Reduced Loss of Hand Bone Density With Prednisolone in Early Rheumatoid Arthritis

Results From a Randomized Placebo-Controlled Trial

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Background: Bone damage in rheumatoid arthritis presents as osteoporosis and joint erosions. Prednisolone has been shown to reduce the rate of hand joint destruction as seen on radiography but has not been shown to reduce the rate of hand bone loss.

Methods: In a double-blind study comparing oral prednisolone (7.5 mg/d for 2 years) with placebo, hand bone density assessed with digital x-ray radiogrammetry was examined in 95 patients with rheumatoid arthritis with disease duration of less than 2 years.

Results: The mean loss of hand bone density was less in prednisolone-treated patients compared with placebo-treated patients at the 1-year follow-up (−0.011 vs −0.022 g/cm²) (P = .005) and at the 2-year follow-up (−0.026 vs −0.039 g/cm²) (P = .03). The mean percentage group difference in loss of hand bone density was 2.8% (P = .004) at the 1-year follow-up and 3.5% (P = .01) at the 2-year follow-up. In the first year, C-reactive protein, a marker of inflammation, was strongly correlated with hand bone loss in placebo-treated patients but not in prednisolone-treated patients, suggesting that prednisolone breaks the link between bone loss and inflammation.

Conclusions: To our knowledge, this is the first double-blind randomized study to show that disease-related loss of hand bone density in rheumatoid arthritis can be decelerated by prednisolone. This finding suggests that the deleterious effect of prednisolone on bone may be countered by its anti-inflammatory effect.

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GLUCOCORTICOIDS SUPPRESS SIGNS AND SYMPTOMS OF INFLAMMATION IN RHEUMATOID ARTHRITIS AND REDUCE THE RATE OF JOINT DESTRUCTION AS SEEN ON RADIOGRAPHY,1,2 BUT THEY MAY CAUSE OSTEOPOROSIS.3 Bone damage in rheumatoid arthritis includes accelerated bone loss and joint destruction, which appear on hand radiographs as periarticular osteoporosis and joint erosions.4 Accelerated hand bone loss in early rheumatoid arthritis has been found in bone measurements of the whole hand and locally around finger joints.5-7 Therefore, quantitative measurement of hand bone density has been proposed as an outcome measure in rheumatoid arthritis and, hence, as a potential measure of response to treatment.

The benefits of low-dose glucocorticoids in controlling erosive joint damage have to be balanced against the potential dangers of bone loss. To our knowledge, immunosuppressive treatment, including glucocorticoids, has not been assessed in relation to disease-related hand bone loss in rheumatoid arthritis.

The primary objective of this study was, therefore, to examine the effect of prednisolone on hand bone loss as seen in the radiographs from the first randomized, double-blind, placebo-controlled trial of low-dose prednisolone in patients with rheumatoid arthritis.1 Second, we sought associations between changes in hand bone loss and inflammation and joint damage as seen on radiography.

METHODS

STUDY POPULATION

This study reports hand bone density data from a previously published 2-year randomized, double-blind, placebo-controlled trial comparing the addition of a fixed daily dose of prednisolone (7.5 mg) or placebo with routine treatment in rheumatoid arthritis patients with disease duration of less than 2 years at inclusion.1 The clinical, biochemical, and radiographic joint damage data have been published, and the data collection and study design were described in detail.1,9,10 In short, clinical and laboratory measures of disease were recorded every 3 months, and posteroanterior hand radiographs were performed at baseline and after the 1-year and 2-year follow-ups. Markers of disease in the present analysis include acute-phase response, measured as C-
reactive protein, and the Health Assessment Questionnaire Disability Index score. In the original article, 106 of 128 patients included had hand radiographs available at baseline and at the 2-year follow-up. For the present analysis, archived radiographs were retrieved for 93 patients having at least 2 radiographs from the 3 assessments. Of these, 71 patients had x-ray films for all 3 time points, 4 patients had no films at baseline, 9 patients had no films at year 1, and 11 patients had no films at year 2. The patients with missing films were distributed evenly across the 2 groups. Identifying labels were disguised on all radiographs, and hand bone density measurements were made without knowledge of the treatment groups. The data were analyzed blindly by one of us (G.H.), and the treatment code was opened after the completion of the primary analysis.

HAND BONE DENSITY

Hand bone density was measured on the plain radiographs of the hand using digital x-ray radiogrammetry (Pronosco Xposure System 2.0; Pronosco, Vedbaek, Denmark), a computerized version of the traditional technique of radiogrammetry originally proposed by Barnett and Nordin. A mean surrogate bone density value is calculated from cortical thickness from regions of interest measured at the center of the second, third, and fourth metacarpals. This surrogate bone density measurement (expressed as grams per square centimeter) is based on measurement of the outer and inner diameter, measuring combined cortical thickness. The theoretical background for this method has been fully described, and because it is based not on the absolute values of absorbed x-rays but on metric measurements, this method can be applied to conventional radiographs.

For analysis of hand bone density, we used the mean values from the left and the right sides. Long-term and short-term in vivo precision for digital x-ray radiogrammetry was expressed as a percentage coefficient of variation, which is the ratio of the standard deviation to the mean of the measurements. In our hands, long-term precision based on daily measurements, this method can be applied to conventional radiographs, and hand bone density measurements were made without knowledge of the treatment groups. The data were analyzed blindly by one of us (G.H.), and the treatment code was opened after the completion of the primary analysis.

RADIOGRAPHS

Data for the Larsen score for hand radiographs were extracted from the original study database. In short, the hand radiographs (including wrists) were assessed jointly by a radiologist and a rheumatologist who were unaware of the treatment assignment and the time point at which the films were obtained. Each hand was classified as erosive or nonerosive and in the placebo-treated patients by −0.011 g/cm² (95% confidence interval [CI], −0.015 to −0.006 g/cm²) and in the placebo-treated patients by −0.022 g/cm² (95% CI, −0.035 to −0.016 g/cm²). After the second year, the rate of bone loss was significantly lower in the prednisolone group compared with the placebo group. At 1-year follow-up, the Larsen score progressed by a mean of 0.6 in the prednisolone-treated patients and by 2.8 in the placebo-treated patients, and at 2-year follow-up, by 1.0 and 4.5, respectively (Figure 1).

STATISTICAL ANALYSIS

Descriptive statistics for continuous variables included means and standard deviations (with normal distribution), means and ranges (with nonnormal distribution), and 95% confidence intervals. The primary outcome analysis was the change in hand bone density in relation to the study treatment group, and comparisons between groups were examined by independent and within-group paired 2-tailed t tests. For continuous variables with a skewed distribution, the Wilcoxon rank sum test was used for comparisons between groups. χ² Test was used for comparison of categorical data. The secondary outcome analysis, testing prednisolone-treated and placebo-treated patients separately, sought relationships between change in hand bone density and inflammation, measured as C-reactive protein, for the first and second years of follow-up. Strengths of relations were tested using Spearman rank correlation coefficient because of the skewed distribution for C-reactive protein. In patients with missing data at baseline, bone loss in year 1 was estimated by using the same rate of bone loss as observed in year 2, and in patients with missing data at 2 years of follow-up, bone loss in year 2 was estimated by using the same rate of bone loss as observed in year 1. In patients with missing data at 1 year of follow-up, a constant rate of bone loss was assumed for years 1 and 2. All analyses were performed with SPSS version 11.0 (SPSS Inc, Chicago, Ill). P ≤ .05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

For the 95 patients in this study, no statistically significant differences were found at baseline between the prednisolone and the placebo groups (Table 1). Patients in both groups improved their clinical status similarly during the study, as previously reported. Analysis for the first and second years of follow-up revealed a significant difference between the treatment groups only for the change in Health Assessment Questionnaire Disability Index score at 1 year. During follow-up, no significant difference in the use of routine treatment for rheumatoid arthritis, including disease-modifying drugs, was found between the 2 groups. For the Larsen score, similar results were found for our slightly reduced number of patients as were reported in the original article, with less progression of joint damage in the prednisolone group compared with the placebo group. At 1-year follow-up, the Larsen score progressed by a mean of 0.6 in the prednisolone-treated patients and by 2.8 in the placebo-treated patients, and at 2-year follow-up, by 1.0 and 4.5, respectively (Figure 1).

HAND BONE DENSITY

After the first year, the mean hand bone density was reduced in the prednisolone-treated patients by −0.011 g/cm² (95% confidence interval [CI], −0.015 to −0.006 g/cm²) and in the placebo-treated patients by −0.022 g/cm² (95% CI, −0.031 to −0.013 g/cm²). After the second year, the changes were −0.026 g/cm² (95% CI, −0.035 to −0.016 g/cm²) and −0.039 g/cm² (95% CI, −0.051 to −0.027 g/cm²), respectively. The rate of bone loss was significantly lower in the prednisolone group compared with the placebo group at the 1-year (P = .005) and 2-year (P = .03) follow-ups. The percentage change in the prednisolone group was −1.8% (95% CI, −2.6% to −1.0%) at 1 year and −3.6% (95% CI, −5.1% to −2.2%) at 2 years, and in the placebo group it was −4.6% (95% CI, −6.4% to −2.9%) at 1 year and −7.1% (95% CI, −9.4% to −4.8%) at 2 years (Figure 1). The percentage difference in hand bone density loss, favoring prednisolone compared with placebo, was 2.8% (95% CI, 0.9%–4.8%) (P = .004) after
The first year and 3.5% (95% CI, 0.8%–6.2%) \((P = .01)\) after the second year. The overall bone loss was greater in women than in men in both treatment groups (Figure 2).

**ROBUSTNESS OF THE DATA**

When calculations for hand bone density were performed excluding patients with missing data at baseline or at the 1-year or 2-year follow-up, the mean differences in hand bone density between prednisolone-treated patients \((n=36)\) \((-0.010 \text{ g/cm}^2 [95\% \text{ CI}, -0.016\text{ to } -0.004 \text{ g/cm}^2])\) and placebo-treated patients \((n=35)\) \((-0.026 \text{ g/cm}^2 [95\% \text{ CI}, -0.038 \text{ to } -0.013 \text{ g/cm}^2])\) remained statistically significant at the 1-year follow-up \((P = .02)\) but not at the 2-year follow-up \((P = .14)\). At the 2-year follow-up, the mean differences were \(-0.021 \text{ g/cm}^2\) (95% CI, \(-0.032 \text{ to } -0.010 \text{ g/cm}^2\)) for prednisolone-treated patients and \(-0.035 \text{ g/cm}^2\) (95% CI, \(-0.049 \text{ to } -0.020 \text{ g/cm}^2\)) for placebo-treated patients.

**ASSOCIATIONS BETWEEN CHANGE IN HAND BONE DENSITY AND INFLAMMATION**

In the first year of follow-up, a strong inverse correlation between mean changes in hand bone density and C-reactive protein was found in the placebo group but not in the prednisolone group (Table 2). In the second year, a significant association was observed in the prednisolone group but not in the placebo group.

### Comment

The main finding in this placebo-controlled study is that low-dose prednisolone reduces inflammatory-related hand bone loss in patients with early rheumatoid arthritis. Substantial data from double-blind randomized controlled trials in rheumatoid arthritis have shown that treatment with some disease-modifying antirheumatic drugs, particularly blocking agents (eg, tumor necrosis factor α or interleukin 1)\(^1\)\(^7\) and glucocorticoids,\(^1\)\(^2\) retards joint damage as seen on radiography. However, ours is the first report, to our knowledge, from a double-blind randomized controlled trial to show that it is possible to retard or suppress disease-related hand or periarticular bone loss in rheumatoid arthritis. Our results fit into the current pathophysiological understanding of bone damage in...
rheumatoid arthritis that bone loss and joint destruction are related to the inflammatory disease process involving the osteoclast cell.18,19

The data from the present study support the findings by Gough et al,20 who reported that inflammation contributed more significantly to generalized bone loss than low-dose prednisolone in rheumatoid arthritis patients with active disease. This suggests that the negative effect of glucocorticoids on bone may at least partially be counteracted by decreasing disease activity in rheumatoid arthritis. In our study, bone density was only measured at the hand, a measure site for periarticular osteoporosis, and not, for example, at the spine or hip, measure sites for generalized osteoporosis, which limits the interpretation of our results. Convincing data exist that prednisolone has an overall deleterious effect on bone, with an increased risk for fractures,22,23 beyond the potential beneficial effect of prednisolone in reducing inflammatory-related bone loss in rheumatoid arthritis. In rheumatoid arthritis, the disease itself, the use of glucocorticoids, and reduced generalized bone density have been identified as independent risk factors for vertebral fractures.23,24

In the secondary analysis, hand bone loss in the first year correlated with inflammation, assessed as C-reactive protein, but only in the placebo-treated group. In the prednisolone-treated group, there was no link to C-reactive protein, despite the fact that the clinical status of patients did not differ overall between the 2 groups. This finding was consistent using multivariate linear regression analysis adjusting for age, sex, physical function (Health Assessment Questionnaire Disability Index score), and baseline Larsen score (data not shown). In the second year, a significant correlation between C-reactive protein and bone loss was observed in the prednisolone group but was no longer present in the placebo group. Therefore, it seems that prednisolone may break the link between bone loss and inflammation in the first year of prednisolone treatment but not in the following year.

The greater bone loss in women compared with men may be explained by the effect of postmenopausal osteoporosis, as no differences for disease measures between the sex groups were found for placebo-treated and prednisolone-treated patients (data not shown). The treatment effect was also observed in women and was greater than in men (Figure 2), which may indicate that the antiinflammatory effect of prednisolone on bone is demonstrated even in women with estrogen deficiency.

Quantitative bone measures have been proposed as a new outcome measure and a prognostic indicator of future disease course in rheumatoid arthritis.8 This view is supported by data indicating that loss of hand bone density in rheumatoid arthritis occurs early in the disease process and is associated with inflammation,6 damage visible on radiography,25,26 and poor functional outcome.27

A limitation for digital x-ray radiogrammetry hand bone density measurement compared with dual energy absorptiometry, which is considered the gold standard for bone density measurement, may be that the method is less validated and that only cortical bone and not trabecular bone from the metacarpal hand regions is measured. However, in rheumatoid arthritis patients, an increased hand bone loss is seen for measurements of the whole hand and more locally around the finger joints.6,7 There are several potential reasons for bone loss in the rheumatoid arthritis hand, including inflammation, immobility, and estrogen deficiency (in postmenopausal women). The radiogrammetry bone density value is calculated from cortical thickness from regions of interest measured at the center of the second, third, and fourth metacarpals. It should be considered as a surrogate bone

Table 2. Spearman Rank Correlation Coefficients Between Mean Changes in Hand Bone Density and C-reactive protein in the Prednisolone and Placebo Groups*

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Prednisolone Group (n = 46)†</th>
<th>Placebo Group (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman ρ</td>
<td>P Value†</td>
</tr>
<tr>
<td>Baseline</td>
<td>−0.14</td>
<td>.35</td>
</tr>
<tr>
<td>First year</td>
<td>−0.08</td>
<td>.60</td>
</tr>
<tr>
<td>Second year</td>
<td>−0.32</td>
<td>.03</td>
</tr>
</tbody>
</table>

* Spearman rank-order correlation coefficients between hand bone density and C-reactive protein at baseline and between changes in hand bone density in the first and second year and mean value of C-reactive protein during the first and second year in prednisolone- and placebo-treated patients.
† One patient in this group had no mean value of C-reactive protein values.
‡ Two-tailed.

Figure 2. The mean changes with 95% confidence intervals in hand bone density during treatment, according to sex and study group. P values represent differences between prednisolone-treated and placebo-treated patients by the independent t test.
density measurement, which in previous studies has been associated with inflammation and joint damage as seen on radiography in patients with rheumatoid arthritis. The present study adds evidence to the potential usefulness of this measurement in clinical trials of anti-inflammatory therapies that may have effects on disease-related periarticular bone loss.

To maintain the original study design of a blinded randomized controlled trial, the treatment code was kept secret for one of us who analyzed the data (G.H.), and the code was opened after the analyses had been performed. When our study was performed, only 95 patients having at least 2 radiographs from the baseline and 1-year and 2-year follow-ups could be identified. This is a limitation compared with the originally studied cohort that included 106 patients with radiographs. However, the results regarding progression as seen on radiography were similar in the 95 patients examined in our study to those in the original study, indicating that the loss of 11 patients does not represent any major limitation and does not reduce the significance of the results.

In conclusion, this is the first double-blind randomized study to show that disease-related hand bone loss in early rheumatoid arthritis can be reduced by treatment with low-dose prednisolone. As a consequence of our findings, quantitative bone measurement may be an alternative to radiographic imaging for assessing periarticular bone involvement in rheumatoid arthritis, especially in early disease. However, use of glucocorticoids may have a negative overall effect on generalized bone loss, leading to increased fracture risk.

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REFERENCES