panel B) are shown for 441 subjects who were included in a substudy of measurements of bone mineral density. As compared with subjects in the placebo group, subjects in the denosumab group had a relative increase of 9.2% in bone mineral density at the lumbar spine and 6.0% at the total hip. Changes in mean values for serum C-telopeptide of type I collagen (CTX) (Panel C) and serum procollagen type I N-terminal propeptide (PINP) (Panel D) are shown for 160 subjects who were included in a substudy of bone-turnover markers. P<0.001 for all between-group comparisons at all time points on the basis of analysis-of-covariance (ANCOVA) models. For bone mineral density, the comparisons were adjusted for study group, baseline bone mineral density, type of machine used to analyze bone mineral density, and interaction between the type of machine and the baseline bone mineral density; for CTX and PINP, the comparisons were calculated with the use of the Wilcoxon rank-sum test.

a 20% relative reduction (Table 2 and Fig. 1B). Denosumab also decreased 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; 95% CI, 0.37 to 0.97; P=0.04) — a 40% relative reduction (Table 2 and Fig. 1C).

After 36 months, denosumab was associated with a relative increase in bone mineral density of 9.2% (95% CI, 8.2 to 10.1) at the lumbar spine and 6.0% (95% CI, 5.2 to 6.7) at the total hip, as compared with placebo (Fig. 2). As compared with placebo, denosumab decreased serum C-telopeptide levels by 86% at 1 month, by 72% before treat-

ment was administered at 6 months, and by 72% at 36 months. Levels of PINP, a marker of bone formation, were 18%, 50%, and 76% below those in the placebo group at the same time points.

ADVERSE EVENTS

There were no significant differences between subjects who received denosumab and those who received placebo in the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events (Table 3). Similarly, there were no significant differences in the overall incidence of cancer, cardio-

Table 3. Adverse Events.*

Event	Denosumab (N=3886)	Placebo (N=3876)	P Value†
	no. (%)		
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of a study drug	192 (4.9)	202 (5.2)	0.55
Adverse events			
Infection	2055 (52.9)	2108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcemia	0	3 (0.1)	0.08
Osteonecrosis of the jaw	0	0	NA
Serious adverse events			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	178 (4.6)	0.74
Stroke	56 (1.4)	54 (1.4)	0.89
Coronary heart disease	47 (1.2)	39 (1.0)	0.41
Peripheral vascular disease	31 (0.8)	30 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Adverse events occurring in at least 2% of subjects‡			
Eczema	118 (3.0)	65 (1.7)	<0.001
Falling§	175 (4.5)	219 (5.7)	0.02
Flatulence	84 (2.2)	53 (1.4)	0.008
Serious adverse events occurring in at least 0.1% of subjects¶			
Cellulitis (including erysipelas)	12 (0.3)	1 (<0.1)	0.002
Concussion	1 (<0.1)	11 (0.3)	0.004

* NA denotes not applicable.
† P values are based on the log-rank test, except for between-group comparisons of deaths and cardiovascular events, which were based on the Cox proportional-hazards model with adjustment for the baseline cardiovascular risk score.
‡ P≤0.05 for the between-group comparison. Among terms listed in the *Medical Dictionary for Regulatory Activities* (MedDRA), the incidence of adverse events corresponding to 58 MedDRA-preferred terms was at least 2% in either study group.
§ This category excludes falls that occurred on the same day as a fracture.
¶ P≤0.01 for the between-group comparison. There were 152 MedDRA-preferred terms of serious adverse events that had an incidence of at least 0.1% in either group.

(1.8%) died in the denosumab group and 90 (2.3%) in the placebo group (P=0.08).

No cases of osteonecrosis of the jaw occurred in either group. Delayed fracture healing was reported for two subjects in the denosumab group and four subjects in the placebo group, and one case of nonunion of a humerus fracture was reported in the placebo group. There were no fractures of the femoral shaft in the denosumab group and three such fractures in the placebo group (0.1%). There were no reports of hypocalcemia in the denosumab group and three events (0.1%) in the placebo group. Decreases in serum calcium to levels below 8.0 mg per deciliter occurred in four subjects in the denosumab group and five in the placebo group. Local reactions after injection of a study drug occurred in 33 subjects (0.8%) in the denosumab group and 26 subjects (0.7%) in the placebo group. Neutralizing antibodies to denosumab did not develop in any of the subjects.

Eczema was reported in 3.0% of subjects in the denosumab group and 1.7% in the placebo group (P<0.001). Falls that were not associated with a fracture were reported in 4.5% of subjects in the denosumab group and 5.7% in the placebo group (P=0.02). Flatulence was reported more frequently in the denosumab group (2.2%) than in the placebo group (1.4%, P=0.008). Twelve subjects (0.3%) in the denosumab group reported serious adverse events of cellulitis, as compared with one subject (<0.1%) in the placebo group (P=0.002). There were no significant differences in the overall incidence of adverse events of cellulitis, with 47 (1.2%) in the denosumab group and 36 (0.9%) in the placebo group.

DISCUSSION

In postmenopausal women with osteoporosis, the subcutaneous administration of 60 mg of denosumab every 6 months for 36 months significantly reduced the risk of vertebral and nonvertebral fractures and the risk of hip fracture. The reduction in the risk of vertebral fracture was similar in the first and subsequent years and for both clinically diagnosed and multiple vertebral fractures.

Denosumab prevents the interaction of RANKL with RANK, its receptor, on osteoclasts and their precursors, thereby blocking the formation, function, and survival of osteoclasts.[3] In contrast, bisphosphonates chemically bind to calcium hydroxy-

vascular events, or either adverse or serious adverse events of infection. Four cases of opportunistic infections were reported in the denosumab group and three in the placebo group. Seventy subjects

apatite in bone; they decrease bone resorption by blocking the function and survival, but not the formation, of osteoclasts.[16]

The magnitude of the risk reduction of vertebral fracture with denosumab was similar to that reported for intravenously administered zoledronic acid and appears to be greater than reductions reported for oral osteoporosis agents.[17-20] For nonvertebral fractures, the risk reduction with denosumab was similar to those reported for alendronate, risedronate, and zoledronic acid.[17,20,21] However, comparisons of efficacy are limited because there has been no head-to-head trial comparing rates of fracture reduction associated with denosumab and bisphosphonates. In addition, trials have included various subgroups of nonvertebral fractures,[22-24] and study populations have varied. At least 50% of patients stop bisphosphonate treatment within 1 year after receiving a prescription for an oral agent.[25] Twice-yearly subcutaneous injections might improve adherence.

During 36 months of treatment, denosumab increased bone mineral density at the lumbar spine by about 9% and at the total hip by about 6%. A separate 12-month trial showed that denosumab increased bone mineral density significantly more than alendronate at the total hip and spine.[26]

Denosumab reduced bone resorption by a median of 86% at 1 month, which is greater than the reductions seen with other antiresorptive drugs.[21,27] In retrospective analyses from trials of antiresorptive drugs, the magnitude of the decrease in bone-turnover markers was shown to be associated with the reduction in fracture risk.[28] Whether this finding also applies to denosumab requires further study. Impaired fracture healing and osteonecrosis of the jaw have been reported with bisphosphonate therapy in postmarketing case reports, raising concern that these conditions may be caused by decreased bone resorption. No significant adverse effects on fracture healing and no cases of osteonecrosis of the jaw occurred in our study. There have also been reports of cases of unusual fractures of the femoral shaft associated with long-term administration of alendronate. No fractures of the femoral shaft occurred in the denosumab group during 36 months of study. Patients in the trial are continuing to receive denosumab, to assess the potential effects of long-term treatment, including fractures, fracture healing, infections, and cancer.

RANKL and RANK are members of the tumor necrosis factor superfamily that are expressed by a variety of lymphoid cells.[29] It has been theorized that the inhibition of RANKL might increase the risk of cancer or infection.[30] In this trial, there was no significant difference in the incidence of cancer or in the overall incidence of infection, serious adverse events of infection, or opportunistic infection during 36 months of treatment; longer follow-up is under way. An increased incidence of hospitalization for cellulitis was observed in subjects who were treated with denosumab; however, there was no significant difference in the overall incidence of cellulitis between the two groups.

Before a new treatment for osteoporosis can be approved, the Food and Drug Administration and the European Committee for Medicinal Products for Human Use have required that placebo-controlled trials be conducted for 3 years in subjects with osteoporosis. Some observers have raised concern about the enrollment of subjects with osteoporosis in placebo-controlled trials, although there is no consensus about an allowable risk for inclusion.[9,10] To reduce the risk for control subjects, trials involving subjects at reduced risk for osteoporosis might be considered. However, the effects of treatment on the risk of nonvertebral fracture in women with a bone mineral density T score above –2.5 may be weaker and not applicable to women with osteoporosis.[18,19,31] In addition, although shorter trials have been considered,[10] the results may be misleading because treatments may have greater efficacy for vertebral fracture in the first year than in subsequent years.[32-35]

In conclusion, denosumab offers an alternative approach to the treatment of osteoporosis by decreasing bone resorption and increasing bone mineral density through the inhibition of RANKL. Denosumab was associated with a significant reduction in the risk of vertebral, hip, and nonvertebral fractures in postmenopausal women with osteoporosis.

APPENDIX

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