

The Effect of Discontinuing Denosumab in Patients With Rheumatoid Arthritis Treated With Glucocorticoids

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Objective. To evaluate changes in bone turnover and bone mineral density (BMD) in patients with rheumatoid arthritis (RA) receiving glucocorticoids, after discontinuation of denosumab for 12 months.

Methods. We conducted a randomized, double-blind, placebo-controlled, phase II study of RA patients. Patients received placebo, denosumab 60 mg, or denosumab 180 mg every 6 months for 12 months and were followed up for an additional 12 months after discontinuation, during which no bone loss prevention therapy was instituted. Changes from baseline in serum C-terminal telopeptide of type I collagen (CTX), serum procollagen type I N-terminal propeptide (PINP), and lumbar spine and total hip BMD were evaluated.

Results. In this post hoc analysis of patients treated with glucocorticoids at study baseline ($n = 82$), levels of CTX and PINP decreased significantly from baseline in both denosumab groups. Following denosumab discontinuation, CTX returned to baseline and was not significantly different from the placebo group 6 and 12 months after discontinuation. Median percentage changes from baseline PINP in those treated with denosumab 60 mg were -0.16% and 15.3% at 6 and 12 months, respectively, after discontinuation ($P = 0.062$ and $P = 0.017$, versus placebo); corresponding changes with denosumab 180 mg were 9.0% and 75.8% , respectively ($P = 0.018$ and $P = 0.002$ versus placebo). Compared to placebo, lumbar spine and total hip BMD increased in patients receiving denosumab and returned to baseline 12 months after discontinuation. No osteoporotic fractures were reported during treatment or in the off-treatment period.

Conclusion. In this analysis of short-term denosumab use in RA patients receiving glucocorticoids, denosumab discontinuation resulted in a gradual increase in bone turnover, which was associated with a return to baseline lumbar spine and total hip BMD.

INTRODUCTION

Patients with rheumatoid arthritis (RA) often experience bone loss that can be exacerbated by their frequent use of glucocorticoids, leading to an increased risk of fragility fractures (1–3). Mechanisms underlying the adverse effects of glucocorticoids on fracture risk include decreased bone formation and increased bone resorption, which is driven in part by greater expression of RANKL and reduced expression of the RANKL inhibitor osteoprotegerin (4–6). In general, patients receiving glucocorticoids have a higher risk of spine and hip fractures (7),

which may be twice that of RA patients who are not receiving glucocorticoids (8,9).

Denosumab, a monoclonal antibody that inhibits RANKL, is approved for the treatment of glucocorticoid-induced osteoporosis in the US and other countries (10). Patients receiving glucocorticoids may have only transient indications for bone therapies, such as denosumab, if glucocorticoids are stopped. Unlike bisphosphonates, denosumab does not bind to bone matrix, and denosumab's clearance from the circulation is accompanied by a loss of its antiresorptive effect (11). Studies involving 2 years of denosumab therapy show that denosumab discontinuation leads

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to a transient increase in bone turnover markers (BTMs) above baseline levels, with peak levels occurring ~12 months after the last administered dose and resolution ~12 months later (12,13). This transient high-turnover state is associated with a reduction in bone mineral density (BMD) (12,13) and an increased risk of vertebral fractures, particularly multiple vertebral fractures (14). Therefore, it is necessary to better understand the effects of denosumab discontinuation, including bone turnover and BMD responses, in RA patients receiving glucocorticoid therapy. Further, the optimal timing and type of subsequent therapy on denosumab discontinuation is an important topic for patients and clinicians.

The primary objective of this post hoc analysis was to assess BMD and BTM results for a subgroup of patients who were receiving glucocorticoid therapy at baseline, in a randomized, placebo-controlled, phase II study of denosumab in patients with RA (ClinicalTrials.gov identifier: NCT00095498), including assessments of BMD and BTMs after discontinuation of denosumab treatment for 12 months.

PATIENTS AND METHODS

Study design. The design of this study has previously been described (15,16). Patients were stratified according to current use of glucocorticoids and prior use of biologic agents (e.g., etanercept and infliximab) and were then randomized 1:1:1 to receive placebo, denosumab 60 mg, or denosumab 180 mg once every 6 months by subcutaneous injection, at baseline (month 0) and month 6. The 180-mg dose was selected for this dose-finding study to ensure maximal suppression of bone turnover in this patient population. All patients were to take daily supplements of elemental calcium 0.5–1.0 gm and vitamin D 400–800 IU. As part of preplanned analyses, patients were monitored for an additional 12 months after discontinuing their assigned treatment during a follow-up period that extended from 6 to 18 months after their last treatment, ending at month 24.

Study population. Eligibility criteria for this study have previously been described (15,16). Recruited patients were included in the study if they were ages ≥ 18 years at the time of screening, were receiving a stable dosage of methotrexate 7.5–25 mg/week for ≥ 8 weeks, had active RA (duration ≥ 24 weeks) and erosive disease (≥ 3 erosions of the hands and feet), or had both a C-reactive serum protein level ≥ 2 mg/dl and positive test results for cyclic citrullinated peptide antibodies. Patients were included in the present subgroup analysis if they had received glucocorticoids at baseline.

Patients were excluded from the study if they had received any biologic agent or leflunomide within 8 weeks before randomization (previous use of these agents was allowed). Other exclusion criteria included pregnancy, potential or scheduled surgery of the hands/wrists or feet, Felty syndrome, any uncontrolled clinically significant systemic disease, a malignancy within 5 years,

and a positive test for hepatitis B surface antigen, hepatitis C virus, or HIV. Since this was a placebo-controlled study and the effects of denosumab in preventing glucocorticoid-induced loss were unknown, patients receiving >15 mg/day of prednisone or its equivalent were also excluded from the study.

Outcome measures. Assessments for this subgroup analysis included percentage changes from baseline in the bone resorption marker C-terminal telopeptide of type I collagen (CTX), the bone formation marker procollagen type I N-terminal propeptide (PINP), and lumbar spine and total hip BMD during 12 months of denosumab or placebo treatment, and up to 12 months following treatment discontinuation. Fractures were recorded as adverse events (AEs).

Statistical analysis. Baseline demographic and clinical characteristics were analyzed descriptively for patients receiving glucocorticoids at baseline. Percentage changes from baseline in BTMs and BMD were assessed in this subgroup. Serum CTX and PINP data were reported as the median and interquartile range. Data on BMD were reported as the least squares mean (LSM) and 95% confidence interval (95% CI). Percentage changes from baseline in BTMs at each time point were assessed by 2-sided van Elteren stratified rank test, with adjustment for baseline use of glucocorticoids and previous use of biologic agents. Percentage changes from baseline in lumbar spine and total hip BMD at each time point were assessed based on a repeated-measures model, with adjustment for baseline use of glucocorticoids, previous use of biologics, and baseline BMD values. Reported *P* values were not adjusted for multiplicity.

Data availability. Qualified researchers may request data from Amgen clinical studies. Complete details are available at <https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/>.

RESULTS

Of the 218 patients receiving treatment in the phase II study, 82 patients (placebo, $n = 26$; denosumab 60 mg, $n = 27$; and denosumab 180 mg, $n = 29$) were receiving glucocorticoids at baseline and were, therefore, included in the present analysis. Treatment groups were balanced at baseline for mean age, BTM levels, prednisolone equivalent dose, and duration of glucocorticoid use. The mean PINP level was lowest in the denosumab 180-mg group (Table 1). The denosumab 60-mg group had more men ($n = 12$; 44%) compared to the placebo group ($n = 8$; 31%), and had fewer women ages ≥ 55 years ($n = 5$; 19%) compared to the denosumab 180-mg group ($n = 11$; 38%). Fewer patients in the denosumab 60-mg group had a history of fracture ($n = 9$; 33%) compared to those in the denosumab 180-mg group ($n = 17$; 59%).

Table 1. Demographic and clinical characteristics at baseline*

	Baseline use of glucocorticoids			
	Placebo (n = 26)	Denosumab 60 mg (n = 27)	Denosumab 180 mg (n = 29)	Total (n = 82)
Age, years	55.5 ± 12.8	53.0 ± 12.3	57.2 ± 11.5	55.3 ± 12.2
Sex, no. (%)				
Women	18 (69)	15 (56)	18 (62)	51 (62)
<55 years	10 (38)	10 (37)	7 (24)	27 (33)
≥55 years	8 (31)	5 (19)	11 (38)	24 (29)
Men	8 (31)	12 (44)	11 (38)	31 (38)
<50 years	2 (25)	1 (8)	1 (9)	4 (13)
≥50 years	6 (75)	11 (92)	10 (91)	27 (87)
Fracture history, no. (%)†	12 (46)	9 (33)	17 (59)	38 (46)
Bisphosphonate use, no. (%)	8 (31)	8 (30)	10 (34)	26 (32)
Lumbar spine BMD T score	−0.48 ± 1.3	−0.33 ± 1.2	−0.74 ± 1.6	−0.52 ± 1.4
Lumbar spine T score range, no. (%)‡				
≤−2.5	2 (8)	0	5 (17)	7 (9)
>−2.5 to <−1.0	5 (19)	6 (22)	8 (28)	19 (23)
≥−1.0	18 (69)	21 (78)	15 (52)	54 (66)
Total hip BMD T score	−0.83 ± 1.0	−0.80 ± 1.3	−0.80 ± 1.4	−0.81 ± 1
Total hip T score range, no. (%)§				
≤−2.5	1 (4)	2 (7)	2 (7)	5 (6)
>−2.5 to <−1.0	14 (54)	7 (26)	10 (34)	31 (38)
≥−1.0	11 (42)	17 (63)	17 (59)	45 (55)
Serum CTX, ng/ml	0.31 ± 0.19	0.37 ± 0.23	0.33 ± 0.24	0.33 ± 0.22
Serum PINP, µg/liter	44.86 ± 27.61	43.73 ± 22.36	35.29 ± 17.09	41.10 ± 22.71
DAS28	5.15 ± 1.11	4.56 ± 0.96	5.30 ± 1.11	5.01 ± 1.10
CRP, mg/liter	23.65 ± 23.87	16.61 ± 15.66	31.20 ± 38.94	24.00 ± 28.56

* Except where indicated otherwise, values are the mean ± SD. Treatments were administered every 6 months. BMD = bone mineral density; CTX = serum C-terminal telopeptide of type I collagen; PINP = procollagen type I N-terminal propeptide; DAS28 = Disease Activity Score in 28 joints; CRP = C-reactive protein.

† Defined as osteoporosis-related fractures.

‡ Missing data on 1 patient in the placebo group and 1 in the denosumab 180-mg group.

§ Missing data on 1 patient in the denosumab 60-mg group.

The proportions of patients receiving glucocorticoid therapy at month 12 were 81%, 85%, and 86% in the placebo, denosumab 60-mg, and denosumab 180-mg groups, respectively, with corresponding proportions of 54%, 44%, and 55% at month 24. Overall, the mean ± SD duration of glucocorticoid use at the end of the study period (month 24) was 19.4 ± 6.4 months, with a mean ± SD prednisone equivalent dose of 5.8 ± 2.6 mg/day, with no significant difference between treatment groups. At month 12, the proportions of patients receiving disease-modifying antirheumatic drug therapy were 89%, 100%, and 93% in the placebo, denosumab 60-mg, and denosumab 180-mg groups, respectively, while a corresponding 23%, 11%, and 21% were receiving biologic treatment for RA.

Throughout the 12-month treatment period, serum CTX in both denosumab groups was reduced relative to baseline and placebo (Figure 1A). Median percentage changes from baseline were −21.4% in the placebo group, −41.6% in the denosumab 60-mg group ($P = 0.014$), and −56.6% in the denosumab 180-mg group ($P = 0.006$) at month 12 of the treatment period. In both denosumab groups, CTX returned to pretreatment levels by month 6 of the off-treatment period (i.e., month 18) and remained at those levels until the end of the observation period,

with no significant differences compared to the placebo control value. Median percentage changes from baseline in serum CTX in the denosumab 60-mg group were 0% ($P = 0.184$ versus placebo) and 22.7% ($P = 0.220$ versus placebo) at months 6 and 12, respectively, of the off-treatment period. In the denosumab 180-mg group, median percentage changes from baseline CTX were 10.0% ($P = 0.056$ versus placebo) and 1.8% ($P = 0.677$ versus placebo) at months 6 and 12, respectively, of the off-treatment period.

Serum PINP was decreased in both denosumab groups relative to baseline and the placebo group, throughout the treatment period (Figure 1B). Median percentage changes from baseline were −12.0% in the placebo group, −46.9% in the denosumab 60-mg group ($P = 0.028$), and −41.6% in the denosumab 180-mg group ($P = 0.002$) at month 12 of the treatment period. In the denosumab 60-mg group, PINP returned to baseline levels at months 6 and 12 during the off-treatment period and was significantly higher compared to the placebo group at month 12 off treatment (median percentage change 15.3%; $P = 0.017$ versus placebo). In the denosumab 180-mg group, PINP returned to baseline levels by 6 months off treatment and increased above baseline at 12 months off treatment to levels significantly higher

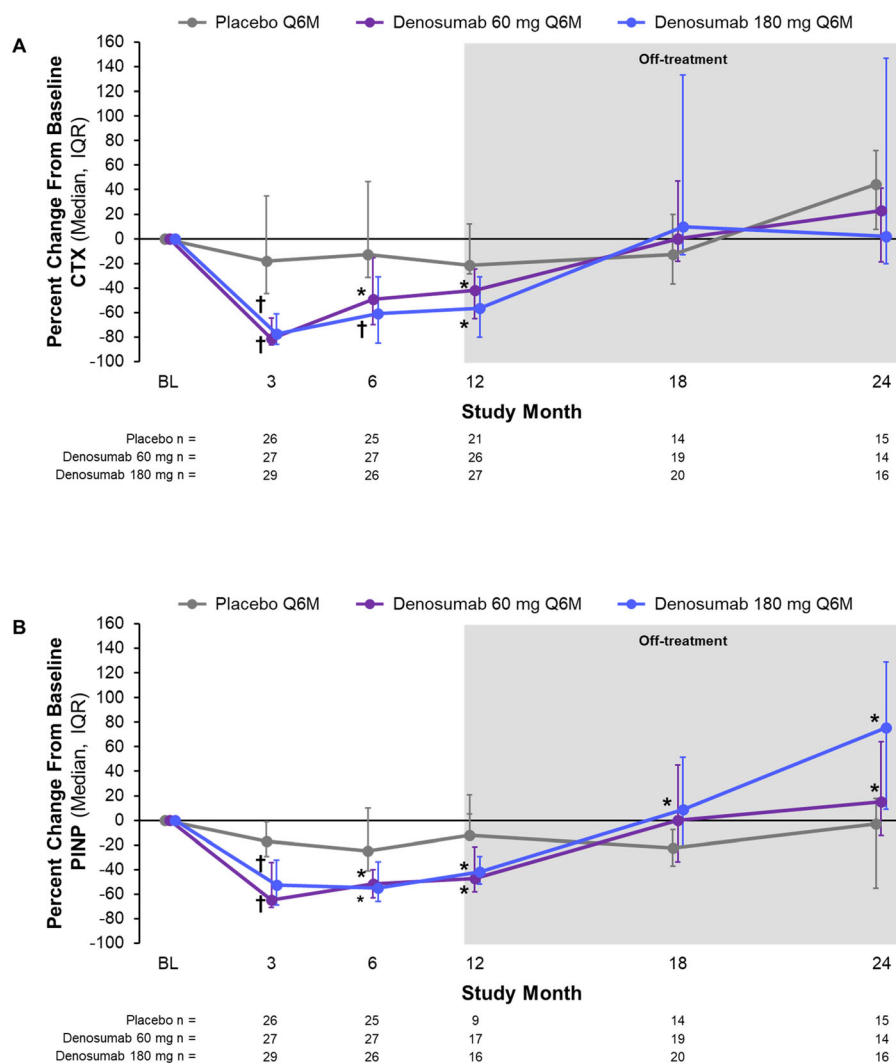


Figure 1. Changes in C-terminal telopeptide of type I collagen (CTX) (A) and procollagen type I N-terminal propeptide (PINP) (B) from baseline (BL) in rheumatoid arthritis patients receiving placebo, denosumab 60 mg, or denosumab 180 mg, during treatment and after discontinuation of treatment. Includes patients enrolled in the off-treatment phase with observed values at month 0 and the time point of interest. * = $P \leq 0.05$; † = $P \leq 0.001$, versus placebo. Q6M = every 6 months; IQR = interquartile range.

than the placebo control value at both time points. Median percentage changes from baseline PINP in the denosumab 180-mg group were 9.0% ($P = 0.018$ versus placebo) and 75.8% ($P = 0.002$ versus placebo) at months 18 and 24, respectively.

During the treatment period, both denosumab groups exhibited lumbar spine and total hip BMD gains relative to baseline and the placebo group (Figure 2). Gains in lumbar spine BMD were significant for the denosumab 60-mg group at months 1, 6, and 12 of the treatment period, and for the denosumab 180-mg group at months 6 and 12, compared to the placebo group. Gains in total hip BMD were significant for the denosumab 60-mg group at month 12 of the treatment period, and for the denosumab 180-mg group at months 6 and 12, compared to the placebo group. By 12 months after treatment discontinuation, lumbar spine BMD in both denosumab groups decreased to the level of the

placebo control value, which was slightly above pretreatment levels. LSM percentage changes from baseline lumbar spine BMD were 2.30% (95% CI -0.35%, 4.94%) in the placebo group, 1.31% (95% CI -1.17%, 3.79%) in the denosumab 60-mg group, and 0.12% (95% CI -2.45%, 2.68%) in the denosumab 180-mg group at month 24. Additionally, total hip BMD decreased in both denosumab groups during the off-treatment period. LSM percentage changes from baseline total hip BMD 12 months after treatment discontinuation were -2.20% (95% CI -4.03%, -0.36%) in the placebo group, -0.54% (95% CI -2.37%, 1.29%) in the denosumab 60-mg group, and -1.71% (95% CI -3.52%, 0.10%) in the denosumab 180-mg group at month 24. Thus, total hip BMD in the denosumab 60-mg and denosumab 180-mg groups reverted to levels similar to or slightly above the placebo control value ($P = 0.210$ and $P = 0.706$, respectively).

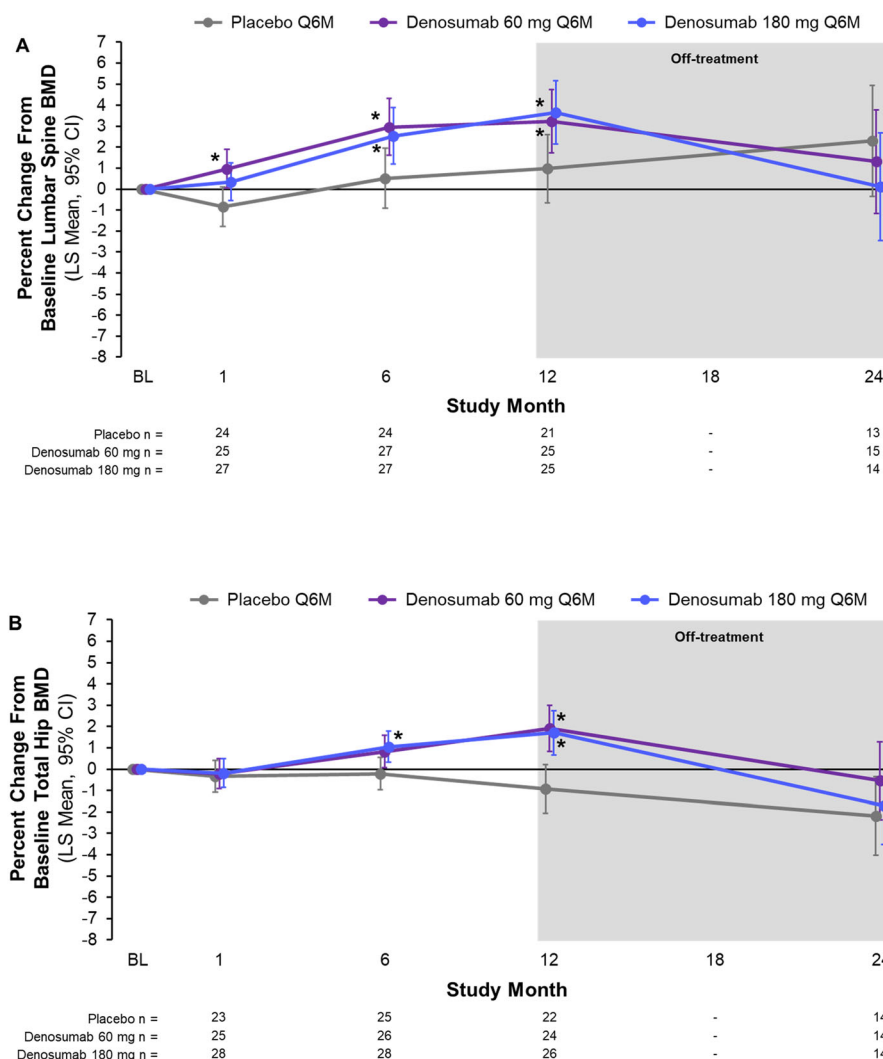


Figure 2. Changes in lumbar spine bone mineral density (BMD) (A) and total hip bone BMD (B) from baseline (BL) in rheumatoid arthritis patients receiving placebo, denosumab 60 mg, or denosumab 180 mg, during treatment and after discontinuation of treatment. Includes patients enrolled in the off-treatment phase with observed values at month 0 and the time point of interest. * = $P \leq 0.05$ versus placebo. Q6M = every 6 months; LS = least-squares; 95% CI = 95% confidence interval.

Overall rates of AEs, serious AEs, treatment-related AEs, and AEs leading to study discontinuation were balanced between the denosumab and placebo groups during the treatment and off-treatment periods. During the treatment period, AEs in RA were reported in 12 patients in the placebo group (46%), 13 in the denosumab 60-mg group (38%), and 9 in the denosumab 180-mg group (31%); during the off-treatment period, the corresponding numbers of AEs were 3 (12%), 4 (15%), and 6 (21%), respectively. Arthralgia AEs were uncommon (≤ 2 per group) and were balanced between the treatment and off-treatment periods. Infection AEs reported in both the treatment and off-treatment periods included sinusitis, upper respiratory tract infection, bronchitis, influenza, and nasopharyngitis. The incidence of these events was generally similar among the 3 groups, although more upper respiratory infections were observed in the denosumab 60-mg

group during the treatment period ($n = 4$; 15%) and the denosumab 180-mg group during the off-treatment period ($n = 4$; 14%), compared to the placebo group ($n = 1$; 3.8%; and $n = 0$, respectively). Bronchitis was reported in 7 patients in the denosumab 180-mg group (24%) during the treatment period compared to 1 (4%) in the placebo group (Table 2). There were no serious infection AEs reported.

Very few patients required anti-tumor necrosis factor rescue therapy after 6 months (2 patients in the placebo group, 1 in the denosumab 60-mg group, and 4 in the denosumab 180-mg group), and thus, no conclusions could be made regarding the risk of infections with concomitant biologic and denosumab use. There were no treatment-related serious AEs, deaths, or fractures in these 3 groups during the treatment or off-treatment periods.

Table 2. Adverse events of infection*

	During treatment			Off-treatment		
	Placebo (n = 26)	Denosumab 60 mg (n = 27)	Denosumab 180 mg (n = 29)	Placebo (n = 26)	Denosumab 60 mg (n = 27)	Denosumab 180 mg (n = 29)
Sinusitis	4 (15.4)	1 (3.7)	7 (24.1)	2 (7.7)	2 (7.4)	1 (3.4)
URI	1 (3.8)	4 (14.8)	2 (6.9)	0 (0)	2 (7.4)	4 (13.8)
Bronchitis	1 (3.8)	0 (0)	7 (24.1)	0 (0)	1 (3.7)	1 (3.4)
Influenza	0 (0)	2 (7.4)	2 (6.9)	0 (0)	1 (3.7)	1 (3.4)
Nasopharyngitis	3 (11.5)	2 (7.4)	2 (6.9)	1 (3.8)	0 (0.0)	1 (3.4)

* Values are the number (%) of patients. Treatments were administered every 6 months. Percentages were calculated by dividing the number of patients reporting ≥ 1 adverse event of interest by the number of randomized patients who had a baseline measurement and ≥ 1 postbaseline measurement up to month 12, and then multiplying this by 100. Events were coded using MedDRA version 9.0 and include only treatment-emergent adverse events that began before the month 12 evaluation. URI = upper respiratory tract infection.

DISCUSSION

The results of this subgroup analysis involving RA patients receiving glucocorticoid therapy indicate that discontinuation of treatment with denosumab 60-mg or 180-mg (once every 6 months) after 1 year resulted in the reversal of its inhibitory effect on BTMs and BMD gains. For the clinically approved denosumab 60-mg dose administered every 6 months, serum CTX returned to pretreatment levels, and PINP levels were slightly above baseline 12 months after the last denosumab dose. Additionally, lumbar spine and total hip BMD gains during the treatment period decreased to pretreatment levels 18 months after the last dose. Studies in postmenopausal women with low BMD have also shown that treatment-related gains in BMD are lost after discontinuing denosumab therapy (12,13). Those findings and the present data highlight the need for follow-on osteoporosis therapy to preserve BMD gains in patients who discontinue denosumab.

The present study in RA patients receiving glucocorticoids showed that CTX was not increased above baseline when measured 6 and 12 months after completing a course of 2 doses of denosumab. This is in contrast to previous studies in postmenopausal women who discontinued denosumab after receiving 4 doses (once every 6 months) (12,13). These discordant responses during the off-treatment period could have biochemical or biomechanical bases. Biochemically, patients with RA who are receiving glucocorticoid therapy may have more bioavailable RANKL than postmenopausal women, leading to a lesser ability of denosumab to inhibit osteoclasts for the entire 6-month dosing interval and thus to a more muted osteoclast response after denosumab discontinuation (17). Possible sources of RANKL unique to the current population include bone cells and synovial cells expressing RANKL in response to glucocorticoids or proinflammatory cytokines (4,6,18–20). Further, glucocorticoids inhibit cellular expression and serum levels of the RANKL inhibitor osteoprotegerin (4,5,21), which may further increase bioavailable RANKL. In support of this biochemically based theory, median CTX reduction at the end of the initial 6-month dosing interval was $<50\%$ in the present study's denosumab 60-mg group compared to nearly 80% in postmenopausal women receiving the same dose (12).

From a biomechanical perspective, previous denosumab discontinuation studies showing increases in CTX above baseline also showed BMD gains during the treatment period that were approximately twice those observed in the current study (12,13). Greater increments in BMD are likely associated with greater reductions in habitual skeletal strain, which may trigger more osteocytes to express factors that are positioned to aggressively increase bone resorption upon denosumab discontinuation. This “mechanostat-based” theory (22) also aligns with evidence that BMD tends to return to an individual's pretreatment baseline level after discontinuing denosumab (12,13). Serum CTX also increased above baseline after discontinuing the antiresorptive agent odanacatib (23) and the dual-acting (bone-forming and antiresorptive) agent romosozumab (24) after substantial BMD gains during treatment had accrued.

The bone formation marker serum PINP was slightly above baseline levels 12 months after discontinuing denosumab 60 mg and increased above baseline after discontinuing denosumab 180 mg. A study in postmenopausal women showed that serum PINP increased above baseline after discontinuing denosumab 60 mg following 24 months of treatment (12), and the more muted PINP discontinuation response in our denosumab 60-mg group could have similar bases as those previously described for serum CTX. Mechanisms underlying the increase in serum PINP above baseline after discontinuing denosumab 180 mg are unclear. Bone formation markers generally increase after discontinuing glucocorticoid therapy (25), and although patients in the present denosumab 180-mg group had similar rates of glucocorticoid therapy as the other groups, it cannot be excluded that they may have had greater glucocorticoid dose reductions during the off-treatment period. The off-treatment PINP response in the denosumab 180-mg group could also reflect a greater degree of osteoclast inhibition throughout the treatment period compared to the denosumab 60-mg group, but the lack of a commensurate increase in CTX above baseline suggests that the PINP response at month 24 in the denosumab 180-mg group may be a chance finding, likely due to the small sample size and variability in BTM values in this analysis.

The elevated risk of fragility fractures partially decreases when patients with RA discontinue glucocorticoid therapy (8).

It may, therefore, be appropriate to discontinue antiresorptive treatment in coordination with the end of glucocorticoid therapy, at least in patients without a high underlying risk of fragility fracture. The present findings indicate that although BTMs did not increase markedly above baseline after discontinuation of denosumab 60 mg, gains in lumbar spine and total hip BMD during treatment were nonetheless lost within a year of discontinuation, highlighting the need to follow up with alternative osteoporosis therapies to preserve prior BMD gains. This guidance would apply to patients who continue receiving glucocorticoid therapy and to those who may discontinue glucocorticoid therapy but remain at high risk of fracture due to underlying osteoporosis or other risk factors (26). The type, timing, and effects of therapy after denosumab discontinuation, however, remain controversial and require further study (27).

Strengths of the present analysis include the randomized, placebo-controlled nature of the trial. The study also involved a novel experimental denosumab regimen comprising 12 months of active treatment followed by 12 months with no treatment. The duration of these periods likely provided sufficient time to assess major post-discontinuation changes in bone turnover and BMD in this population under these conditions. Although the lack of follow-up beyond month 24 limits definitive conclusions regarding possible longer-term effects of denosumab discontinuation on BMD, the findings are applicable to RA patients in whom suppression of relatively temporary glucocorticoid-induced bone turnover is sought. Findings of this analysis provide additional insights into denosumab discontinuation, which is a timely and important clinical question given the identified risk of multiple vertebral fractures associated with denosumab discontinuation in postmenopausal women with osteoporosis who typically receive longer courses of denosumab therapy (28); however, the baseline fracture risk was likely higher among such women than for those in the present analysis.

This study has limitations, including the relatively small sample size and the post hoc nature of this analysis from a study not specifically designed to assess denosumab discontinuation. Participation in the follow-up extension period was not mandated, and the lack of bone-sparing therapy may have led to many patients choosing not to continue beyond the 12-month study period. Fluctuations in the use of glucocorticoids among patients, which could have had an impact on fracture risk, were not captured in this study. Fractures were not systematically evaluated and were recorded as AEs, which may have missed some asymptomatic vertebral fractures. The study was not designed to identify effective follow-on therapies to mitigate reductions in BMD after denosumab discontinuation, although bisphosphonates have been shown to reduce bone loss to varying degrees in postmenopausal women with osteoporosis who discontinue denosumab (29–33). Finally, the 12-month treatment duration may not reflect the benefits or risks of longer-term denosumab treatment and subsequent discontinuation.

In summary, like all non-bisphosphonate medications for osteoporosis, the pharmacologic effects of denosumab are readily reversible after discontinuation. In the present subgroup of glucocorticoid-treated patients with RA, BMD gains achieved with 12 months of denosumab therapy were lost upon denosumab discontinuation, consistent with previous observations in postmenopausal women who discontinued denosumab after 24 months of therapy for osteoporosis (12,13). Post-discontinuation bone loss in the present study was associated with a return of serum CTX to pretreatment baseline levels in both denosumab groups and an increase in serum PINP to above baseline levels, particularly in the denosumab 180-mg group. These results provide further support for recommendations that patients discontinuing denosumab should transition to follow-on osteoporosis therapy to prevent or minimize remodeling-induced bone loss (26,27).

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Saag had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Saag, Cohen.

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ROLE OF THE STUDY SPONSOR

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