Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension

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ABSTRACT
Denosumab reduces bone resorption and vertebral and nonvertebral fracture risk. Denosumab discontinuation increases bone turnover markers 3 months after a scheduled dose is omitted, reaching above-baseline levels by 6 months, and decreases bone mineral density (BMD) to baseline levels by 12 months. We analyzed the risk of new or worsening vertebral fractures, especially multiple vertebral fractures, in participants who discontinued denosumab during the FREEDOM study or its Extension. Participants received ≥2 doses of denosumab or placebo Q6M, discontinued treatment, and stayed in the study ≥7 months after the last dose. Of 1001 participants who discontinued denosumab during FREEDOM or Extension, the vertebral fracture rate increased from 1.2 per 100 participant-years during the on-treatment period to 7.1, similar to participants who received and then discontinued placebo (n = 470; 8.5 per 100 participant-years). Among participants with ≥1 off-treatment vertebral fracture, the proportion with multiple (>1) was larger among those who discontinued denosumab (60.7%) than placebo (38.7%; p = 0.049), corresponding to a 3.4% and 2.2% risk of multiple vertebral fractures, respectively. The odds (95% confidence interval) of developing multiple vertebral fractures after stopping denosumab were 3.9 (2.1–7.2) times higher in those with prior vertebral fractures, sustained before or during treatment, than those without, and 1.6 (1.3–1.9) times higher with each additional year of off-treatment follow-up; among participants with available off-treatment total hip (TH) BMD measurements, the odds were 1.2 (1.1–1.3) times higher per 1% annualized TH BMD loss. The rates (per 100 participant-years) of nonvertebral fractures during the off-treatment period were similar (2.8, denosumab; 3.8, placebo). The vertebral fracture rate increased upon denosumab discontinuation to the level observed in untreated participants. A majority of participants who sustained a vertebral fracture after discontinuing denosumab had multiple vertebral fractures, with greatest risk in participants with a prior vertebral fracture. Therefore, patients who discontinue denosumab should rapidly transition to an alternative antiresorptive treatment. Clinicaltrails.gov: NCT00089791 (FREEDOM) and NCT00523341 (Extension). © 2017 American Society for Bone and Mineral Research.

KEY WORDS: DENOSUMAB; VERTEBRAL FRACTURES; MULTIPLE VERTEBRAL FRACTURES; BONE RESORPTION; DISCONTINUATION

Introduction
Denosumab reduces bone resorption and improves bone mineral density (BMD).1,2 In FREEDOM, a 3-year randomized study of denosumab in postmenopausal women with osteoporosis, denosumab given subcutaneously (sc) once every 6 months (Q6M) for 3 years reduced the risk of vertebral fractures detected on radiographs by 68%, along with significant reductions in nonvertebral and hip fractures.3 The low rates continued through the active-treatment Extension study.4-6

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Unlike bisphosphonates, denosumab is not incorporated into bone; therefore, its effect on bone resorption stops after treatment discontinuation (ie, a scheduled dose is omitted). A randomized, placebo-controlled trial evaluated the effects of discontinuing denosumab. Four 60-mg doses of denosumab Q6M over 24 months decreased bone turnover, as measured by serum CTx and serum P1NP, and increased lumbar spine BMD by 6.4% and total hip BMD by 3.6% compared with placebo. Mean CTx began increasing by month 27, reaching a peak 63% median increase above baseline at 30 months and returned to baseline by 48 months. P1NP displayed a similar pattern. Spine and total hip BMD decreased to baseline by 36 months. In another study, discontinuing denosumab 210 mg Q6M after 2 years resulted in similar increases in CTx levels above baseline, with a decrease in spine and total hip BMD to baseline by 12 months after discontinuation.

An analysis of FREEDOM assessing fracture risk in 797 participants who discontinued treatment after receiving at least two doses of denosumab found no increase in the risk of a combination of nonvertebral and vertebral fractures (hazard ratio = 0.82; 95% confidence interval [CI] 0.49–1.38) during a median 0.5 years of off-treatment follow-up. However, the effects of discontinuation on the risk of vertebral fractures were not analyzed separately.

There have been case reports of patients who developed multiple new vertebral fractures after discontinuation of denosumab. These reports, which have been aggregated in a recent review, could not analyze changes in risk of vertebral fractures after discontinuation of denosumab compared with the rate during treatment with or after discontinuation of placebo.

To estimate the risks of new or worsening vertebral fractures, particularly multiple vertebral fractures, after cessation of denosumab, we analyzed data of participants from the FREEDOM study and its Extension who discontinued denosumab or placebo and continued study participation.

Materials and Methods

Participants in the studies

We used data from the 3-year FREEDOM study and its 7-year Extension. FREEDOM was a randomized, placebo-controlled study of 7808 postmenopausal 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. Participants were excluded from FREEDOM if they had taken an oral bisphosphonate for ≥3 years cumulatively. If they had taken an oral bisphosphonate for ≥3 months but <3 years, they were eligible if they had ≥1 year washout between the last dose and enrollment. Participants who used intravenous bisphosphonate, fluoride, or strontium for osteoporosis within the past 5 years were excluded. Participants were randomized to receive placebo or denosumab 60 mg sc Q6M for 3 years along with 1 g supplemental calcium and >400 IU of vitamin D daily. Participants who completed the last visit at year 3 in FREEDOM and missed ≤1 dose of denosumab or placebo could enroll in the Extension to receive open-label denosumab 60 mg Q6M for 7 years; participants randomized to denosumab in FREEDOM could receive denosumab for up to 10 years, whereas those randomized to placebo could receive denosumab for up to 7 years. Participants were encouraged to remain enrolled in the study and continue with study assessments should the investigational product be discontinued in FREEDOM or Extension. All research complied with the World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects. The study 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. All participants provided informed consent.

As in a previous study, participants in FREEDOM and the Extension who received ≥2 doses of denosumab or placebo, discontinued treatment, and continued to participate in the study for ≥7 months (6 months since the last dose received plus a 1-month study-visit window) were included in the off-treatment analysis. At least two doses were required because 12 months is the earliest time point at which antifracture efficacy has been observed with denosumab treatment.

Participants in the Extension continued to have thoracic and lumbar spine radiographs per scheduled assessments in the protocol—years 5, 6, 8, and 10 from FREEDOM baseline (ie, years 2, 3, 5, and 7 of the Extension)—as well as unscheduled assessments due to back pain.

Vertebral fractures, including clinical vertebral fractures largely captured during unscheduled assessments by the investigator, were identified by a central facility (Synarc, Inc.) using a semiquantitative (SQ) grading scale. A prevalent vertebral fracture was defined as a vertebral body with a semiquantitative grade ≥1 at baseline. When compared with the most recent on-treatment spine radiograph, an off-treatment new vertebral fracture was defined by ≥1 grade increase from a previous grade 0 (ie, normal) in any vertebra between T4 and L4, and an off-treatment worsening vertebral fracture was defined by ≥1 grade increase from a previous vertebral fracture. Both new and worsening vertebral fractures were considered and analyzed as off-treatment vertebral fractures. Multiple vertebral fractures were defined as ≥2 new and/or worsening vertebral fractures confirmed on either a single or serial spine radiographs during the off-treatment period. Nonvertebral fractures required confirmation by a radiologist’s report or diagnostic imaging. Lumbar spine and proximal femur BMD assessments continued in the Extension protocol at years 1, 2, 3, 5, and 7 of the Extension. During the off-treatment period, if the study investigator determined that the overall fracture risk of a participant required additional treatment for osteoporosis, they could treat the participants with an approved therapy.

Statistical methods

To account for variable follow-up duration after discontinuing treatment, data were summarized by exposure-adjusted participant incidence of vertebral fractures per 100 participant-years with 95% CI. Because of the small number of participants sustaining vertebral fractures during the off-treatment period, the off-treatment vertebral fracture rate for the denosumab group was calculated based on participants who discontinued denosumab during either FREEDOM or Extension. Potential predictors of off-treatment vertebral fracture and multiple vertebral fractures, defined at the beginning of and during both on- and off-treatment periods, were included in multiple logistic regression models with stepwise selection procedure. Treatment group was included at all steps. The covariates at treatment baseline included prevalent vertebral fracture; prior nonvertebral fracture; age; body mass index (BMI); BMD T-scores at the lumbar spine, total hip, and femoral neck; and CTx at FREEDOM baseline. Covariates associated with treatment phase included treatment duration; prior bisphosphonate use,
defined as bisphosphonate use initiated before or during treatment; annualized on-treatment total hip and femoral neck BMD percentage change; incident vertebral fracture; and incident nonvertebral fracture. Vertebral fractures sustained before or during treatment were combined as prior vertebral fractures with respect to the off-treatment period. The covariates assessed during the off-treatment period included age at the beginning of the off-treatment period (ie, 7 months after the last dose), off-treatment follow-up duration, use of postdiscontinuation osteoporosis therapy (excluding therapies initiated after the off-treatment vertebral fracture, if any), and annualized off-treatment total hip and femoral neck BMD percentage change between last on-treatment and last off-treatment BMD measurement, if available.

Results

Of the 1783 participants who discontinued treatment in FREEDOM, data beyond 7 months from the last dose were available for 470 participants from the placebo group and 327 participants from the denosumab group; of the 1995 participants who discontinued denosumab in the Extension, data were available for 678 (Fig. 1). The reasons for discontinuing treatments during FREEDOM were similar between the denosumab and placebo groups except that more participants in the placebo group discontinued because of disease progression and requirement for alternative therapy (Table 1). The median (quartile [Q] 1, Q3) follow-up time during the off-treatment period was 0.5 (0.3, 1.4) years after discontinuing placebo and 0.5 (0.2, 1.4) and 0.2 (0.1, 0.7) years after discontinuing denosumab in FREEDOM and Extension, respectively (Table 2). Of participants who discontinued denosumab during the Extension, 70% discontinued study participation within 6 months into the off-treatment period. Characteristics at FREEDOM baseline of participants in the off-treatment study were similar to FREEDOM or Extension (Table 2). Prevalent vertebral fractures at FREEDOM baseline were present in 26% of participants who discontinued placebo and 27% and 23% of participants who discontinued denosumab in FREEDOM and Extension, respectively.

At least one spine radiograph was taken during the off-treatment period in 327 of 470 (69.6%) participants from FREEDOM placebo, 205 of 327 (62.7%) from FREEDOM denosumab, and 270 of 678 (39.8%) from Extension. More than 97% of 1214 spine radiographs during the off-treatment period were taken at scheduled visits.

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**Fig. 1.** Flow of participants from FREEDOM or its Extension through treatment discontinuation and fracture occurrence. The off-treatment follow-up period begins from the last dose plus 7 months through the end of study. *The 4 participants who were included in both FREEDOM and Extension off-treatment analyses were not counted double. DMAb = denosumab; EXT = Extension; FU = follow-up; OP Tx = osteoporosis therapy; PBO = placebo; VFx = vertebral fracture.*
Table 1. Reasons for Discontinuation of the Investigational Product by Participants Who Were Included or Excluded From the FREEDOM and Extension Off-Treatment Analysis

<table>
<thead>
<tr>
<th>Reason</th>
<th>FREEDOM placebo</th>
<th>FREEDOM denosumab</th>
<th>Extension denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Includeda (N = 470) n (%)</td>
<td>Excludedb (N = 520) n (%)</td>
<td>Includeda (N = 327) n (%)</td>
</tr>
<tr>
<td>Ineligibility determined</td>
<td>1 (0.2)</td>
<td>8 (1.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>16 (3.4)</td>
<td>11 (2.1)</td>
<td>11 (3.4)</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>4 (0.9)</td>
<td>13 (2.5)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>124 (26.4)</td>
<td>79 (15.2)</td>
<td>104 (31.8)</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>92 (19.6)</td>
<td>230 (44.2)</td>
<td>64 (19.6)</td>
</tr>
<tr>
<td>Participant requestc</td>
<td>54 (11.5)</td>
<td>32 (6.2)</td>
<td>54 (16.5)</td>
</tr>
<tr>
<td>Disease progressionc</td>
<td>56 (11.9)</td>
<td>7 (1.3)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Requirement for alternative therapy</td>
<td>60 (12.8)</td>
<td>9 (1.7)</td>
<td>24 (7.3)</td>
</tr>
<tr>
<td>Administrative decision</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>16 (3.4)</td>
<td>22 (4.2)</td>
<td>12 (3.7)</td>
</tr>
<tr>
<td>Death</td>
<td>8 (1.7)</td>
<td>50 (9.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (3.6)</td>
<td>19 (3.7)</td>
<td>22 (6.7)</td>
</tr>
</tbody>
</table>

N/A = not applicable.
aParticipants who discontinued treatment after receiving ≥2 doses of investigational product and were followed for ≥7 months after the last dose were included in the off-treatment analysis.
bParticipants who discontinued treatment after receiving 1 dose of investigational product or ≥2 doses of investigational product and were followed for <7 months after the last dose were excluded from the off-treatment analysis.
c“Participant request” and “disease progression” were not included as possible reasons for discontinuing treatment on the End of Investigational Product Case Report Form (CRF) in the Extension.

Table 2. Characteristics of Participants at FREEDOM Baseline in the Off-Treatment Study Compared With Characteristics of Those Who Participated in the FREEDOM Study and Extension

<table>
<thead>
<tr>
<th>Characteristic (mean values)</th>
<th>FREEDOM Discontinued treatment from FREEDOM and had &gt;7 months of follow-up</th>
<th>FREEDOM Extension Discontinued treatment from FREEDOM Extension and had &gt;7 months of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All FREEDOM participants (N = 7808)</td>
<td>Placebo (N = 470)</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Age at the beginning of off-treatment study (years)</td>
<td>N/A</td>
<td>75</td>
</tr>
<tr>
<td>Baseline vertebral fracture (%)</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Off-treatment follow-up time (years)</td>
<td>N/A</td>
<td>0.5 (0.3–1.4)</td>
</tr>
<tr>
<td>Baseline lumbar spine BMD T-score</td>
<td>–2.8</td>
<td>–2.8</td>
</tr>
<tr>
<td>Baseline total hip BMD T-score</td>
<td>–2.1</td>
<td>–2.0</td>
</tr>
<tr>
<td>Baseline serum CTx, ng/dL</td>
<td>0.578</td>
<td>0.604</td>
</tr>
</tbody>
</table>

N/A = not applicable.
aMedian (interquartile range).
Fracture rates after discontinuing treatment

Among 1471 participants who discontinued treatment during FREEDOM or Extension with ≥7 months of follow-up after the last dose (1001, denosumab; 470, placebo), the rate (95% CI) of vertebral fractures (new and worsening) was lower during the on-treatment period in participants receiving denosumab compared with placebo (1.2 [0.9–1.6] versus 7.0 [5.2–8.7] per 100 participant-years; Fig. 2A). After discontinuing denosumab, the rate (95% CI) of vertebral fractures increased to 7.1 (5.2–9.0) per 100 participant-years, similar to the rate before and after discontinuing placebo (7.0 [5.2–8.7] and 8.5 [5.5–11.5] per 100 participant-years, respectively) (Fig. 2A). Among the 56 participants who developed at least one vertebral fracture after stopping denosumab, 34 (60.7%) had multiple vertebral fractures: 21 had 2 to 3, and 13 had ≥4. Among the 31 participants who developed at least one vertebral fracture after stopping placebo, 12 (38.7%) had multiple vertebral fractures: 10 had 2 to 3, and 2 had ≥4. The rate (95% CI) of multiple vertebral fractures was slightly higher after discontinuing denosumab than placebo (4.2 [2.8–5.7] versus 3.2 [1.4–5.1] per 100 participant-years; Fig. 2B). Vertebral fracture rates were higher in participants with prevalent vertebral fracture that had been sustained before treatment (Fig. 3).

Among participants who sustained a vertebral fracture after stopping denosumab or placebo, most had only new vertebral fractures (49/56 and 26/31, respectively). Two participants had only worsening vertebral fractures after stopping placebo; the remainder of participants had both new and worsening vertebral fractures (7 and 3 after stopping denosumab and placebo, respectively). Some participants also sustained clinically recognized vertebral fractures: 22/56 (39.3%) after stopping denosumab and 7/31 (22.6%) after stopping placebo. Among 34 and 12 participants who had multiple vertebral fractures after stopping denosumab and placebo, 16 (50.0%) and 4 (33.3%) were clinically recognized as multiple vertebral fractures, respectively. In addition, among participants who had a vertebral fracture after discontinuation, 82% in the denosumab group and 71% in the placebo group had at least one vertebra with a SQ increase of at least 2 grades from the previous radiograph.

During the follow-up intervals, 23 of 1001 participants who discontinued denosumab and 14 of 470 who discontinued placebo had at least one nonvertebral fracture, representing rates (95% CI) of 2.8 (1.7–4.0) and 3.8 (1.8–5.8) per 100 participant-years, respectively.

Comparisons of participants who fractured and those who did not after discontinuing treatment

Among participants who discontinued treatment and stayed in the study, there were no noticeable differences in age; BMI; and lumbar spine, total hip, and femoral neck BMD T-scores at treatment baseline between (i) participants who sustained off-treatment vertebral fracture versus those who did not and (ii) participants who sustained single versus multiple vertebral fractures (in either FREEDOM or Extension). There were also no noticeable differences in baseline levels of bone resorption (assessed by serum CTx at FREEDOM baseline); treatment duration; and lumbar spine, total hip, and femoral neck BMD T-scores at the beginning of the off-treatment period between the subgroups listed above. However, participants with vertebral fracture had longer median (Q1, Q3) follow-up time (years) compared with those without vertebral fracture after discontinuation of placebo (1.4 [0.4–1.9] versus 0.5 [0.2–1.4]) or denosumab (1.3 [0.5–1.4] versus 0.5 [0.2–1.4]) in FREEDOM and after discontinuation of denosumab in Extension (1.4 [0.4–3.4] versus 0.2 [0.1–0.6]).

Postdiscontinuation osteoporosis therapies

Excluding osteoporosis therapies initiated after off-treatment vertebral fracture, 145 (14.5%) participants from the combined denosumab group and 201 (42.8%) from FREEDOM placebo received osteoporosis therapy after their last dose (Table 3); overall, 88% of these participants received oral bisphosphonates.
The rates of vertebral fracture per 100 participant-years were similar between the two subgroups and balanced between the treatment groups (denosumab versus placebo: 8.0 versus 9.1 [1.1 difference, 95% CI 0.6–2.2] for those receiving therapy and 6.7 versus 7.9 [1.2 difference, 95% CI 0.6–2.2] for those not receiving therapy). Osteoporosis therapies were initiated somewhat earlier in the placebo group, perhaps because those subjects had a lower BMD at the end of treatment than participants in the denosumab group.

**Off-treatment change in BMD**

Approximately half of participants included in the current analysis had hip dual-energy X-ray absorptiometry (DXA) assessments at scheduled visits during the off-treatment period in FREEDOM and Extension. Among 465 combined denosumab and 307 placebo participants with available off-treatment BMD change, the mean annualized percentage change in total hip BMD was −1.9% and +0.6% per year after stopping denosumab and placebo, respectively, for those with no off-treatment vertebral fracture; −2.2% and −1.3% per year for those with single vertebral fracture; and −3.5% and −1.2% per year for those with multiple vertebral fractures. Among participants stopping denosumab, those with multiple vertebral fractures had significantly greater annualized BMD loss than those without any vertebral fracture (−3.5% versus −1.9%; p = 0.014); however, changes in BMD would be smaller during intervals of less than 1 year.

**Predictors of off-treatment multiple vertebral fractures**

From the multivariate logistic regression model, prior vertebral fracture was the strongest predictor of off-treatment multiple vertebral fractures (odds ratio [OR] = 3.9; 95% CI 2.1–7.2), followed by off-treatment duration (OR = 1.6; 95% CI: 1.3–1.9; Table 4). Among participants with available BMD change assessment during the off-treatment period (n = 772), annualized percentage change in total hip BMD after discontinuation (between the last on- and off-treatment BMD assessments [range, 1–7 years]) was weakly associated with multiple vertebral fractures (OR = 1.2; 95% CI: 1.1–1.3). Original treatment group (combined denosumab vs placebo), duration of on-treatment

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**Table 3. Summary of Vertebral Fractures in Participants Who Discontinued Placebo or Denosumab in the FREEDOM Study or Denosumab in the Extension by Postdiscontinuation Osteoporosis Therapy Status**

<table>
<thead>
<tr>
<th>Osteoporosis therapy: yes</th>
<th>Osteoporosis therapy: no</th>
</tr>
</thead>
</table>
| **FREEDOM placebo**  
N = 201 | Combined denosumab  
N = 145 | **FREEDOM placebo**  
N = 269 | Combined denosumab  
N = 856 |
| Vertebral fractures, n (%) | 18 (9.0) | 19 (13.1) | 13 (4.8) | 37 (4.3) |
| Single, n (%) | 10 (5.0) | 6 (4.1) | 9 (3.3) | 16 (1.9) |
| Multiple, n (%) | 8 (4.0) | 13 (9.0) | 4 (1.5) | 21 (2.5) |
| Rate per 100 participant-years (95% CI) | 9.1 (4.9–13.3) | 8.0 (4.3–11.8) | 7.9 (3.6–12.1) | 6.7 (4.5–8.9) |
| Single | 4.9 (1.8–7.9) | 2.4 (0.5–4.3) | 5.4 (1.9–8.9) | 2.8 (1.4–4.2) |
| Multiple | 4.0 (1.2–6.8) | 5.4 (2.3–8.4) | 2.4 (0.0–4.7) | 3.8 (2.1–5.4) |

N/A = not applicable; Q = quartile.
Table 4. Significant Predictors of Off-treatment Multiple Vertebral Fractures Based on a Multivariate Logistic Regression Model

<table>
<thead>
<tr>
<th>Significant covariates</th>
<th>1471 Participants included&lt;sup&gt;a&lt;/sup&gt;</th>
<th>772 participants included&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior VFx&lt;sup&gt;c&lt;/sup&gt; (yes versus no)</td>
<td>3.9 (2.1–7.2)</td>
<td>3.6 (1.8–7.1)</td>
</tr>
<tr>
<td>Off-treatment duration (per year)</td>
<td>1.6 (1.3–1.9)</td>
<td>1.4 (1.1–1.7)</td>
</tr>
<tr>
<td>Off-treatment annualized total hip BMD loss&lt;sup&gt;d&lt;/sup&gt; (per 1%)</td>
<td>Not included</td>
<td>1.2 (1.1–1.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1471 participants included 470 participants who discontinued placebo and 1001 participants who discontinued denosumab.

<sup>b</sup> 772 participants included 307 participants who discontinued placebo and 465 participants who discontinued denosumab, and had available off-treatment annualized total hip BMD change assessments.

<sup>c</sup> Prior VFx<sup>c</sup> includes any VFx sustained before or during treatment.

<sup>d</sup> Off-treatment annualized total hip BMD loss<sup>d</sup> was defined as annualized percent change in total hip BMD after treatment discontinuation, ie, between the last on- and off-treatment BMD assessments.

Discussion

Among participants who discontinued denosumab, the risk of new and worsening vertebral fractures quickly increased to levels similar to the risk in untreated participants; about half of participants who sustained a vertebral fracture sustained more than one. Furthermore, the risks of single and multiple vertebral fractures were higher among participants who had a history of vertebral fracture before or during FREEDOM or Extension. This confirms case reports of multiple vertebral fractures occurring after stopping denosumab.<sup>10–15</sup> These data further demonstrate that patients at high risk, particularly those with prior vertebral fractures, should continue therapy. Furthermore, physicians who prescribe denosumab should carefully track the dates when a patient’s dose of denosumab is due and decide whether to continue or switch to an alternative treatment.

The increased risk of vertebral fracture soon after stopping denosumab may be due to the increase in bone resorption within 3 months after a scheduled dose is omitted. Rapid increases in bone turnover after stopping denosumab combined with our observation of an increased risk of vertebral fractures during a median of 0.5 and 0.2 years of follow-up in FREEDOM and Extension, respectively, raises the possibility that missing one dose—or delaying a dose by a few months—may put the patient at an increased risk of vertebral fractures.<sup>15</sup>

Those who developed multiple vertebral fractures had a higher rate of BMD loss than those who developed a single vertebral fracture; however, the value of monitoring BMD soon after a scheduled dose is omitted is uncertain: The difference in annualized change in BMD in this analysis was small and would be much smaller still if assessed at 6 months, when the increased risk of vertebral fracture was already apparent. Additionally, too few participants received treatment after discontinuation of denosumab to draw conclusions from this study regarding the value of alternative osteoporosis treatment after denosumab discontinuation.

We found no difference in the rate of nonvertebral fractures after discontinuing denosumab or placebo; however, the number of fractures was small and the duration of follow-up was short. This is consistent with the previous analysis of the rates of all fractures after discontinuation of denosumab or placebo in the FREEDOM study, which found no increase in the risk of a combination of nonvertebral and vertebral fractures (hazard ratio = 0.82; 95% CI 0.49–1.38) compared with placebo during a median of 0.5 years of off-treatment follow-up.<sup>9</sup> That analysis did not analyze nonvertebral and vertebral fractures separately. However, this suggests that discontinuation of denosumab has a different effect on risk of nonvertebral fractures. There is apparently no early increase in nonvertebral fractures but an increase in multiple vertebral fractures after discontinuing denosumab. It is possible that the increase in cortical bone mass after at least 2 years of denosumab treatment and little change soon after discontinuation compensates for the biomechanical effects of increased resorption of trabecular and endocortical bone when denosumab is discontinued. In contrast, high rates of bone turnover have greater adverse effects on the amount and microstructure of trabecular bone that makes a much greater contribution to the strength of vertebral bodies.<sup>17</sup>

Bisphosphonates bind to the surface of bone and recirculate in the local microenvironment long after treatment cessation, accounting for the persistent gains in BMD and continued decreases in bone resorption. Other treatments (eg, raloxifene, estrogen, and teriparadine) improve bone mass and decrease fracture risk during treatment, but bone turnover returns to baseline levels and efficacy for fracture risk is lost after treatment discontinuation.<sup>18</sup> Thus, if a reversible antiresorptive treatment for osteoporosis is discontinued, a period of treatment with a bisphosphonate or use of another antiresorptive agent should be considered to preserve the gains in BMD and reduction in fracture risk. The findings presented here indicate that if patients receive two or more doses of and then discontinue denosumab, they should transition rapidly to another antiresorptive therapy, especially patients with a history of vertebral fracture.

This analysis has several limitations. A minority of participants who discontinued denosumab or placebo in FREEDOM and Extension were observed beyond 7 months after their last dose. The off-treatment follow-up period was short for the vast majority of participants, and there was no systematic surveillance for vertebral fractures after treatment cessation. This study of treatment withdrawals was not designed for long-term off-treatment follow-up, nor was it based on a randomized comparison of those who discontinued placebo or denosumab. Because of the very short follow-up period, only a minority of participants who discontinued from Extension had a scheduled radiograph and, therefore, the analysis may have substantially underestimated the risk of vertebral fracture after discontinuing denosumab in those...
participants. There was no placebo comparison group for participants in the Extension. Somewhat more participants in the placebo than denosumab group had discontinued study treatment because of disease progression or requirement for alternative therapy. Among participants who had a vertebral fracture after treatment discontinuation, 11/31 (35%) from the placebo group and 1/56 (2%) from the denosumab group discontinued treatment for either reason listed above. These imbalances might explain the higher risk of vertebral fracture after stopping placebo; as such, the risk of vertebral fracture after stopping denosumab would even more closely resemble the risk in those who stopped placebo (Fig. 2A).

The analysis had insufficient power to determine whether participants who discontinued treatment and had a vertebral fracture during the off-treatment period lost more BMD than those who discontinued and did not have a vertebral fracture. BMD data during the off-treatment period were not available for all participants, and the timing of BMD assessment during the off-treatment period relative to the last dose of placebo or denosumab, as well as the occurrence of fracture, varied among participants. Because bone turnover markers were measured only in a small subset of participants after discontinuation, this study cannot assess whether monitoring bone turnover after treatment discontinuation identifies patients at highest risk of vertebral fracture.

Nevertheless, these data are the best available: They include a placebo group and compare rates of fracture during and after treatment. Vertebral fractures were assessed by a standardized method and blinded to the participant’s treatment in FREEDOM.

In conclusion, denosumab substantially reduces the risk of vertebral fractures, and soon after treatment discontinuation, a patient’s risk of vertebral fracture returns to the level before treatment initiation. Additionally, more than half of patients who sustain a vertebral fracture have multiple vertebral fractures. Physicians should keep careful track of the dates when a patient’s next dose of denosumab is due. If a patient discontinues denosumab, particularly if she has had a vertebral fracture, the patient should promptly receive a bisphosphonate or another antiresorptive agent to prevent the increased risk of vertebral fractures, especially multiple vertebral fractures, that develop soon after stopping denosumab.

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