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Effect of Denosumab Treatment on the Risk of Fractures in Subgroups of Women With Postmenopausal Osteoporosis

Michael R McClung,[1] Steven Boonen,[2] Ove Törring,[3] Christian Roux,[4] René Rizzoli,[5] Henry G Bone,[6] Claude-Laurent Benhamou,[7] Willem F Lems,[8] Salvatore Minisola,[9] Johan Halse,[10] Hans C Hoeck,[11] Richard Eastell,[12] Andrea Wang,[13] Suresh Siddhanti,[13] and Steven R Cummings[14]

[1]Oregon Osteoporosis Center, Portland, OR, USA
[2]Division of Geriatric Medicine, Leuven University, Leuven, Belgium
[3]Karolinska Institutet Sodersjukhuset, Stockholm, Sweden
[4]Department of Rheumatology, Cochin Hospital, Paris Descartes University, Paris, France
[5]University Hospital, Geneva, Switzerland
[6]Michigan Bone and Mineral Clinic, Detroit, MI, USA
[7]INSERM U658, Orleans, France
[8]VU University Medical Center, Amsterdam, The Netherlands
[9]Sapienza, Università di Roma, Rome, Italy
[10]Osteoporoseklinikken, Oslo, Norway
[11]CCBR, Aalborg, Denmark
[12]National Institute for Health Research, Bone Biomedical Research Unit, University of Sheffield, Sheffield, United Kingdom
[13]Amgen Inc., Thousand Oaks, CA, USA
[14]San Francisco Coordinating Center, California Pacific Medical Center Research Institute and UCSF, San Francisco, CA, USA

ABSTRACT

Denosumab reduces the risk of new vertebral and nonvertebral fractures. Previous trials suggest that the efficacy of antiresorptives on fractures might differ by patients' characteristics, such as age, bone mineral density (BMD), and fracture history. In the FREEDOM study, 7808 women aged 60 to 90 years with osteoporosis were randomly assigned to receive subcutaneous injections of denosumab (60 mg) or placebo every 6 months for 3 years. New vertebral and nonvertebral fractures were radiologically confirmed. Subgroup analyses described in this article were prospectively planned before study unblinding to evaluate the effect of denosumab on new vertebral and nonvertebral fractures across various subgroups. Compared with placebo, denosumab decreased the risk of new vertebral fractures in the overall study population over 3 years. This effect did not significantly differ for any of the nine subgroups analyzed ($p > 0.09$ for all potential interactions). Denosumab also reduced all nonvertebral fractures by 20% in the full study cohort over 3 years. This risk reduction was statistically significant in women with a baseline femoral neck BMD *T*-score ≤ -2.5 but not in those with a *T*-score > -2.5; in those with a body mass index (BMI) $< 25\ kg/m^2$ but not $\geq 25\ kg/m^2$; and in those without but not with a prevalent vertebral fracture. These differential treatment effects were not explained by differences in BMD responses to denosumab. Denosumab 60 mg administered every 6 months for 3 years in women with osteoporosis reduced the risk of new vertebral fractures to a similar degree in all subgroups. The effect of denosumab on nonvertebral fracture risk differed by femoral neck BMD, BMI, and prevalent vertebral fracture at baseline.

KEY WORDS: DENOSUMAB; POSTMENOPAUSAL OSTEOPOROSIS; NEW VERTEBRAL FRACTURES; NONVERTEBRAL FRACTURES; SUBGROUP ANALYSIS

Introduction

Denosumab (Prolia, Amgen Inc., Thousand Oaks, CA, USA) is a fully human monoclonal IgG2 antibody that binds receptor activator of NF-κB (RANK) ligand with high affinity and specificity. Administration of denosumab 60 mg by subcutaneous injection every 6 months rapidly and substantially reduced bone turnover and increased bone mineral density (BMD).[1,2] In the FREEDOM

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Address correspondence to: Michael R McClung, MD, Oregon Osteoporosis Center, 5050 Northeast Hoyt, Suite 626, Portland, OR 97213, USA.
E-mail: mmcclung@orost.com

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study, denosumab therapy for 3 years reduced the incidence of new vertebral fractures by 68%, hip fractures by 40%, and nonvertebral fractures by 20% in postmenopausal women with osteoporosis.[3]

Several risk factors for fracture are recognized, including age, BMD, body mass index (BMI), and a history of vertebral or nonvertebral fracture. The therapeutic effects of antiresorptive agents may differ across categories of risk factors. The effect of alendronate, risedronate, and strontium ranelate on vertebral fracture risk was similar among various subgroups of postmenopausal women, including strata of age, BMD, and history of fracture.[4–6] However, zoledronic acid appeared to be less effective in reducing vertebral fracture risk in older and lighter postmenopausal women and in patients with modest renal impairment.[7]

Interactions between treatment and risk factors have been reported with antiresorptive agents on nonvertebral fracture risk. In a preplanned analysis, alendronate reduced the risk of nonvertebral fractures among women with a femoral neck BMD *T*-score ≤ -2.5 but not in those with a *T*-score > -2.5.[8] In post hoc analyses, ibandronate and bazedoxifene appeared to reduce nonvertebral fracture risk in patients with low femoral neck BMD *T*-scores but not in women with higher BMD values.[9,10] Similarly, strontium ranelate was shown to reduce hip fracture risk in a post hoc analysis of a high-risk subgroup but not in the overall study population.[11] Furthermore, risedronate significantly reduced the risk of hip and nonvertebral fractures in women aged 70 to 79 years with femoral neck BMD *T*-scores < -4.0 but did not significantly reduce fracture risk in women aged 80 years and older with fall-related risk factors for fracture.[12,13] With zoledronic acid, on the other hand, there were no significant treatment interactions for nonvertebral fractures.[7]

Denosumab is an antiresorptive drug with a unique mechanism of action. We evaluated the effects of therapy with this agent on new vertebral and nonvertebral fracture risk in subjects from the FREEDOM study with several predefined subgroups of risk factors to determine whether these risk factors affected the efficacy of treatment.

Materials and Methods

Study population

Subjects included in these analyses were enrolled in FREEDOM, an international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial that has been previously reported.[3] In FREEDOM, 7808 women aged 60 to 90 years with a BMD *T*-score < -2.5 at either the lumbar spine or total hip and ≥ -4.0 at both sites were randomly assigned to receive subcutaneous injections of denosumab (60 mg) or placebo every 6 months for 3 years. Women with more than two moderate vertebral fractures or any severe vertebral fracture, assessed by the semiquantitative grading of lateral spine radiographs,[14] were excluded. Subjects who had used oral bisphosphonates for >3 years were excluded; subjects with ≤ 3 years of oral bisphosphonate use and no use within 1 year of enrollment could enroll in the study. All subjects received daily supplements of calcium ($\geq$1 g) and vitamin D ($\geq$ 400 IU). Local institutional review board approval was obtained for the protocol. All subjects provided informed consent before any study-related procedures. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Fracture assessment

New vertebral fractures were radiologically confirmed on lateral spine radiographs taken annually and assessed by a semiquantitative grading scale[14] in a central imaging center (Synarc, San Francisco, CA, USA). A new vertebral fracture was defined as an increase of ≥ 1 grade in a vertebral body between T4 and L4 that was normal at baseline. Nonvertebral fractures were confirmed by diagnostic imaging or a radiologist's report. Fractures of the skull, face, mandible, metacarpal, fingers, and toes were excluded, as were fractures associated with severe trauma and pathologic (ie, metastatic) fractures.

Subgroups

Subgroups for analyses were prospectively planned to evaluate the efficacy of denosumab on new vertebral fracture (nine subgroups) and nonvertebral fracture (five subgroups). The choice of subgroups was based on previous studies documenting differences between subgroups in fracture risk and/or response to therapy. The subgroups of age, BMI, femoral neck BMD *T*-score, prevalent vertebral fracture, and prior nonvertebral fracture were included in the assessment of denosumab treatment effect on both new vertebral and nonvertebral fracture. Subgroups based on estimated creatinine clearance, geographic region, race, and prior use of osteoporosis medications also were evaluated for new vertebral fracture. Prior nonvertebral fracture and prior use of osteoporosis medications were based on patient history. Creatinine clearance was estimated using the Cockcroft-Gault equation.[15]

Bone mineral density

BMD by dual-energy X-ray absorptiometry (DXA) was measured at baseline and annually at the hip in all subjects. We compared percent change in femoral neck BMD from baseline to month 36 for subgroups in which denosumab had significantly different effects on risk of nonvertebral fracture.

Statistical analysis

Fracture endpoints in subgroups were analyzed according to the same prespecified methods used to calculate fracture risk in the entire FREEDOM population. Crude rates were calculated to summarize the new vertebral fracture incidence over 3 years. The risk ratios were adjusted for age strata (60 to 64, 65 to 69, 70 to 74, and $\geq$ 75 years) using the Mantel-Haenszel method. The effect of denosumab on the risk reduction in new vertebral fracture was based on a logistic regression adjusting for age strata. Nonvertebral fracture incidence was based on the Kaplan-Meier estimate at year 3. Hazard ratios were calculated using a Cox proportional hazards model adjusting for age strata. Score tests were used to calculate the *p* values for either fracture endpoint. A total of 14 subgroups were prespecified for analysis. The probability of observing ≥ 1 statistically significant treat-

ment-by-risk subgroup interaction test ($p < 0.05$) was >50% owing to chance alone, assuming all tests are independent. No adjustments for multiplicity were made. As recommended by guidelines[16] for subgroup analyses, we prespecified the number of subgroup analyses examined and calculated the potential magnitude of the false-positive rate.

Quantitative treatment-by-risk subgroup interactions were used to evaluate the consistency of the antifracture efficacy across various categories within a subgroup variable. The interaction for new vertebral fracture was calculated using a logistic regression model including treatment, age strata, individual subgroup, and treatment-by-risk subgroup interaction. The interaction for nonvertebral fracture was based on the score test from a stratified Cox proportional hazard model including treatment, individual subgroup, and treatment-by-risk subgroup interaction as main effects and age strata as the stratified variable. The interaction for changes in BMD was based on an analysis of covariance (ANCOVA) model including treatment, age strata, baseline BMD, DXA machine type, baseline BMD-by-machine type interaction, individual subgroup, and treatment-by-risk subgroup interaction. If the quantitative p value of the interaction term was < 0.05, the treatment-by-subgroup interaction was considered significant. If the treatment-by-subgroup interaction was significant, the Gail and Simon test[17] was then used to test for qualitative interaction.

Results

Baseline characteristics

The proportions of subjects in the various subgroups are presented in Table 1. Majorities of subjects were white, under age 75 years, had a calculated creatinine clearance of ≥ 60 mL/minute, femoral neck BMD T-score values > -2.5, or had not experienced previous vertebral or nonvertebral fractures. The distribution of subjects by risk factors was balanced, however, between the denosumab and placebo groups.

New vertebral fracture

In the entire study population, denosumab reduced the incidence of new vertebral fractures from 7.2% in the control group to 2.3% (risk ratio 0.32; 95% confidence interval [CI] 0.26 to

Table 1. Baseline Characteristics[a]

	Placebo ($N = 3906$) n (%)	Denosumab ($N = 3902$) n (%)
Age (years)		
<75	2670 (68.4)	2667 (68.3)
≥75	1236 (31.6)	1235 (31.7)
Body mass index (kg/m^2)		
<25	1698 (43.5)	1703 (43.6)
25 to <30	1580 (40.5)	1557 (39.9)
≥30	607 (15.5)	626 (16.0)
Estimated creatinine clearance (mL/min)		
<60	1436 (36.8)	1454 (37.3)
≥60	2466 (63.1)	2445 (62.7)
Region		
Western Europe, Australia, New Zealand	1821 (46.6)	1805 (46.3)
Eastern Europe	1326 (33.9)	1343 (34.4)
Latin America	462 (11.8)	472 (12.1)
North America	297 (7.6)	282 (7.2)
Femoral neck BMD T-score		
≤−2.5	1406 (36.0)	1384 (35.5)
>−2.5	2484 (63.6)	2495 (63.9)
Prevalent vertebral fracture		
Yes	915 (23.4)	929 (23.8)
No	2854 (73.1)	2864 (73.4)
Prior nonvertebral fracture at age ≥55 years		
Yes	1177 (30.1)	1163 (29.8)
No	2729 (69.9)	2739 (70.2)
Race		
White	3629 (92.9)	3609 (92.5)
Non-white	277 (7.1)	293 (7.5)
Prior use of osteoporosis medications		
Yes	1278 (32.7)	1189 (30.5)
No	2628 (67.3)	2713 (69.5)

[a]Percentages do not add up to 100% in all cases because of missing data at baseline for BMI ($n = 37$), estimated creatinine clearance ($n = 7$), femoral neck BMD T-score ($n = 39$), and prevalent vertebral fracture status ($n = 246$).

0.41, $p < 0.001$). As expected, older age, lower femoral neck BMD, and a history of prior vertebral or nonvertebral fractures were associated with higher risk of new vertebral fractures. Estimated creatinine clearance, BMI, and history of previous osteoporosis therapy were not predictors of new vertebral fracture risk. Overall, the efficacy of denosumab in reducing new vertebral fracture risk was similar for all nine subgroups analyzed ($p > 0.09$ for all treatment-by-subgroup interactions, Fig. 1). Significant effects were observed in subjects from Western and Eastern Europe, whereas the reduction in vertebral fracture risk was not significant in the smaller cohorts of subjects from both North and Latin America. The interaction with geography, however, was not significant ($p > 0.09$). A trend toward higher risk in whites than non-whites was not statistically significant.

Nonvertebral fracture

Three years of denosumab use reduced the incidence of nonvertebral fractures by 20% (hazard ratio 0.80; 95% CI 0.67 to 0.95, $p = 0.01$) in the overall study population. The absolute reduction in risk was 1.5% (8.0% with placebo and 6.5% with denosumab). The risk of nonvertebral fractures was increased in the placebo group for all of the subgroups evaluated: older age, lower femoral neck BMD, lower BMI, presence of prevalent vertebral fracture, and a history of nonvertebral fractures.

The effect of denosumab treatment on reduction in risk of nonvertebral fractures was similar (interaction p value > 0.05) in subjects older or younger than age 75 years and in those with or without prior nonvertebral fractures. In contrast, a significant difference in the response to denosumab treatment over 3 years was observed in three subgroup categories: BMI, femoral neck BMD *T*-score, and prevalent vertebral fracture (Fig. 2). Denosumab reduced the risk of nonvertebral fractures by 38% in women with a BMI < 25 kg/m^2 (3.4% absolute reduction in risk; 95% CI 1.5% to 5.3%). Similarly, denosumab reduced the risk of nonvertebral fractures by 35% in women with a femoral neck BMD *T*-score ≤ -2.5 (4.1% absolute reduction in risk; 95% CI 1.8% to 6.5%). Finally, the risk of nonvertebral fractures was reduced by 29% with denosumab in women without a prevalent vertebral fracture (2.1% absolute reduction in risk; 95% CI 0.7% to 3.4%).

Subgroup	Placebo (N = 3906) % (n/N)	Denosumab (N = 3902) % (n/N)	Risk Ratio (95% CI)	Interaction *P* value
Overall FREEDOM Population	7.2% (264/3691)	2.3% (86/3702)	0.32 (0.26, 0.41)	NA
Age (years)				0.4822
< 75	6.5% (166/2545)	2.0% (50/2547)	0.30 (0.22, 0.41)	
≥ 75	8.6% (98/1146)	3.1% (36/1155)	0.36 (0.25, 0.53)	
Body mass index (kg/m^2)				0.2909
< 25	7.3% (117/1605)	2.0% (33/1626)	0.28 (0.19, 0.41)	
25 to < 30	7.0% (104/1492)	2.8% (41/1462)	0.40 (0.28, 0.57)	
≥ 30	7.3% (42/575)	1.8% (11/599)	0.26 (0.13, 0.49)	
Estimated creatinine clearance (mL/min)				0.1315
< 60	7.1% (95/1342)	2.9% (39/1363)	0.41 (0.28, 0.58)	
≥ 60	7.2% (169/2346)	2.0% (47/2337)	0.28 (0.20, 0.38)	
Region				0.0986
Western EU, Australia, New Zealand	8.0% (138/1730)	1.9% (32/1721)	0.23 (0.16, 0.34)	
Eastern EU	7.1% (88/1248)	2.8% (36/1270)	0.40 (0.28, 0.59)	
Latin America	5.3% (23/436)	2.7% (12/447)	0.51 (0.26, 1.01)	
North America	5.4% (15/277)	2.3% (6/264)	0.41 (0.16, 1.04)	
Race				0.5166
White	7.3% (251/3427)	2.3% (80/3424)	0.32 (0.25, 0.41)	
Non-white	4.9% (13/264)	2.2% (6/278)	0.44 (0.17, 1.14)	
Prior use of osteoporosis medications				0.8209
Yes	7.7% (93/1208)	2.4% (27/1119)	0.31 (0.21, 0.48)	
No	6.9% (171/2483)	2.3% (59/2583)	0.33 (0.25, 0.44)	
Femoral neck BMD T-score				0.6398
≤ –2.5	9.9% (130/1309)	3.1% (40/1303)	0.31 (0.22, 0.44)	
> –2.5	5.6% (132/2367)	1.9% (45/2380)	0.34 (0.24, 0.47)	
Prevalent vertebral fracture				0.9248
Yes	13.6% (116/853)	4.6% (41/883)	0.34 (0.24, 0.48)	
No	5.2% (143/2727)	1.7% (45/2727)	0.31 (0.22, 0.44)	
Prior nonvertebral fracture				0.3545
Yes	9.4% (105/1118)	3.5% (39/1101)	0.38 (0.26, 0.54)	
No	6.2% (159/2568)	1.8% (47/2599)	0.29 (0.21, 0.40)	

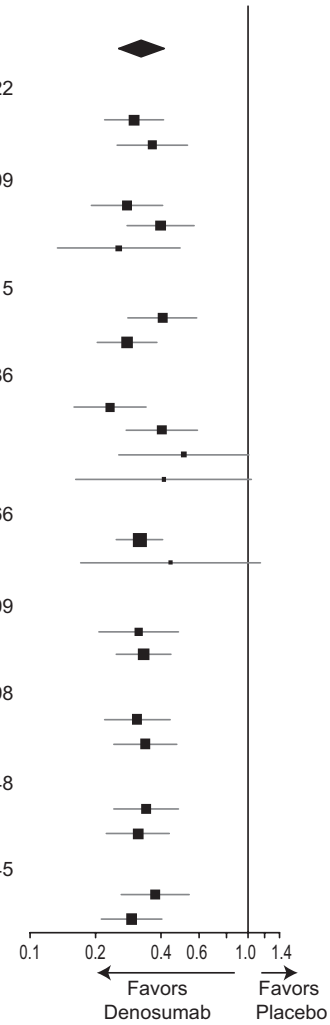

Fig. 1. Effect of denosumab treatment on new vertebral fractures by subgroup.

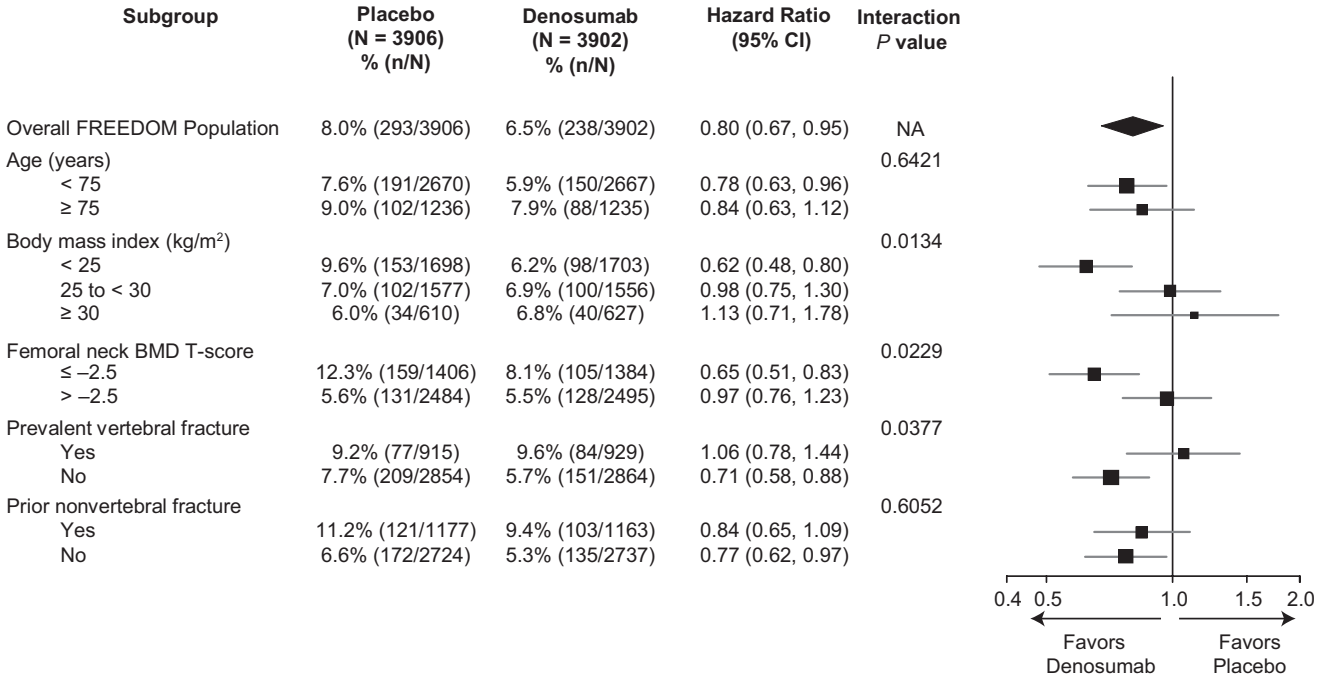

Fig. 2. Effect of denosumab treatment on nonvertebral fractures by subgroup.

There was not a significant effect of denosumab on nonvertebral fracture risk in women with a BMI $\geq 25\,kg/m^2$, a baseline femoral neck BMD *T*-score > -2.5, or a prevalent vertebral fracture.

Changes in femoral neck BMD in subgroups

Differences in the effect of therapy on fracture risk between subgroups could be expected if BMD responses to treatment differed in the subgroups. In the overall study population, denosumab, compared with placebo, improved femoral neck BMD by 5.2% (95% CI 5.0% to 5.4%) over 3 years. In exploratory analyses, the BMD response to denosumab was evident in all subgroups (Table 2). The 3-year improvement in femoral neck BMD was 5.7% (95% CI 5.3% to 6.1%) among subjects with a femoral neck BMD *T*-score ≤ -2.5 versus 5.0% (95% CI 4.7% to 5.2%) in those with a higher BMD (treatment-by-subgroup interaction $p = 0.002$). Similarly, the absolute change in BMD in response to denosumab therapy was different between these two subgroups (data not shown). There was also a trend toward greater relative net improvements in femoral neck BMD with lower BMI: 5.4% (95% CI 5.1% to 5.7%) among subjects with a BMI $< 25\,kg/m^2$; 5.2% (95% CI 4.9% to 5.5%) for those with a BMI between 25 and $< 30\,kg/m^2$; and 4.9% (95% CI 4.3% to 5.5%) in subjects with a BMI $\geq 30\,kg/m^2$. These differences were not statistically significant (treatment-by-subgroup interaction $p = 0.28$) and also could be explained by the lower baseline BMD in those with low BMI. Among the subgroup of women with a prevalent vertebral fracture at baseline, the improvement in

Table 2. Baseline Femoral Neck BMD *T*-score and Percent Change in Femoral Neck BMD at 36 Months Among Selected Subgroups

	Placebo			Denosumab		
	Baseline femoral neck BMD *T*-score	Femoral neck BMD % change from baseline at month 36		Baseline femoral Neck BMD *T*-score	Femoral neck BMD % change from baseline at month 36	
	Mean (SD)	LS Mean	(95% CI)	Mean (SD)	LS Mean	(95% CI)
Body mass index (kg/m²)						
<25	−2.3 (0.7)	−0.9%	(−1.2% to −0.6%)	−2.3 (0.7)	4.5%	(4.2% to 4.7%)
25 to <30	−2.1 (0.7)	−0.9%	(−1.2% to −0.6%)	−2.1 (0.7)	4.3%	(4.0% to 4.6%)
≥30	−1.9 (0.7)	−0.5%	(−1.0% to 0.0%)	−1.9 (0.7)	4.4%	(3.9% to 4.9%)
Femoral neck BMD *T*-score						
≤−2.5	−2.9 (0.3)	−0.6%	(−1.0% to −0.2%)	−2.9 (0.3)	5.1%	(4.7% to 5.5%)
>−2.5	−1.8 (0.5)	−0.9%	(−1.1% to −0.7%)	−1.7 (0.5)	4.1%	(3.8% to 4.3%)
Prevalent vertebral fracture						
Yes	−2.3 (0.7)	−0.9%	(−1.3% to −0.5%)	−2.3 (0.7)	4.7%	(4.3% to 5.1%)
No	−2.1 (0.7)	−0.8%	(−1.0% to −0.6%)	−2.1 (0.7)	4.3%	(4.1% to 4.5%)

LS = least squares.

femoral neck BMD was 5.6% (95% CI 5.1% to 6.1%) compared with 5.1% (95% CI 4.9% to 5.4%) in those without a prevalent vertebral fracture (treatment-by-subgroup interaction $p = 0.10$).

Discussion

Denosumab 60 mg every 6 months for 3 years in women with osteoporosis reduced the risk of new vertebral fractures to a similar degree in all subgroups tested. Similar consistency of treatment effect among subgroups has been observed with alendronate, risedronate, and strontium ranelate.[4–6,8,12] We did not observe different effects on new vertebral fracture risk in patients stratified by BMI or renal function as was seen with zoledronic acid.[7]

As has been observed in studies with some bisphosphonates, the effect of denosumab therapy on nonvertebral fracture risk was influenced by baseline BMD. As expected, in the placebo group, nonvertebral fracture risk was more than double (12.3% versus 5.6%) in the subgroup with a femoral neck BMD *T*-score ≤ -2.5 than those with a femoral neck BMD *T*-score > -2.5. We observed a 35% decreased risk with denosumab treatment in patients with femoral neck BMD *T*-score values consistent with osteoporosis, whereas no effect was observed in subjects with femoral neck BMD *T*-score values > -2.5. These results are similar to those observed with some other antiresorptives where the benefits of treatment on nonvertebral fractures were not evident in women with femoral neck BMD *T*-scores > -2.5. Current guidelines suggest that decisions about pharmacological treatment be made on the basis of absolute fracture risk, not solely on BMD. However, it remains to be proven that drug therapy reduces nonvertebral fracture risk in women who do not have osteoporosis by BMD criteria at the femoral neck, regardless of other risk factors.

Denosumab reduced nonvertebral fracture incidence in subjects with BMI $< 25\ kg/m^2$, whereas no effect was observed in subjects with BMI $\geq 25\ kg/m^2$. Again, fracture risk was higher in the subgroup with low BMI.

The reason for the treatment interactions with BMD and BMI is not clear. It could simply be a function of the lower risk of fractures in the subgroups in which treatment effect was not seen. However, BMD and BMI are highly correlated,[18,19] and subjects in the low BMD and low BMI subgroups show considerable overlap. The interaction between treatment and BMI and BMD may reflect a common underlying biology. The differences in BMD response among subgroups cannot account for the disparity in the apparent treatment effects. There are several possible explanations for an effect of BMI on treatment response, including differences in levels of leptin and other adipocytokines. Women with low BMI also tend to have lower estradiol levels[20,21] that increase bone turnover and fracture risk. Perhaps antiresorptive therapies are more effective in those with lower estradiol levels. Intracortical porosity is correlated with bone strength, and most bone loss in older women occurs from the surfaces of pores within the cortex.[22] It is possible that lower estradiol levels are associated with more cortical porosity and that inhibiting intracortical bone resorption has proportionally greater effects on biomechanical strength in patients with low estradiol, BMD, and BMI. In addition, the differences between heavy and light subjects could be due to differing effects of a fixed dose of drug. In a recent study, the clearance and volume of distribution of denosumab were correlated with body weight, as observed for other monoclonal antibodies, with modestly lower exposures for the fixed 60-mg-every-6-months dose regimen in heavier versus lighter subjects. However, this did not result in differences in pharmacodynamic effects.[22]

The effect of denosumab on nonvertebral fractures did not differ significantly by age or prior nonvertebral fractures. This is similar to subgroup analyses for other antiresorptive therapies. Although subjects with a prevalent vertebral fracture at baseline were at higher risk for nonvertebral fracture than those without a prevalent vertebral fracture, denosumab appeared to be more effective in reducing nonvertebral fractures in subjects without prevalent vertebral fractures compared with the higher-risk subset with prevalent vertebral fractures at baseline. The reason for this interaction is not clear. The proportion of patients with prevalent vertebral fractures in our study was low compared with other major osteoporosis studies and, because of the inclusion criteria of the study, the severity of these vertebral fractures was predominantly mild. As a consequence, the number of nonvertebral fractures observed in this subset of patients was relatively low. We have calculated that the power of our analysis to observe a 20% reduction in nonvertebral fracture risk in subjects with prevalent vertebral fractures (the effect observed in the overall study population) was 26%. The presence of a vertebral fracture appeared to be a weaker determinant of risk for nonvertebral fractures in this population than low BMD or low BMI.

A strength of our study is that all of the subgroups we tested were defined before the trial was unblinded, and analyses were limited to those that were specified in advance, in accordance with guidelines for subgroup analysis. We chose these groups based on findings from previous studies (age, BMD, and BMI) because of a possible biological interaction (BMI, renal function, prior therapy) or to test for consistency across populations, such as regions of the world.

As is true for all subgroup analyses, our study has important limitations.[16] Subgroup analyses inherently have limited power to detect interactions in small subgroups with few events. In this study, the subgroups in which a significant effect was not observed were either small or had a low risk of fracture (nonwhites, North and Latin America, higher BMD and BMI, prevalent vertebral fractures, and prior nonvertebral fractures). Thus, our analyses cannot exclude the possibility that treatment has an effect in these small or lower-risk subgroups because our study was not powered for these subanalyses. In addition, no adjustment was made for the multiple analyses undertaken.

In summary, in postmenopausal women with osteoporosis, denosumab therapy for 3 years was similarly effective in reducing the incidence of new vertebral fractures among various predefined subgroups of risk factors. However, the effect of therapy on nonvertebral fracture risk appeared to be greater in subjects with low femoral neck BMD rather than those with higher BMD, in those with lower rather than higher BMI, and in those without rather than with a prevalent vertebral fracture at baseline.

Disclosures

MRM has received research grants and served as a consultant, advisor, lecturer, and speaker for Amgen Inc. He also receives consultant fees from Lilly, Merck, Novartis, and Warner Chilcott. SB has received funding for serving as a trial investigator and a member of a steering committee for Amgen Inc. He has also received consulting fees and lecture fees from Amgen Inc. He is senior clinical investigator of the Fund for Scientific Research, Flanders, Belgium (F.W.O.-Vlaanderen). OT has served on advisory boards and in speaker bureaus for Amgen Inc., GSK, Novartis, Nycomed, and Sanofi-Aventis and has been a clinical trial investigator for Amgen Inc., Novartis, and Sandoz. RR has served on advisory boards and in speaker bureaus for Amgen Inc., Eli Lilly, Novartis, Roche, Merck, Nycomed, Servier, and Danone. HGB has received research support, consulting fees, and speaker's honoraria from Amgen Inc., as well as research support from Merck, Nordic Bioscience, Novartis, and Takeda, and consulting fees from Merck, Takeda, and Tarsa Pharmaceuticals. C-LB has received research support and has served as a consultant, speaker, and advisory board member for Amgen Inc., Novartis, Roche, Servier, and Warner Chilcott. WFL has received speaker's fees and consulting fees from Amgen Inc., Merck, Procter and Gamble, Novartis, Lilly, Servier, and Roche. SM has served as speaker for Amgen Inc., Eli Lilly, Merck Sharp & Dohme, Nycomed, Roche, and Warner Chilcott. He also served on a local advisory board of Amgen Inc., Eli Lilly, Medtronic, and Novartis. JH has received fees for consultation and speaking for Amgen Inc. HCH is employed by CCBR, a company engaged in contract research with pharmaceutical companies including Amgen Inc., and has received lecture and consulting fees from Amgen Inc. RE has received consulting fees from Amgen Inc., Novartis, Pfizer, Procter and Gamble, Servier, Ono, and GSK. He also received lecture fees from Amgen Inc. and Eli Lilly, and grant support from Amgen Inc., AstraZeneca, Procter and Gamble, and Novartis. AW and SS are employees of Amgen Inc. and own stock/stock options in Amgen Inc. SRC has received research grants from Amgen Inc. and has served as a consultant for Amgen Inc., Merck, Novartis, Eli Lilly, Pfizer, and Medtronic.

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