ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 9, September 2017, pp 1741–1750
DOI 10.1002/art.40156

Effects of Teriparatide on Joint Erosions in Rheumatoid Arthritis

A Randomized Controlled Trial

D. H. Solomon,[1] J. Kay,[2] J. Duryea,[1] B. Lu,[1] M. B. Bolster,[3] R. A. Yood,[4] R. Han,[1] S. Ball,[2] C. Coleman,[1] E. Lo,[1] A. Wohlfahrt,[1] M. Sury,[1] M. Yin,[1] Z. Yu,[1] A. Zak,[1] and E. M. Gravallese[2]

Objective. **Articular erosions correlate with disability in rheumatoid arthritis (RA). Biologic agents reduce erosion progression in RA, but erosion healing occurs infrequently. This study was undertaken to assess the effects of the anabolic agent teriparatide on joint erosion volume in RA patients treated with a tumor necrosis factor inhibitor (TNFi).**

Methods. **We conducted a randomized controlled trial in 24 patients with erosive RA, osteopenia, and disease activity controlled by TNFi treatment for at least 3 months. Half were randomized to receive teriparatide for 1 year and the others constituted a wait-list control group. Subjects and primary rheumatologists were not blinded with regard to treatment assignment, but all outcomes were assessed in a blinded manner. The primary outcome measure was change in erosion volume determined by computed tomography at 6 anatomic sites. Significance within each hand and anatomic site was based on a 2-tailed test, with *P* values less than 0.05 considered significant.**

Results. **Baseline characteristics of the treatment groups were well balanced. After 52 weeks, the median change in erosion volume in the teriparatide group was −0.4 mm^3 (interquartile range [IQR] −34.5, 29.6) and did not differ significantly from that in controls (median change +9.1 mm^3 [IQR −29.6, 26.4]) (*P* = 0.28). No significant difference in change in erosion volume was noted at the radius, ulna, or metacarpophalangeal joints. Bone mineral density improved at the femoral neck and lumbar spine in the teriparatide group.**

Conclusion. **Our findings indicate that teriparatide treatment for 1 year does not significantly reduce erosion volume in the hands or wrists of patients with established RA with disease activity controlled by TNFi treatment.**

Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis, affecting 1% of the adult population and 2% of those 60 years of age or older in the US (1,2). Patients with RA experience substantial disability and pain and have an increased risk of periarticular demineralization, articular erosions, and generalized osteoporosis (3,4). Joint erosions are recognized as correlating strongly with disability (5) and are included in the US Food and Drug Administration's core outcomes for this disease (6).

To date, studies assessing healing of erosions with RA treatment have demonstrated limited erosion repair, although it has clearly been shown that repair can occur (7). Targeting osteoclastic resorption of

ClinicalTrials.gov identifier: NCT01400516.
Supported by Eli Lilly.
[1]D. H. Solomon, MD, MPH, J. Duryea, PhD, B. Lu, DrPH, MD, R. Han, MD, C. Coleman, BA, E. Lo, BA, A. Wohlfahrt, BA, M. Sury, MD, M. Yin, BA, Z. Yu, MPH, A. Zak, BA: Brigham and Women's Hospital, Boston, Massachusetts; [2]J. Kay, MD, S. Ball, BA, E. M. Gravallese, MD: University of Massachusetts Memorial Medical Center, Worcester; [3]M. B. Bolster, MD: Massachusetts General Hospital, Boston; [4]R. A. Yood, MD: Reliant Medical Group, Worcester, Massachusetts.

Dr. Kay has received consulting fees from Amgen, Eli Lilly and Company, and Sandoz (more than $10,000 each) and from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Crescendo Bioscience, Epirus Biopharmaceuticals, Genentech, GlaxoSmithKline, Hospira, Janssen Biotech, Merck Sharp & Dohme, Novartis Pharmaceuticals Corporation, Pfizer, Samsung Bioepis, Roche Laboratories, and UCB (less than $10,000 each). Dr. Gravallese has received consulting fees from Eli Lilly and Company, GlaxoSmithKline, Novo Nordisk, and Merck Sharp & Dohme (less than $10,000 each) and research grants from AbbVie.

Address correspondence to D. H. Solomon, MD, MPH, Division of Rheumatology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. E-mail: dhsolomon@partners.org.

Submitted for publication January 23, 2017; accepted in revised form May 16, 2017.

articular bone has slowed or arrested the progression of articular erosions, but has been unsuccessful in promoting erosion healing. In a randomized controlled trial comparing the bisphosphonate pamidronate with placebo in patients with RA, those taking pamidronate experienced improvement in bone mineral density (BMD) and required less frequent switching of RA treatment (8). However, there was no significant decrease in joint erosion scores among patients taking pamidronate. A second bisphosphonate trial using zoledronic acid showed slowing of erosion progression, but the changes in Sharp scores observed were small (9). Subsequently, a randomized controlled trial comparing denosumab, an antagonist of RANKL, with placebo in patients with RA demonstrated a statistically significant decrease in the number of joint erosions (10); however, patients in the denosumab treatment group had an average of only 1 fewer erosion 52 weeks after treatment compared to baseline. In a followup study comparing the effect of denosumab on healing of erosions in the second metacarpal head in RA patients with that of alendronate, partial repair of erosions was demonstrated in the denosumab-treated group only (11).

Targeted anticytokine treatments for RA, including inhibitors of tumor necrosis factor (TNFi), exhibit evidence of halting progression of articular erosions; however, even when these agents are used in combination with methotrexate (MTX), healing of joint erosions remains uncommon (12,13). In contrast, intermittent parathyroid hormone (PTH), an anabolic agent for bone, used in combination with TNFi, resulted in significant repair of joint erosions in the TNF-transgenic murine model of RA (14).

Prompted by this observation, we conducted this randomized controlled trial of teriparatide (intermittent PTH) in patients with RA who had baseline joint erosions, osteopenia, and well-controlled disease activity treated with a stable dose of TNFi for at least 3 months. The primary end point was the change in joint erosion volume, comparing RA patients who received daily teriparatide for 1 year to a control group of RA patients who continued to receive TNFi without teriparatide. Secondary end points included changes in lumbar and femoral neck BMD, as measured by dual x-ray absorptiometry (DXA), and changes in the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) (15). We hypothesized that erosion volume would be reduced in patients receiving daily teriparatide compared to controls because of augmented osteoblast-mediated bone formation at sites of articular erosion.

PATIENTS AND METHODS

Study design and population. The Teriparatide to Treat Erosions in RA (TERA) trial was a randomized controlled open-label trial of 12 months' duration in men and women with RA. Subjects were randomized to receive daily subcutaneous teriparatide 20 μg (treatment group) or to not receive teriparatide (control group). Subjects randomized to the control group underwent the same testing as those in the treatment group. All patients received 1,000 mg of calcium citrate and 800 international units of vitamin D daily.

The study population included men and women 45 years of age or older with RA who had at least 3 joint erosions on plain radiographs of the hands and wrists. RA was defined according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria (16). All subjects were also required to have osteopenia, defined as a T score between -1.0 and -2.5 on a DXA of either the lumbar spine, femoral neck, or total hip. All subjects had to have been treated with a TNFi for at least 3 months prior to the beginning of the study. Glucocorticoids were permitted at dosages of $\leq$5 mg (prednisone equivalent) per day.

Subjects who met the above criteria and could give informed consent were further assessed for the following exclusion criteria: unstable RA disease activity, a clear indication for or use of an osteoporosis treatment in the prior 12 months, current use of a drug with recognized effects on bone metabolism (anti-osteoporosis drugs, hormone replacement therapy, or anticonvulsants), a medical condition other than RA with recognized effects on bone metabolism, or a contraindication to teriparatide. Further details can be found in the Supplementary Methods, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40156/abstract.

Ethics review and registration. The study protocol was reviewed and approved by the Partners HealthCare and University of Massachusetts Memorial Medical Center Institutional Review Boards. The study and the statistical analysis plan were registered with the National Clinical Trials Registry (NCT01400516).

Study outcome measures. *Primary outcome measure.* The primary outcome measure was change in erosion volume at 6 anatomic sites in each hand or wrist. Detailed erosion assessment methods are described in the Supplementary Methods, which include a figure demonstrating the method, and in a prior publication (17). Briefly, both hands were scanned using a Siemens Somatom Definition AS computed tomography (CT) scanner. Each subject was placed prone on the scanner table, with one arm held above the head with the wrist in a straight position. A semiautomated software tool was used to segment the erosion margins in 3 dimensions; this method has been demonstrated to be reliable and valid (17). The total erosion volume was calculated for each hand and wrist and for each of the 6 subregions: radius, ulna, proximal carpal bones (scaphoid, lunate, triquetrum, and pisiform), distal carpal bones (capitate, hamate, trapezium, trapezoid, and the carpal metacarpal joints), metacarpophalangeal joints, and proximal interphalangeal joints. The hand-level analysis was performed with each individual hand as the study unit.

Secondary outcome measures. The secondary outcome measures included change in BMD, measured by DXA (using a Hologic 5000 bone densitometer) at the lumbar spine and

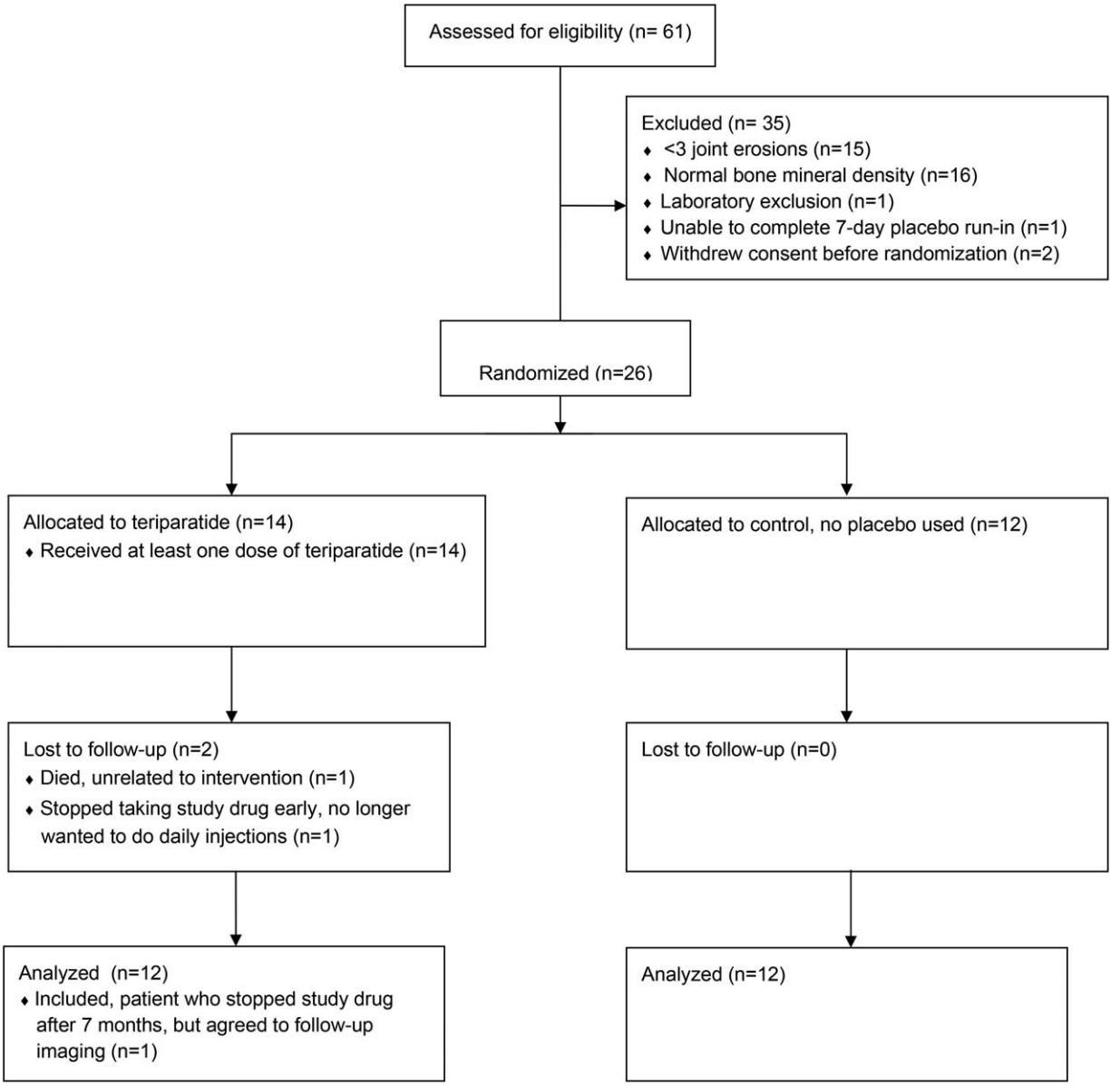

Figure 1. Diagram of subject allocation. Details are given according to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting randomized controlled trials. In the erosion volume analyses, each hand was considered separately. However, 1 subject in the teriparatide group had follow-up imaging that was not according to the imaging protocol and could not be interpreted; this subject was excluded, leaving 22 hands. One subject in the control group had 1 hand with too much hardware, preventing interpretation, leaving 23 hands. One subject in the control group had uninterpretable lumbar spine bone mineral density due to extensive osteoarthritis with osteophytes.

femoral neck. Change in BMD at each anatomic site was analyzed as a continuous variable using the nontransformed values. We assessed the actual change in BMD from baseline to 12-month follow-up, as well as the percent change. Plain radiographs of the hands and wrists were all scored by a single experienced musculoskeletal radiologist (RH) using the van der Heijde modification of the total Sharp score (SHS) (18,19). All images were de-identified and read in a blinded manner. Each subject's radiographs were read in pairs without knowledge of sequence.

Sample size considerations. We used estimates derived from the pretrial replication study (17) to determine the sample size for this trial. We considered analyses both at the level of the subject and at the level of the individual hand. Assessing individual hands provided twice as many observations (2 hands for each patient), but these observations were not independent. In the pilot analysis that evaluated 5 patients (10 hands), log transformation was applied to total volumes to achieve an approximately normal distribution. The average value of log-transformed total volume was 5.32, with a standard deviation

Table 1. Baseline characteristics of subjects by treatment group in the TERA trial*

	Control subjects (n = 12)	Subjects receiving teriparatide (n = 12)
Female	9 (75)	9 (75)
Age, median (IQR) years	61 (56, 65)	63 (56, 69)
RA disease duration, median (IQR) years	18 (6, 33)	19 (13, 24)
Oral glucocorticoid use†	0 (0)	3 (25)
Rheumatoid factor or anti-CCP positive	9 (75)	11 (92)
TNF antagonist use	12 (100)	12 (100)
Etanercept	8 (67)	5 (42)
Adalimumab	1 (8)	4 (33)
Infliximab	3 (25)	2 (17)
Golimumab	0 (0)	1 (8)
Nonbiologic DMARD use	6 (50)	8 (67)
SHS, mean ± SD	80 ± 48	55 ± 37
Erosion score	45 ± 26	31 ± 16
Joint space narrowing	35 ± 24	24 ± 22
Total erosion volume, median (IQR) mm^3	571.4 (160.0, 1,341.6)	369.8 (171.0, 1,163.9)
DAS28-CRP, median (IQR)	3.0 (1.7, 3.6)	2.0 (1.6, 3.6)
Modified Stanford Health Assessment Questionnaire, mean ± SD	0.14 ± 0.25	0.18 ± 0.34
EQ-5D, mean ± SD	0.84 ± 0.21	0.84 ± 0.12
hsCRP, median (IQR) mg/liter	1.1 (0.4, 2.1)	1.3 (1.0, 2.6)
Bone mineral density, mean ± SD gm/cm^2		
Spine, anteroposterior	0.93 ± 0.11	0.91 ± 0.09
Femoral neck	0.73 ± 0.09	0.68 ± 0.06

* Except where indicated otherwise, values are the number (%). *P* values were calculated using Student's *t*-test for continuous variables and chi-square tests for categorical variables, except for the *P* value for total erosion volume, which was calculated using Wilcoxon's rank sum test, and the *P* value for oral glucocorticoid use, which was calculated using Fisher's exact test. No significant differences were observed between the control and teriparatide groups (all $P > 0.10$). TERA = Teriparatide to Treat Erosions in Rheumatoid Arthritis; IQR = interquartile range; RA = rheumatoid arthritis; anti-CCP = anti–cyclic citrullinated peptide; TNF = tumor necrosis factor; DMARD = disease-modifying antirheumatic drug; SHS = modified Sharp/van der Heijde score; DAS28-CRP = Disease Activity Score using the C-reactive protein level; EQ-5D = EuroQol 5-domain instrument; hsCRP = high-sensitivity CRP.

† Dosage was measured in prednisone equivalents. The 3 subjects in the teriparatide group who were receiving glucocorticoids all received 5 mg per day.

of 1.34. Assuming a moderate intracluster correlation between the 2 hands and wrists from the same person of 0.5, we estimated a required sample size of 24 hands per group (12 patients) to achieve 80% power, given a 2-sided significance level (alpha) of 0.05 (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40156/abstract).

Statistical analysis. Relevant baseline subject characteristics were compared between the 2 groups using 2-sample *t*-tests, chi-square tests, or nonparametric tests when applicable. Data are presented as the mean ± SD or median (interquartile range [IQR]).

The outcome for the primary analysis compared the changes in erosion volume from baseline to follow-up for the subjects receiving teriparatide versus controls. Achievement of the primary outcome was defined as a significantly better change in erosion volume in the whole hand (i.e., either less erosion volume or less increase in erosion volume) for teriparatide users than for controls. We also assessed whether change in erosion volume in 3 or more of the 6 subregions was better among teriparatide users than controls. Significance at the subregion level and the whole hand level was based on a 2-tailed test of significance with a *P* value of less than 0.05 considered statistically significant.

For all analyses, we analyzed the data at the level of the hand, adjusting for within-subject correlation between the 2 hands using a linear mixed model, also called a random-effects model. Use of a linear mixed model is a common way to handle correlated continuous data such as repeated measures or clustered data, allowing variation from cluster to cluster (20). We planned to include baseline patient characteristics found to be imbalanced across groups (unadjusted $P < 0.10$), but there were none. We analyzed the data on all subjects with interpretable scans from baseline and 12 months. Of note, one subject decided after 7 months of treatment with teriparatide to withdraw from the study because of personal reasons. She agreed to return for a repeat set of radiographs, CT scans, and DXA, and these values were included in the primary analysis. Also, one hand of one control subject contained hardware, which rendered the CT image uninterpretable, and one intervention subject had follow-up CT scans that were performed using an incorrect imaging protocol. These CT scans were excluded from the analysis. Finally, one subject in the control group had a lumbar spine BMD that was uninterpretable due to extensive osteoarthritis with osteophytes; therefore a lumbar T score was not reported for this subject.

Several exploratory subgroup analyses were performed. These included analyses of patients grouped based on

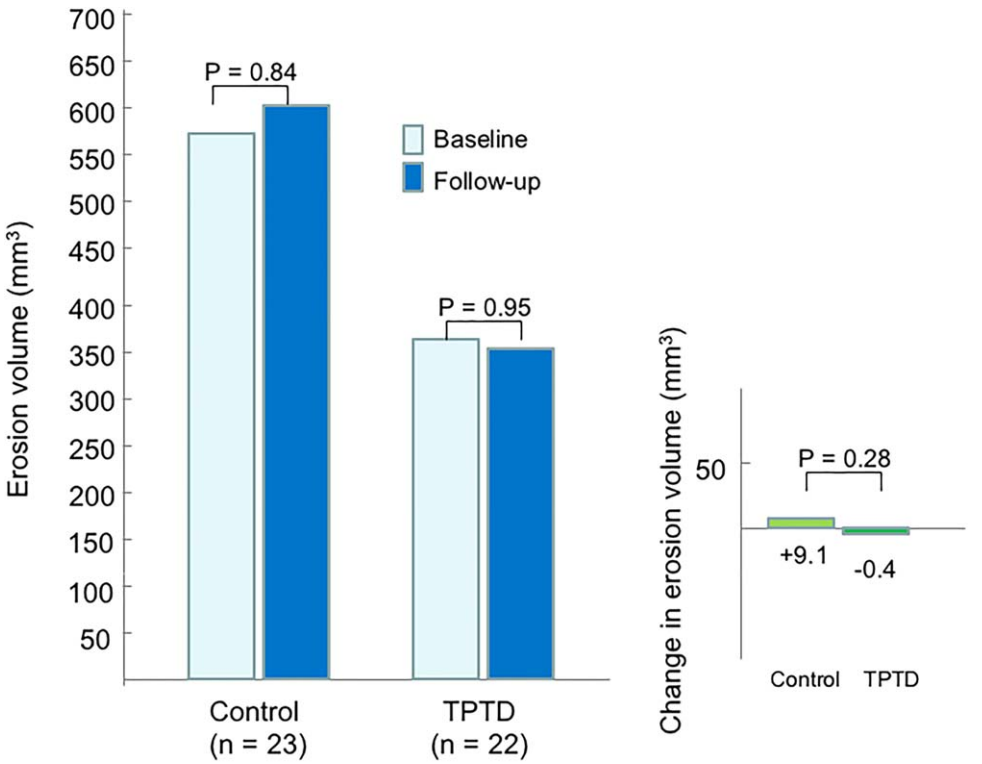

Figure 2. Left, Median total erosion volume at baseline and 1-year follow-up in the control and teriparatide (TPTD) groups. The interquartile range (IQR) for the erosion volume at baseline was 160.0, 1,341.6 for controls and 171.0, 1,163.9 for teriparatide-treated patients. The IQR for the erosion volume at follow-up was 167.8, 1,110.7 for controls and 181.0, 971.9 for teriparatide-treated patients. *P* values were determined by Wilcoxon's rank sum test. Right, Median change in total erosion volume from baseline to 1 year in the control and teriparatide groups. The IQR for the change in erosion volume was −29.6, 26.4 for controls and −34.5, 29.6 for teriparatide-treated patients. The *P* value was determined in a linear mixed model.

corticosteroid use at baseline, RA remission (using the most inclusive criteria, as defined by a DAS28-CRP of ≤2.6), high-sensitivity CRP level of <3 mg/liter, and a total erosion volume less than the median for the total study population (based on SHS). The secondary analyses were all considered exploratory and followed the same analytic strategy as the primary analyses. Due to small sample sizes, unadjusted linear mixed models were used in subgroup analyses. We did not account for potential multiple testing for these exploratory analyses. All analyses were conducted using SAS 9.4.

RESULTS

We randomized 26 subjects; 14 initially received teriparatide but 2 dropped out prematurely and could not be rescanned. This left 12 subjects in the teriparatide group and 12 in the control group who could be analyzed (see Figure 1). All but 1 subject in the teriparatide group, who withdrew for personal reasons, completed the 12-month protocol. By design, all subjects were receiving a stable dose of a TNFi, with most receiving etanercept or adalimumab. The 2 treatment groups were well balanced with respect to baseline characteristics (Table 1). The median age of all study subjects was 62 years, and 75% of the subjects in each group were women. Subjects had established RA with a median disease duration of 18 years, and 83% tested positive for either rheumatoid factor or IgG anti–cyclic citrullinated peptide antibodies. At baseline 3 subjects in the teriparatide group were taking a stable daily glucocorticoid dose equivalent to prednisone 5 mg at baseline; no subjects in the control group were receiving glucocorticoids. The median DAS28-CRP was 3.0 in the control group and 2.0 in the teriparatide group, with about half of all subjects being in remission based on a DAS28-CRP of ≤2.6. The mean modified Health Assessment Questionnaire score (21) was 0.16, and the mean SHS at baseline was 67. T1

The median total erosion volume per hand/wrist at baseline was 571.4 mm^3 (IQR 160.0, 1,341.6) in control subjects and 369.8 mm^3 (IQR 171.0, 1,163.9) in subjects randomized to receive teriparatide; while numerically different, these values were not significantly different ($P = 0.94$). The change in total erosion volume

Table 2. Subregion erosion volume (mm^3) by treatment group in the TERA trial*

	Control subjects (n = 23)	Subjects receiving teriparatide (n = 22)
Radius†		
Baseline	7.7 (0, 52.8)	43.7 (0, 162)
Follow-up	9.8 (0, 75.1)	55.2 (0, 177.4)
Change from baseline to follow-up	0 (–2.9, 0.4)	0 (–7.1, 1)
Ulna		
Baseline	3.9 (0, 39.1)	4.7 (0, 77.6)
Follow-up	2.5 (0, 42.4)	8.9 (0, 63)
Change from baseline to follow-up	0 (–1.1, 0.6)	0 (–2.6, 4.7)
Metacarpophalangeal joints		
Baseline	122 (12.3, 186.1)	67.8 (20.4, 192.6)
Follow-up	127.1 (8.5, 203.1)	72.3 (20.5, 194.4)
Change from baseline to follow-up	−2 (–20, 3.2)	−0.7 (–21.2, 0.7)
Proximal interphalangeal joints		
Baseline	2 (0, 22.3)	3.9 (0, 14.8)
Follow-up	1.4 (0, 15.2)	5 (0, 10.3)
Change from baseline to follow-up	0 (–2.5, 0)	0 (0, 2)

* Values are the median (interquartile range). The n values are the number of hands/wrists included in the analysis. Imaging could not be interpreted for selected anatomic sites in some subjects. Proximal and distal carpal bones were not included because too many of the computed tomography images did not allow separation of erosions into separate subregions. *P* values were calculated using a linear mixed model. There were no significant differences between groups. TERA = Teriparatide to Treat Erosions in Rheumatoid Arthritis.

† The n values were 18 in the control group and 19 in the teriparatide group, due to the fact that the radius could not be separated from the proximal carpal bones on the computed tomography scan assessment.

between baseline and 1-year measurements did not differ between treatment groups, with a difference in change of 9.5 mm^3 ($P = 0.28$) (Figure 2). Several outlier values (extremely high total erosion volumes) were noted when examining each observation separately (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40156/abstract). The results did not change after 1 outlier was excluded from each group.

Erosion volume was assessed in each of the 6 subregions. None of the changes in erosion volume in any of the subregions differed significantly by treatment group (see Table 2), and none of the prespecified subgroup analyses demonstrated significant differences (see Table 3). Based on the clinical observation that the second and third metacarpophalangeal and proximal interphalangeal joints are most likely to develop erosions, we also explored change in erosion volume at these joints and found no significant differences between the teriparatide and control groups (see Supplementary Figures 2 and 3 and Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40156/abstract).

BMD increased significantly in the teriparatide group, compared to the control group, at the lumbar spine (difference in change 0.07 ± 0.08 gm/cm^2; $P = 0.01$) and femoral neck (difference in change 0.05 ± 0.06 gm/cm^2; $P = 0.01$) (Figure 3). The control subjects exhibited small reductions in BMD. In addition, there were no differences between treatment and control groups in the change from baseline to 1 year in SHS (difference in change -0.75 ± 3.47; $P = 0.39$) (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40156/abstract).

DISCUSSION

In RA, inflamed synovial tissues migrate into the bone microenvironment and promote the generation of osteoclasts that resorb bone (3). This results in the articular erosions that are commonly observed in RA and that are associated with substantial disability. Inflammation in the bone microenvironment in RA also suppresses bone formation and erosion repair (22–24). We hypothesized that, in addition to controlling inflammation at sites of erosion, promoting osteoblast differentiation and function through the use of an anabolic agent would affect significant erosion repair. In fact, in the TNF-transgenic mouse model of RA, the addition of PTH allowed for the healing of articular erosions in young mice in which inflammation was well controlled using TNFi (14). Based on this observation, we designed a randomized controlled trial to test whether the anabolic agent teriparatide would repair erosions in RA

Table 3. Total erosion volume (mm^3) in prespecified subgroups by treatment group in the TERA trial*

	Control subjects	Subjects receiving teriparatide
Oral glucocorticoid use, no†		
No.	23	16
Baseline	571.4 (160, 1,341.6)	440.7 (219.6, 1,055.3)
Follow-up	600.3 (167.8, 1,110.7)	479.1 (221.7, 943.9)
Change from baseline to follow-up	9.1 (–29.6, 26.4)	17 (–31.7, 54.3)
Rheumatoid arthritis remission, yes‡		
No.	12	12
Baseline	775 (353.8, 1,170.8)	432.8 (194.1, 900.3)
Follow-up	728.5 (399.4, 1,078.6)	446.6 (182.1, 841.8)
Change from baseline to follow-up	5.4 (–57.3, 45)	−16.2 (–58.3, 25.1)
Rheumatoid arthritis remission, no‡		
No.	11	10
Baseline	242.4 (50, 1,652.8)	302.1 (121.7, 1,192.2)
Follow-up	263.3 (63.7, 1,530.6)	319.1 (181, 1,307.5)
Change from baseline to follow-up	9.1 (–2.8, 20.8)	17 (–31.8, 79)
hsCRP <3 mg/liter		
No.	21	16
Baseline	483.1 (160, 983)	221.9 (144.8, 791.8)
Follow-up	580.5 (167.8, 1,046.5)	221.7 (175.1, 739.3)
Change from baseline to follow-up	11.2 (–6.7, 26.4)	−1 (–38.6, 22.8)
hsCRP ≥3 mg/liter		
No.	2	6
Baseline	1,235.3 (999.9, 1,470.6)	989.3 (503.8, 10,796.9)
Follow-up	1,178 (970.3, 1,385.7)	1,066.8 (641.7, 10,263.1)
Change from baseline to follow-up	−57.3 (–84.9, −29.6)	66.2 (–26.7, 160.8)
Erosion volume less than the median		
No.	10	12
Baseline	105 (35, 242.4)	191.9 (117.2, 266.9)
Follow-up	115.7 (52.1, 244.1)	184.7 (158.5, 261.7)
Change from baseline to follow-up	12.4 (2.5, 17.8)	−1 (–31.7, 19.1)
Erosion volume equal to or greater than the median		
No.	13	10
Baseline	999.9 (687.9, 1,470.6)	1,178 (636.7, 1,377.3)
Follow-up	1,046.5 (650.4, 1,385.7)	1,135.3 (767.7, 1,366)
Change from baseline to follow-up	−6.7 (–84.9, 36.1)	9.7 (–78.5, 138)

* Values are the median (interquartile range). The number of hands/wrists included in the analysis are shown. Imaging could not be interpreted for selected anatomic sites in some subjects. *P* values were calculated using a linear mixed model. There were no significant differences between groups. TERA = Teriparatide to Treat Erosions in Rheumatoid Arthritis; hsCRP = high-sensitivity C-reactive protein.
† No subjects in the control group were receiving oral glucocorticoids, so only the subgroups of nonusers could be analyzed separately.
‡ Rheumatoid arthritis remission was defined as a Disease Activity Score in 28 joints using the C-reactive protein level of ≤2.6.

patients in whom disease activity was well controlled with a TNFi. This was a proof-of-principle study for repair of inflammation-induced bone damage, but the trial did not meet its primary superiority end point. Although improvements in BMD were observed in the teriparatide-treated group, confirming that subjects were compliant with taking study medication, there was no improvement in overall hand/wrist erosion volume or in erosion volume at specific anatomic sites.

Although many drugs approved to treat RA slow or arrest progression of joint erosions, few treatments have been shown to reduce erosion size or repair articular bone damage. Occasional repair of erosions has been seen using advanced imaging in patients in whom inflammation was controlled with TNF inhibition in combination with MTX (12). In addition, studies using high-resolution CT demonstrated limited erosion repair in patients treated with TNF inhibitors plus MTX, with interleukin-6 receptor inhibition (13,25), and with denosumab (11). In all of those studies, repair of erosions was incomplete.

It is worthwhile to consider why teriparatide may have failed to repair erosions in this study. In studies using the serum-transfer model of arthritis in young

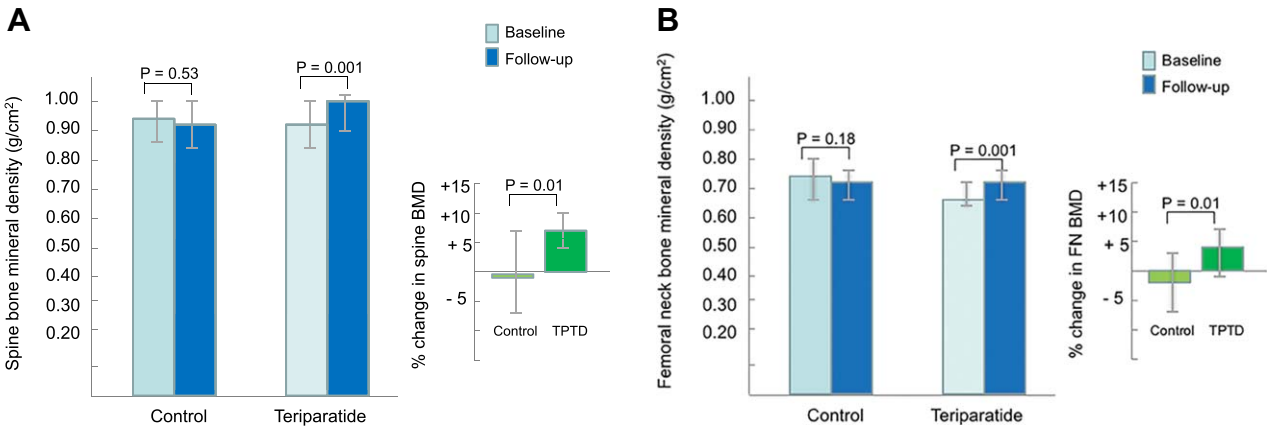

Figure 3. **A,** Left, Lumbar spine bone mineral density (BMD) at baseline and 1-year follow-up in the control and teriparatide (TPTD) groups. Right, Change in lumbar spine BMD from baseline to 1 year in the control and teriparatide groups. **B,** Femoral neck (FN) BMD at baseline and 1-year follow-up in the control and teriparatide groups. Right, Change in femoral neck BMD from baseline to 1 year in the control and teriparatide groups. Values are the mean ± SD. *P* values were determined by Wilcoxon's rank sum test.

mice in the setting of resolution of articular inflammation, it was demonstrated that eroded articular bone is lined by immature cells of osteoblast lineage that differentiate and form bone to repair erosions (22,23). Thus, if inflammation is well controlled, repair of articular bone damage can occur. This is consistent with findings in RA patients demonstrating that erosion repair is seen only in joints that are clinically inactive, without evidence of swelling (24). It is possible that the patients enrolled in this trial may still have had residual joint inflammation, although magnetic resonance imaging or ultrasound was not performed to address this possibility. The mean DAS28-CRP of 2.0 suggests well controlled disease, but it has been shown that even in the setting of clinically controlled inflammation, residual synovitis can exist (26). Thus, inflammation, if present, could continue to inhibit osteoblast differentiation and function.

It is also likely that animal models of RA are imperfect representations of disease in humans. Many of these models, including the serum-transfer model, generate articular inflammation with rapid onset and limited duration. The effects of this limited inflammation in the bone microenvironment may be different from that which occurs in RA patients with a mean disease duration of 18 years, as in this trial. Longstanding inflammation may permanently alter the bone marrow niche, limiting the number of mesenchymal stem cells available or their ability to differentiate to osteoblasts (27). It is possible that if teraparitide had been used in patients with RA of recent onset and/or in younger patients, greater preservation of the bone marrow niche might have yielded a different result. Alternatively, it may be necessary to treat patients with teriparatide for longer than the 1-year duration used in this study, since trials of teriparatide in osteoporosis have demonstrated significant benefit with a second year of treatment (28).

This study has some limitations. Although it was conducted as a randomized controlled trial, control subjects did not receive a daily placebo injection; thus, subjects and their physicians were not blinded with regard to treatment assignment. However, the imaging studies, including plain radiographs, BMD measurements, and 3-dimensional CT scans, were evaluated using objective measures, in a blinded manner. Statistical analyses were also performed in a blinded manner. In addition, while our sample size calculations suggested adequate statistical power, the sample size was small and the assumptions for effect size may not have been as large as predicted. A larger trial would have allowed for subgroup analyses and a more robust conclusion.

In conclusion, addition of teriparatide to the treatment regimen of patients with longstanding RA and low disease activity on a stable dose of TNFi did not reduce joint erosion volume in this study, despite clear improvement in BMD. New anabolic agents are currently being developed for the treatment of osteoporosis that have different mechanisms of action from teriparatide and that may induce erosion healing. These include an antibody to sclerostin, an inhibitor of the Wnt signaling pathway, that promotes osteoblast function (29). However, an anti-sclerostin antibody was studied in TNF-driven murine models of RA and was found to promote TNF signaling and augment inflammation (30), suggesting complex interactions of factors that act on inflammation and bone at erosion sites (30). Further studies in this area will be needed to better define the

changes to the bone marrow niche in RA and the potential effects of teriparatide and other anabolic agents over time on inflammation and articular erosion.

ACKNOWLEDGMENT

The authors thank Joel Finkelstein for serving as the Data Safety Monitor.

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. Solomon 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. Solomon, Kay, Gravallese.

Acquisition of data. Solomon, Kay, Bolster, Yood, Ball, Coleman, Lo, Wohlfahrt, Zak, Gravallese.

Analysis and interpretation of data. Solomon, Kay, Duryea, Lu, Han, Sury, Yin, Yu, Gravallese.

ROLE OF THE STUDY SPONSOR

Eli Lilly had opportunities to review the study design, data analysis plan, and draft of the manuscript. The decision to submit the manuscript for publication was made by the authors. Publication of this article was not contingent upon approval by Eli Lilly.

REFERENCES

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778–99.
2. Rasch EK, Hirsch R, Paulose-Ram R, Hochberg MC. Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States: effect of different methods of case classification. Arthritis Rheum 2003;48:917–26.
3. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol 2012; 8:656–64.
4. Goldring SR. Periarticular bone changes in rheumatoid arthritis: pathophysiological implications and clinical utility. Ann Rheum Dis 2009;68:297–9.
5. Scott DL, Pugner K, Kaarela K, Doyle DV, Woolf A, Holmes J, et al. The links between joint damage and disability in rheumatoid arthritis. Rheumatology (Oxford) 2000;39:122–32.
6. US Department of Health and Human Services. Guidance for industry clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA). February 1999. URL: https://www.fda.gov/downloads/Drugs/Guidances/ucm071579.pdf.
7. Sharp JT, van Der Heijde D, Boers M, Boonen A, Bruynesteyn K, Emery P, et al. Repair of erosions in rheumatoid arthritis does occur: results from 2 studies by the OMERACT Subcommittee on Healing of Erosions. J Rheumatol 2003;30:1102–7.
8. Eggelmeijer F, Papapoulos SE, van Paassen HC, Dijkmans BA, Valkema R, Westedt ML, et al. Increased bone mass with pamidronate treatment in rheumatoid arthritis: results of a three-year randomized, double-blind trial. Arthritis Rheum 1996;39:396–402.
9. Jarrett SJ, Conaghan PG, Sloan VS, Papanastasiou P, Ortmann CE, O'Connor PJ, et al. Preliminary evidence for a structural benefit of the new bisphosphonate zoledronic acid in early rheumatoid arthritis. Arthritis Rheum 2006;54:1410–4.
10. Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT, et al. 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.
11. Yue J, Griffith JF, Xiao F, Shi L, Wang D, Shen J, et al. Repair of bone erosion in rheumatoid arthritis by denosumab: a high-resolution peripheral quantitative computed tomography study. Arthritis Care Res (Hoboken) 2016. E-pub ahead of print.
12. Dohn UM, Ejbjerg B, Boonen A, Hetland ML, Hansen MS, Knudsen LS, et al. No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. Ann Rheum Dis 2011;70:252–8.
13. Finzel S, Rech J, Schmidt S, Engelke K, Englbrecht M, Stach C, et al. Repair of bone erosions in rheumatoid arthritis treated with tumour necrosis factor inhibitors is based on bone apposition at the base of the erosion. Ann Rheum Dis 2011;70:1587–93.
14. Redlich K, Gortz B, Hayer S, Zwerina J, Doerr N, Kostenuik P, et al. Repair of local bone erosions and reversal of systemic bone loss upon therapy with anti-tumor necrosis factor in combination with osteoprotegerin or parathyroid hormone in tumor necrosis factor-mediated arthritis. Am J Pathol 2004; 164:543–55.
15. Van Riel PL. Disease Activity Score in rheumatoid arthritis. URL: http://www.das-score.nl/www.das-score.nl/index.html.
16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
17. Duryea J, Russell R, Gravallese EM, Kay J, Han R, Lu B, et al. Development and validation of a semiautomated method to measure erosion volume in inflammatory arthritis by computed tomography scanning. Arthritis Rheumatol 2016;68: 332–6.
18. Van der Heijde DM, van Riel PL, Gribnau FW, Nuver-Zwart IH, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036–8.
19. Van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van 't Hof MA, van Rijswijk MH, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992;35:26–34.
20. West B, Welch K, Galecki A. Linear mixed models, a practical guide using statistical software. Boca Raton (FL): Chapman & Hall/CRC; 2007.
21. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 1983;26:1346–53.
22. Walsh NC, Reinwald S, Manning CA, Condon KW, Iwata K, Burr DB, et al. Osteoblast function is compromised at sites of focal bone erosion in inflammatory arthritis. J Bone Miner Res 2009;24:1572–85.
23. Matzelle MM, Gallant MA, Condon KW, Walsh NC, Manning CA, Stein GS, et al. Resolution of inflammation induces osteoblast function and regulates the Wnt signaling pathway. Arthritis Rheum 2012;64:1540–50.
24. Lukas C, van der Heijde D, Fatenajad S, Landewe R. Repair of erosions occurs almost exclusively in damaged joints without swelling. Ann Rheum Dis 2010;69:851–5.
25. Finzel S, Rech J, Schmidt S, Engelke K, Englbrecht M, Schett G. Interleukin-6 receptor blockade induces limited repair of

bone erosions in rheumatoid arthritis: a micro CT study. Ann Rheum Dis 2013;72:396–400.
26. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008; 58:2958–67.
27. Lepperdinger G. Inflammation and mesenchymal stem cell aging. Curr Opin Immunol 2011;23:518–24.
28. Lindsay R, Krege JH, Marin F, Jin L, Stepan JJ. Teriparatide for osteoporosis: importance of the full course. Osteoporos Int 2016;27:2395–410.
29. Chen XX, Baum W, Dwyer D, Stock M, Schwabe K, Ke HZ, et al. Sclerostin inhibition reverses systemic, periarticular and local bone loss in arthritis. Ann Rheum Dis 2013;72:1732–6.
30. Wehmeyer C, Frank S, Beckmann D, Bottcher M, Cromme C, Konig U, et al. Sclerostin inhibition promotes TNF-dependent inflammatory joint destruction. Sci Transl Med 2016;8:330ra35.