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Journal

Arthritis & Rheumatology, 74(4)

ISSN

2326-5191

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Publication Date

2022-04-01

DOI

10.1002/art.41981

Peer reviewed

Arthritis & Rheumatology
Vol. 0, No. 0, Month 2022, pp 1–8
DOI 10.1002/art.41981

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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

Supported by Amgen, Inc.
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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.41981&file=art41981-sup-0001-Disclosureform.pdf.

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Submitted for publication February 10, 2021; accepted in revised form September 14, 2021.

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

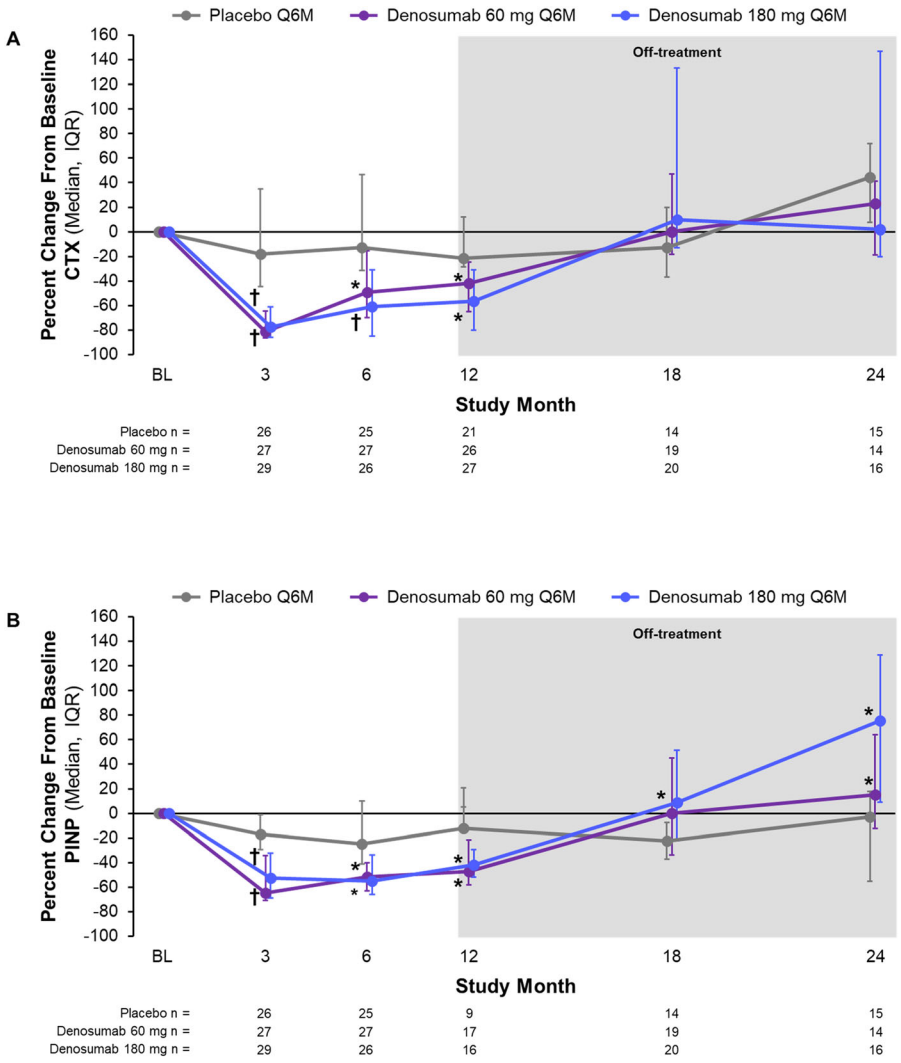

Figure 1. Changes in C-terminal telopeptide of type I collagen (CTX) (**A**) and procollagen type I N-terminal propeptide (PINP) (**B**) from baseline (BL) in rheumatoid arthritis patients receiving placebo, denosumab 60 mg, or denosumab 180 mg, during treatment and after discontinuation of treatment. 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 moths; 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).

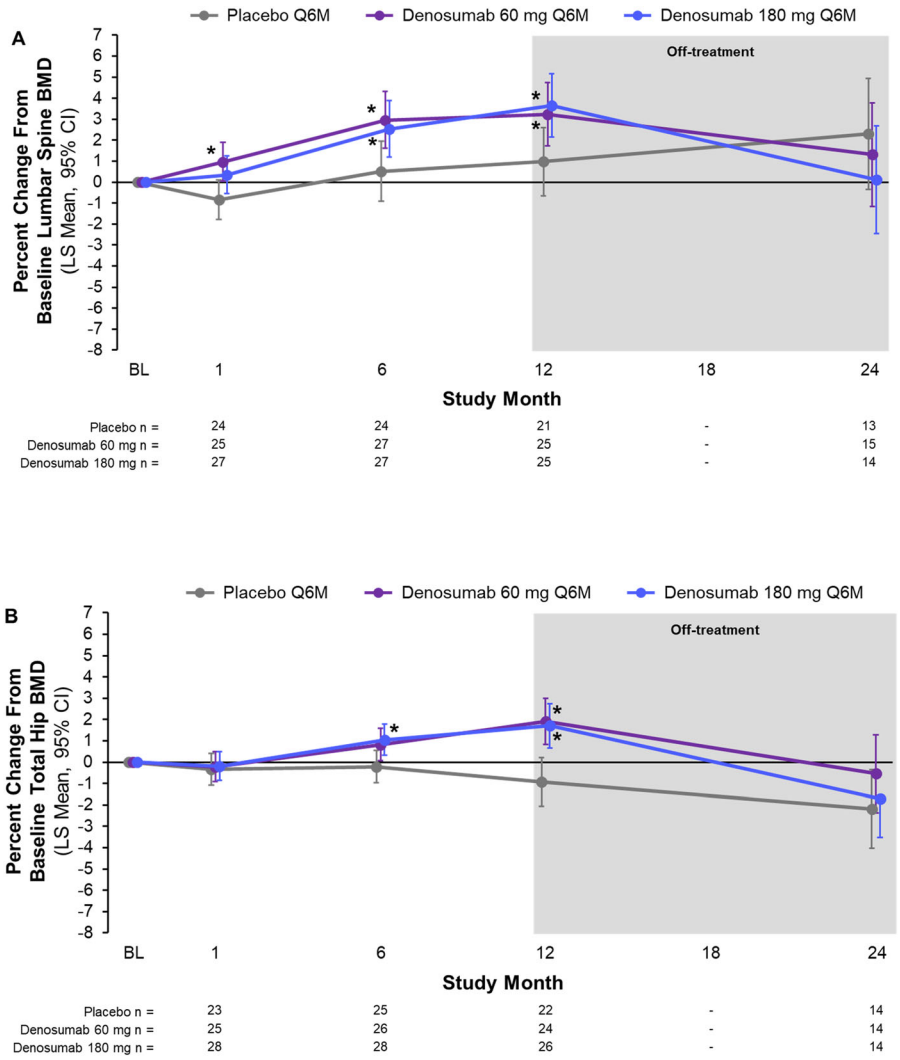

Figure 2. Changes in lumbar spine bone mineral density (BMD) (**A**) and total hip bone BMD (**B**) from baseline (BL) in rheumatoid arthritis patients receiving placebo, denosumab 60 mg, or denosumab 180 mg, during treatment and after discontinuation of treatment. Includes patients enrolled in the off-treatment 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).

ACKNOWLEDGMENTS

Paul J. Kostenuik, PhD (Phylon Pharma Services) and Alexandra Stirling, PharmD (BioScience Communications) provided writing and editorial support, which was funded by Amgen Inc.

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.

Acquisition of data. Lane, Dore, Cohen.

Analysis and interpretation of data. Saag, McDermott, Adachi, Lems, Lane, Geusens, Stad, Chen, Huang, Dore, Cohen.

ROLE OF THE STUDY SPONSOR

Amgen funded this study and participated in the study design, research, analysis, data collection, interpretation of data, and review of the manuscript. All authors participated in manuscript drafting and revision, interpreting results, approved the final draft, and had the final decision to submit the manuscript for publication. Medical writing support was funded by Amgen.

REFERENCES

1. Choi ST, Kwon SR, Jung JY, Kim HA, Kim SS, Kim SH, et al. Prevalence and fracture risk of osteoporosis in patients with rheumatoid arthritis: A multicenter comparative study of the FRAX and WHO criteria. J Clin Med 2018;7:507.
2. Ozen G, Pedro S, Wolfe F, Michaud K. Medications associated with fracture risk in patients with rheumatoid arthritis. Ann Rheum Dis 2019;78:1041–7.
3. Xue AL, Wu SY, Jiang L, Feng AM, Guo HF, Zhao P. Bone fracture risk in patients with rheumatoid arthritis: a meta-analysis. Medicine 2017; 96:e6983.
4. Hofbauer LC, Gori F, Riggs BL, Lacey DL, Dunstan CR, Spelsberg TC, et al. Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic

lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis. Endocrinology 1999;140:4382–9.

5. Kondo T, Kitazawa R, Yamaguchi A, Kitazawa S. Dexamethasone promotes osteoclastogenesis by inhibiting osteoprotegerin through multiple levels. J Cell Biochem 2008;103:335–45.
6. Piemontese M, Xiong J, Fujiwara Y, Thostenson JD, O'Brien CA. Cortical bone loss caused by glucocorticoid excess requires RANKL production by osteocytes and is associated with reduced OPG expression in mice. Am J Physiol Endocrinol Metab 2016;311: E587–93.
7. Steinbuch M, Youket TE, Cohen S. Oral glucocorticoid use is associated with an increased risk of fracture. Osteoporos Int 2004;15: 323–8.
8. Balasubramanian A, Wade SW, Adler RA, Lin CJ, Maricic M, O'Malley CD, et al. Glucocorticoid exposure and fracture risk in patients with new-onset rheumatoid arthritis. Osteoporosis Int 2016;27:3239–49.
9. de Nijs RN, Jacobs JW, Bijlsma JW, Lems WF, Laan RF, Houben HH, et al. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology 2001;40:1375–83.
10. Saag KG, Wagman RB, Geusens P, Adachi JD, Messina OD, Emkey R, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. Lancet Diabetes Endocrinol 2018;6:445–54.
11. Bekker PT, Holloway DL, Rasmussen AS, Murphy R, Martin SW, Leese PT, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res 2004;19:1059–66.
12. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab 2011;96: 972–80.
13. Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, et al., on behalf of the AMG 162 Bone Loss Study Group. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone 2008;43:222–9.
14. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JE, McClung M, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res 2018;33:190–8.
15. Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT, et al., on behalf of the Denosumab Rheumatoid Arthritis Study Group. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. Arthritis Rheum 2008;58:1299–309.
16. Dore RK, Cohen SB, Lane NE, Palmer W, Shergy W, Zhou L, et al., on behalf of the Denosumab RA Study Group. Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. Ann Rheum Dis 2010;69:872–5.
17. Kearns AE, Khosla S, Kostenuik PJ. Receptor activator of nuclear factor κb ligand and osteoprotegerin regulation of bone remodeling in health and disease. Endocr Rev 2008;29:155–92.
18. Hofbauer LC, Lacey DL, Dunstan CR, Spelsberg TC, Riggs BL, Khosla S. Interleukin-1β and tumor necrosis factor-α, but not interleukin 6, stimulate osteoprotegerin ligand gene expression in human osteoblastic cells. Bone 1999;25:255–9.
19. Crotti TN, Smith MD, Weedon H, Ahern MJ, Findlay DM, Kraan M, et al. Receptor activator NF-κB ligand (RANKL) expression in synovial tissue from patients with rheumatoid arthritis, spondyloarthropathy, osteoarthritis, and from normal patients: semiquantitative and quantitative analysis. Ann Rheum Dis 2002;61:1047–54.
20. Rooney T, Edwards CK, Gogarty M, Greenan L, Veale DJ, FitzGerald O, et al. Synovial tissue rank ligand expression and radiographic progression in rheumatoid arthritis: observations from a proof-of-concept randomized clinical trial of cytokine blockade. Rheumatol Int 2010;30: 1571–80.
21. von Tirpitz C, Epp S, Klaus J, Mason R, Hawa G, Brinskelle-Schmal N, et al. Effect of systemic glucocorticoid therapy on bone metabolism and the osteoprotegerin system in patients with active Crohn's disease. Eur J Gastroenterol Hepatol 2003;15:1165–70.
22. Frost HM. Bone's mechanostat: a 2003 update. Anat Rec A Discov Mol Cell Evol Biol 2003;275:1081–101.
23. Eisman JA, Bone HG, Hosking DJ, McClung MR, Reid IR, Rizzoli R, et al. Odanacatib in the treatment of postmenopausal women with low bone mineral density: three-year continued therapy and resolution of effect. J Bone Miner Res 2011;26:242–51.
24. McClung MR, Brown JP, Diez-Perez A, Resch H, Caminis J, Meisner P, et al. Effects of 24 months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, Phase 2, parallel group study. J Bone Miner Res 2018;33:1397–406.
25. Dovio A, Perazzolo L, Osella G, Ventura M, Termine A, Milano E, et al. Immediate fall of bone formation and transient increase of bone resorption in the course of high-dose, short-term glucocorticoid therapy in young patients with multiple sclerosis. J Clin Endocrinol Metab 2004;89:4923–8.
26. Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Rheumatol 2017;69:1521–37.
27. Tsourdi E, Zillikens MS, Meier C, Body JJ, Gonzalez Rodriguez E, et al. Fracture risk and management of discontinuation of denosumab: a systematic review and position statement by ECTS. J Clin Endocrinol Metab 2020. doi: 10.1210/clinem/dgaa756. E-pub ahead of print.
28. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al; for the FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756–65.
29. Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S, et al., on behalf of the DAPS Investigators. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int 2012;23:317–26.
30. Horne AM, Mihov B, Reid IR. Bone loss after romosozumab/denosumab: effects of bisphosphonates. Calcif Tissue Int 2018;103:55–61.
31. Leder BZ, Tsai JN, Jiang LA, Lee H. Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: the Denosumab and Teriparatide Follow-up study (DATA-Follow-up). Bone 2017;98:54–8.
32. Lehmann T, Aeberli D. Possible protective effect of switching from denosumab to zoledronic acid on vertebral fractures. Osteoporos Int 2017;28:3067–8.
33. Søling AS, Harsløf T, Langdahl B. Treatment with zoledronate subsequent to denosumab in osteoporosis: a randomized trial. J Bone Miner Res 2020;35:1858–70.