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CONTRIBUTIONS FROM THE FIELD

Denosumab-Mediated Increase in Hand Bone Mineral Density Associated With Decreased Progression of Bone Erosion in Rheumatoid Arthritis Patients

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Objective. **Periarticular osteoporosis is one of the earliest radiographic signs of bone damage in rheumatoid arthritis (RA). Denosumab, an investigational fully human monoclonal antibody that binds to RANKL, inhibits bone erosion and systemic bone loss in clinical studies of patients with RA. In this hand bone mineral density (BMD) substudy, we investigated the effects of denosumab on hand BMD and its correlation with hand erosion scores.**

Methods. **Patients receiving methotrexate for erosive RA were randomized in a 1:1:1 ratio to receive subcutaneous placebo, denosumab 60 mg, or denosumab 180 mg at 0 and 6 months. Measurements included BMD (by dual x-ray absorptiometry [DXA]) of both hands (0, 1, 6, and 12 months), magnetic resonance images of the hands/wrists (0 and 6 months), and radiographs of the hands/wrists and feet (0, 6, and 12 months).**

Results. **There were 56 patients (13 placebo, 21 denosumab 60 mg, and 22 denosumab 180 mg). Mean changes in hand BMD at 6 and 12 months were: +0.8% and +1.0%, respectively, for denosumab 60 mg; +2.0% and +2.5%, respectively, for denosumab 180 mg; and −1.2% and −2.0%, respectively, for placebo. Erosion scores remained near baseline in the denosumab groups and increased from baseline in the placebo group. A negative correlation was observed between hand BMD and erosion scores.**

Conclusion. **In patients with RA, denosumab provided protection against erosion, and not only prevented bone loss but increased hand BMD as measured by DXA.**

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by focal and generalized bone resorption. Increased osteoclast activity in RA contributes to local and systemic abnormalities of bone remodeling, including bone erosions, juxtaarticular bone loss, and sys-

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temic osteoporosis (1). Marginal bone erosion and juxtaarticular osteoporosis are hallmarks of RA (2). Both types of bone loss are thought to be mediated by osteoclasts and the RANKL pathway, which is a key driver of bone destruction in RA (3). RANKL is essential for osteoclast differentiation, function, and survival.

The effects of RA are often manifested in the hands (4), and are known to correlate with the structural damage measured by radiographic scores that incorporate joint space narrowing and erosions (5,6). Early loss of hand bone density in patients with RA has also been shown to independently correlate with functional loss (7).

Periarticular osteoporosis in the hands as seen on plain radiographs is rarely measured objectively. Quantitative hand bone density measurement can be done directly using dual x-ray absorptiometry (DXA) or indirectly by digital x-ray radiogrammetry (DXR) using digitized radiographs (8,9). The effect of several therapeutic agents on hand bone mineral density (BMD) has been assessed using the indirect method of radiogrammetry; however, no agent has shown efficacy in inhibiting hand bone loss as assessed by both DXA and DXR, including the most recent study using an anti–tumor necrosis factor (anti-TNF) drug (10,11).

Denosumab is an investigational fully human monoclonal antibody that specifically and avidly binds to RANKL. As a result, denosumab inhibits the generation, survival, and activation of osteoclasts, thereby blocking bone resorption (12). The efficacy and safety of denosumab were evaluated in a randomized, double-blind, placebo-controlled, phase II trial of patients with RA who were receiving methotrexate treatment (13). All of the patients in this original study had lumbar spine, hip, femoral neck, and trochanter BMD measurements at baseline and at 1, 6, and 12 months. In addition to these BMD measurements, a subset of patients from the original study also had hand BMD measurements. The objective of this substudy was to evaluate the effects of denosumab on hand BMD measured directly by DXA and to assess the relationships between hand BMD and erosion scores of the hand.

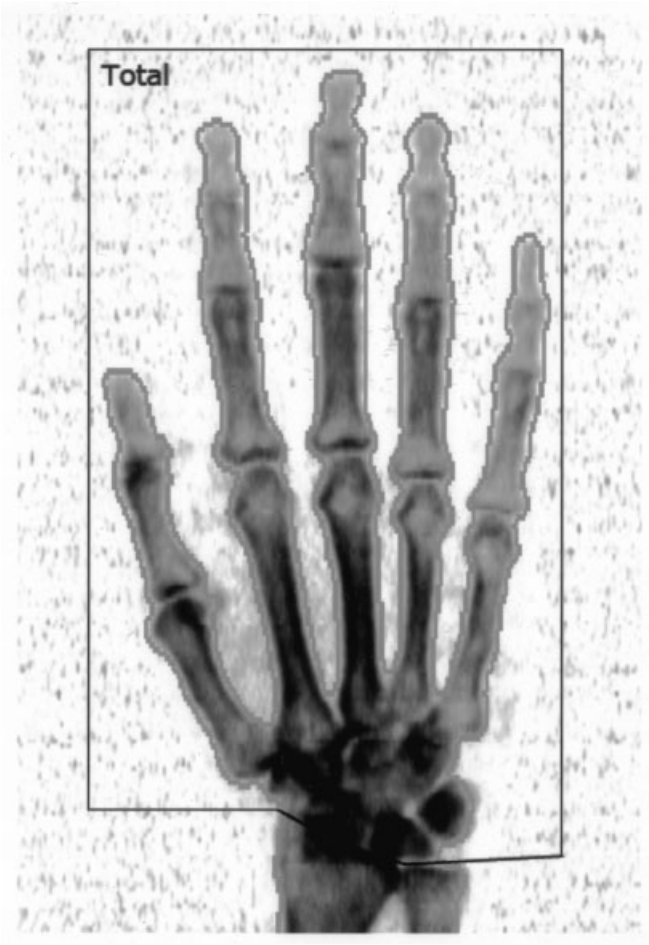

Figure 1. Example of a dual x-ray absorptiometry scan of the hand that was used to determine hand bone mineral density.

Patients and Methods

Study patients. The full details of the study methods were described previously (13). Briefly, patients with RA by the American College of Rheumatology (formerly the American Rheumatism Association) criteria (14) for ≥24 weeks, with ≥6 swollen joints, and with erosive disease or predictors of erosion (either ≥3 erosions of the hands or feet, or both C-reactive protein level ≥2.0 mg/dl and anti–cyclic citrullinated peptide antibodies) were enrolled in the study at 39 centers in the US and Canada. All of the patients were required to have a stable dosage of methotrexate between 7.5 and 25 mg/week for ≥8 weeks prior to the study. Key exclusion criteria included glucocorticoid use >15 mg/day (prednisone or equivalent); scheduled surgery or joint replacement in the hands, wrists, or feet; pregnancy; or use of either a biologic agent for RA or leflunomide within the prior 8 weeks. Patients with contraindications to whole-body magnetic resonance imaging (MRI) were excluded. Subjects were simultaneously enrolled in the hand BMD substudy if their visits were at one of the 9 investigator centers that had a GE Lunar scanner (GE Lunar, Madison, WI) with suitable software.

Study design. Patients were randomly allocated in a 1:1:1 ratio to receive denosumab 60 mg, denosumab 180 mg, or matching placebo, administered subcutaneously at baseline and again at 6 months. All of the patients were instructed to take supplements containing 0.5–1.0 gm of elemental calcium and 400–800 IU of vitamin D daily. Patients were allowed to change doses of methotrexate or add hydroxychloroquine and/or sulfasalazine (alone or in combination), and add or change doses of steroids or nonsteroidal antiinflammatory drugs at any time throughout the study, except within 2 weeks prior to a study visit. Patients were allowed to use bisphosphonates. Rescue with anti-TNF therapy was allowed after 6 months.

Institutional review boards and independent ethics committees of the participating medical centers approved the protocol and amendments. Patients gave written informed consent before initiating any study-related procedures. The principles of the Declaration of Helsinki were followed.

Table 1. Baseline demographics and disease characteristics*

	Hand substudy			All enrolled in original study (n = 227)
	Placebo (n = 13)	Denosumab 60 mg (n = 21)	Denosumab 180 mg (n = 22)	
Women, no. (%)	13 (100)	14 (67)	17 (77)	166 (73)
White, no. (%)	11 (85)	19 (90)	18 (82)	187 (82)
Age (men and women), years	55.2 ± 14.0	57.7 ± 11.0	58.7 ± 11.7	57.4 ± 11.2
Age (women), years	55.2 ± 14.0	56.7 ± 12.2	59.7 ± 13.1	57.0 ± 11.9
Disease duration, years	10.3 ± 6.6	12.6 ± 5.7	15.8 ± 9.9	11.0 ± 9.1
Rheumatoid factor positive, no. (%)	11 (85)	19 (90)	18 (82)	176 (78)
Methotrexate weekly dosage, mg	14.6 ± 3.8	16.2 ± 4.2	17.1 ± 5.0	16.1 ± 4.4
Corticosteroid use, no. (%)	2 (15)	6 (29)	9 (41)	84 (37)
Bisphosphonate use, no. (%)	3 (23)	3 (14)	5 (23)	49 (22)
Lumbar spine T score	−0.20 ± 1.03	−0.04 ± 1.87	−0.42 ± 1.69	−0.50 ± 1.57
Total hip T score	−0.19 ± 0.90	−1.08 ± 1.50	−0.56 ± 1.37	−0.69 ± 1.23
MRI erosion score (hands; range 0–500)	43.2 ± 32.0	61.6 ± 45.7	49.6 ± 48.8	39.8 ± 37.1
Modified Sharp erosion score (hands; range 0–160)	9.9 ± 11.2	19.3 ± 16.2	15.9 ± 18.3	12.6 ± 15.0
Total modified Sharp score (hands; range 0–280)	18.9 ± 19.6	39.7 ± 31.9	32.4 ± 38.4	24.7 ± 29.2
Total modified Sharp score (hands and feet; range 0–448)	35.4 ± 41.5	56.1 ± 46.5	57.0 ± 65.8	40.4 ± 46.8

* Values are the mean ± SD unless otherwise indicated. MRI = magnetic resonance imaging.

Study assessments. BMD of both hands was measured by DXA at baseline and at 1, 6, and 12 months. The entire hand (including the wrist bones but excluding the ends of the radius and ulna) was included in the analysis (Figure 1). All of the measurements were made using the "Hand" software package on GE Lunar scanners (the precision of repeat measurements is ±0.01 gm/cm^2). All of the scans were analyzed by a single technician. The calibration of each DXA scanner was monitored to verify stable performance during the course of the trial. A calibration phantom was measured daily on each scanner and the results were collected and analyzed using cumulative sum control charts (15). No drift in scanner calibration occurred during the trial. In addition, calibration differences among scanners were assessed using a traveling calibration phantom that was scanned once on each scanner. Calibration variation was within ±1%.

MRIs of the metacarpophalangeal joints and wrists of both hands were obtained at baseline and 6 months (13). All of the images were obtained using standardized methods at 1.5T. Two different fat-suppressed image acquisitions were used: 3-dimensional fast gradient-recalled echo (thin, contiguous sections for high resolution) and coronal 2-dimensional STIR (weighted to emphasize fluid and tissue water). Gadolinium contrast enhancement was not used in this study. The Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System score (16–18) of the metacarpophalangeal joints and wrists of both hands was modified with volume-based scoring of bone erosion for each joint from 0 to 10 with increments of 0.5 (total of 21 points and maximum total erosion score of 500). All of the images were sent to a central facility and were independently read by 2 radiologists who were experienced in MRI assessment. Reported results were the average of the 2 scores.

Radiographs of the hands/wrists and feet were obtained at baseline and at 6 and 12 months and were sent to a central facility, where they were scored by the modified Sharp/van der Heijde method (5,6). Results were the average of the scores determined by 2 physicians experienced in scoring radiographic changes who were blinded to treatment and time sequence. The correlation between changes in hand BMD and changes in erosion scores (MRI erosion score and modified Sharp erosion score) was analyzed using the Spearman's rank correlation. No statistical comparisons between treatment groups were made because of the small sample size.

Results

Of the 227 patients in the original study, 56 had DXA evaluations of hand BMD, including 13 in the placebo group, 21 in the denosumab 60 mg group, and 22 in the denosumab 180 mg group. Baseline demographic characteristics of the patients with hand BMD evaluations were similar between treatment groups and were similar to those of the original study population (Table 1). Of the patients who obtained hand BMD measurements, the patients who received denosumab tended to have higher baseline erosion scores compared with the patients who received placebo.

Mean hand BMD at 6 and 12 months increased from baseline in each of the denosumab groups and decreased from baseline in the placebo group (Figure 2A). At 6

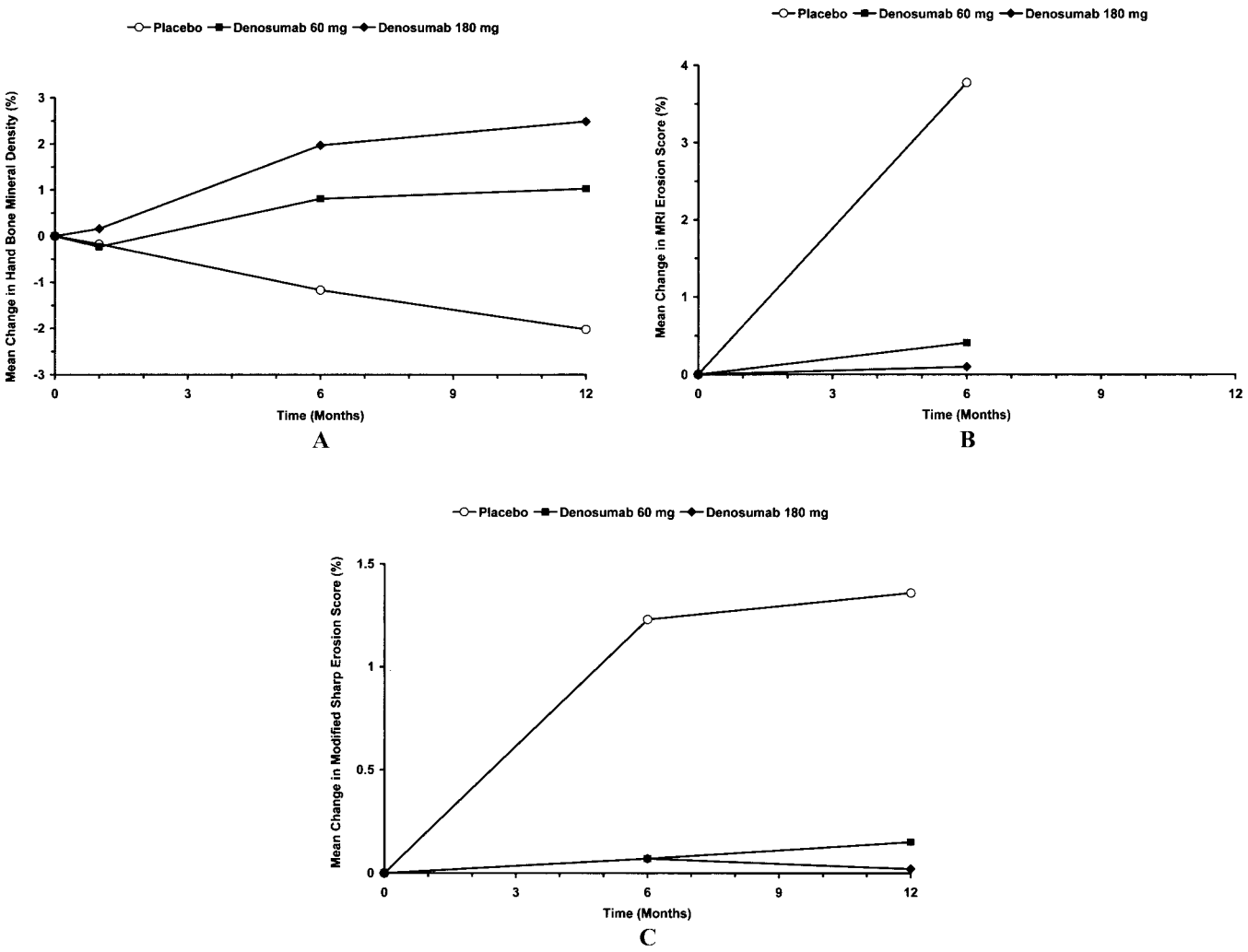

Figure 2. **A**, Mean change over time in hand bone mineral density: placebo (n = 8–9), denosumab 60 mg (n = 18–19), and denosumab 180 mg (n = 12–14). **B**, Mean change over time in magnetic resonance imaging (MRI) erosion score (hands): placebo (n = 9), denosumab 60 mg (n = 17), and denosumab 180 mg (n = 19). **C**, Mean change over time in modified Sharp erosion score (hands): placebo (n = 11), denosumab 60 mg (n = 19), and denosumab 180 mg (n = 21–22).

months, the mean changes from baseline were −1.2% in the placebo group, +0.8% in the denosumab 60 mg group, and +2.0% in the denosumab 180 mg group. At 12 months, the mean changes from baseline were −2.0% in the placebo group, +1.0% in the denosumab 60 mg group, and +2.5% in the denosumab 180 mg group.

Mean MRI hand erosion scores at 6 months for the patients in this substudy (Figure 2B) were near the baseline values in the denosumab groups (+0.4% for 60 mg and 0.1% for 180 mg) and increased from baseline in the placebo group (3.8%). Mean modified Sharp erosion scores in the hands at 6 and 12 months (Figure 2C) also remained near the baseline values in the denosumab groups (month 6: +0.07% for both 60 mg and 180 mg, month 12: +0.15% for 60 mg and 0.02% for 180 mg) and increased from baseline in the placebo group (month 6: 1.2%, month 12: 1.4%) in this subset of patients.

Scores for hand BMD and the changes from baseline in hand BMD were negatively correlated with the erosion scores and changes from baseline in erosion scores with the exception of the change in hand BMD and the change in MRI erosion score at 6 months (Table 2). The observed correlations based on those exploratory analyses were significant between hand BMD and MRI erosion score at baseline and 6 months, between hand BMD and modified Sharp erosion score in the hand at baseline, and between the change in hand BMD and the change in the modified Sharp erosion score of the hands and feet combined at 12 months.

Rates of adverse events with denosumab were similar to those with placebo. Analyses of adverse events in this trial were reported previously (13).

Discussion

In patients with RA, denosumab provided protection against erosion, and not only prevented bone loss but increased hand BMD as measured by DXA. This was demonstrated by directly measuring bone loss using DXA, the widely accepted standard of BMD measurement, and by assessing the erosions using plain radiography and also MRI, the most sensitive method available.

Table 2. Correlations between hand BMD and erosion scores*

	Not adjusted for treatment group		Adjusted for treatment group	
	Spearman's correlation†	*P*‡	Spearman's correlation†	*P*‡
Hand BMD and MRI erosion score (hands)				
Baseline (n = 38)	−0.39	0.02	−0.40	0.02
6 months (n = 35)§	−0.45	< 0.01	−0.45	< 0.01
Change from baseline to 6 months (n = 35)§	−0.08	0.66	0.07	0.71
Hand BMD and modified Sharp erosion score (hands)				
Baseline (n = 41)	−0.31	0.05	−0.31	0.05
12 months (n = 41)	−0.28	0.07	−0.27	0.09
Change from baseline to 12 months (n = 41)	−0.32	0.04	−0.28	0.07
Hand BMD and modified Sharp erosion score (hands and feet)				
Baseline (n = 41)	−0.22	0.16	−0.22	0.17
12 months (n = 41)	−0.19	0.23	−0.18	0.27
Change from baseline to 12 months (n = 41)	−0.44	< 0.01	−0.40	0.01

* BMD = bone mineral density; MRI = magnetic resonance imaging; n = number of subjects with observed values at the time point(s) of interest.
† Data were pooled from all patients with hand BMD, regardless of treatment group.
‡ Data were pooled from all patients with hand BMD, regardless of treatment group. *P* values are exploratory.
§ MRI scanning was only performed at baseline and 6 months.

Bone loss in the hands and feet of patients with RA is one of the first indications of impending bone erosions, and has been shown to be predictive of long-term RA damage. In the original study, denosumab inhibited RANKL-mediated osteoclast activity, inhibited structural damage, and significantly increased lumbar spine, hip, femoral neck, and trochanter BMD compared with the placebo group.

The results of this substudy indicated that administration of denosumab at 60 mg and 180 mg every 6 months inhibited focal bone loss in patients with RA compared with the placebo group at both 6 and 12 months. Since previous findings by Deodhar et al demonstrated that loss of hand BMD in RA patients is predictive of worse hand function, denosumab inhibition of hand BMD loss may help prevent functional deterioration of the hand (7).

Additionally, hand erosion was inhibited by denosumab as quantified by the MRI erosion score and the modified Sharp erosion score. Hand BMD also negatively correlated with erosion scores detected by MRI and radiography.

Previous studies of biologic agents have successfully shown prevention of erosions, but no agent studied to date inhibited periarticular bone loss as assessed by both DXA and DXR, including the most recent study using an anti-TNF drug (10,11). Although both types of bone loss are a consequence of RANKL-mediated osteoclast activity, the failure of anti-TNF agents to prevent periarticular bone loss may indicate two different pathologic mechanisms for these two types of bone damage. One can postulate that periarticular osteoporosis may have a TNF-independent mechanism such as inactivity. Denosumab may in part be successful due to its final downstream inhibitory effect on osteoclasts.

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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 submitted for publication. Dr. Deodhar 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. Deodhar, Peterfy, Wang, Tsuji, Newmark.

Acquisition of data. Dore, Mandel, Schechtman, Shergy, Trapp, Ory, Fuerst, Tsuji, Newmark.

Analysis and interpretation of data. Deodhar, Dore, Ory, Peterfy, Fuerst, Wang, Zhou, Tsuji, Newmark.

ROLE OF THE STUDY SPONSOR

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Erratum

In the article by Wilson et al published in the February 2009 issue of *Arthritis Care & Research* (pp. 233–239), the grant support information was inadvertently omitted from the publication. The following statement should have been included: "Supported by a grant from the Rochester Epidemiology Project (grant AR-30582-43 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases).

We regret the error.