PREDNISONE TREATMENT OF ELDERLY-ONSET RHEUMATOID ARTHRITIS

Disease Activity and Bone Mass In Comparison with Chloroquine Treatment

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Objective. Prednisone is frequently used in the treatment of elderly-onset rheumatoid arthritis (RA), but the balance between efficacy and toxicity, including the effect on bone mass, has not been investigated in long-term studies. This prospective, randomized study was undertaken to compare disease activity and bone mass during long-term treatment with prednisone versus chloroquine in this patient population.

Methods. Patients with active RA diagnosed at age ≥60 were randomized to receive prednisone (15 mg/day for 1 month, with the dosage tapered as low as possible thereafter) (n = 28) or chloroquine (n = 28). Patients who did not show a response received other second-line drugs as an adjunct to prednisone or as a replacement for chloroquine. Bone mass was measured by dual-energy x-ray absorptiometry. The study duration was 2 years.

Results. During the 2 years, treatment with other second-line drugs was needed for 12 patients in the prednisone group (43%) and 8 in the chloroquine group (29%). Functional capacity and disease activity improved significantly in both groups and did not differ significantly between the groups, except for a greater improvement in the prednisone group at 1 month. Radiographic scores for joint destruction progressed similarly in both groups. There was a nonsignificant excess bone loss of 1.8% in the spine and 1.5% in the hip in the prednisone group, compared with the chloroquine group.

Conclusion. Neither treatment was entirely satisfactory since a significant number of patients needed an additional second-line drug over the 2-year period.

Since their introduction in 1949 (1), the use of corticosteroids in the management of rheumatoid arthritis (RA) has remained controversial (2-4). In the initial long-term studies of cortisone, a greater reduction of disease activity in the first 2 months was found compared with aspirin treatment, but later evaluations showed no differences between treatment groups in disease activity, functional capacity, or radiographic progression (5-7). Adverse events due to cortisone were substantial (6,7). Two other long-term studies demonstrated a greater reduction of disease activity (8) and fewer erosions (8-10) in patients treated with prednisolone compared with patients treated with analgesic agents (8,9), or in patients treated with prednisone in combination with a disease-modifying antirheumatic drug (DMARD) compared with patients treated with only a DMARD (10). It has been reported that long-term low-dose prednisone (usually at <10 mg/day) has been used in the treatment of approximately one-third of RA patients seen in clinical practice (11,12). Open studies have shown good results with prednisone as the only second-line drug, in particular for patients with elderly-onset RA (13,14).

A major drawback with the use of prednisone is osteoporosis. Cross-sectional studies have shown that RA patients tend to have lower bone mass compared with controls, which has mainly been attributed to...
physical inactivity and corticosteroid use (15,16). An increased risk of fractures in RA patients has been observed in association with prednisone treatment at >5 mg/day (17–20). However, no long-term randomized trials of prednisone for RA that included measurements of bone mass have thus far been reported. The purpose of the present study was to compare the efficacy and toxicity of long-term low-dose prednisone versus chloroquine as the initial second-line treatment in active elderly-onset RA. Loss of bone mass was the feature that was focused on with respect to toxicity.

**PATIENTS AND METHODS**

**Patients.** Inclusion criteria were as follows: a diagnosis of definite or classic RA according to the 1958 criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (21) at the age of 60 years or over, and active disease that was unresponsive to 3 months of nonsteroidal antiinflammatory drug (NSAID) therapy. Active disease was defined as the presence of ≥3 swollen joints and at least 2 of the following: a modified Ritchie quine group.

Prednisone was given in a dosage of 15 mg/day as a single morning dose for 1 month. If there was clinical improvement in the opinion of the patient after 1 month, the dosage was decreased by 2.5 mg/day at intervals of 4 weeks until the lowest possible dosage was reached where the clinical improvement was maintained. If the patient then reported increasing disease activity, the dosage was increased in the same stepwise manner to a maximum level of 15 mg/day. A failure of prednisone was defined as the absence of clinical improvement in the opinion of the patient 3 months after the start of treatment or, at a later stage, the need for a dosage of 15 mg/day for more than 1 month. In either of these events, chloroquine was added to the regimen in the same dosage as used for the other treatment group, and the prednisone dosage was adjusted as described above. Chloroquine was also prescribed when prednisone had to be decreased or discontinued because of adverse events and the disease activity criteria were fulfilled. The patients were seen monthly during the first 3 months and at intervals of 1–3 months thereafter.

All patients were treated with a stable dosage of NSAID, 500 mg of an oral calcium preparation in the evening, and, if the serum level of 25-hydroxyvitamin D was <30 nmoles/liter prior to treatment, 400 units/day of cholecalciferol. Prednisone-treated patients with a history of tuberculosis were prescribed isoniazid 300 mg/day.

**Clinical assessment.** The clinical assessments were performed by a research nurse who was blinded to the treatment. The following parameters were measured at 0, 1, 3, 12, and 24 months: patient assessment of disease in comparison with baseline (4-point scale: worse, equal, slight improvement, or marked improvement), the Dutch Health Assessment Questionnaire (HAQ) (23), which is a translated and validated version of the original questionnaire (24), number of swollen joints (counting metacarpophalangeal, proximal interphalangeal, or metatarsophalangeal joints on 1 side as 1 joint; maximum 20), a modified RAI (maximum value 69), and ESR. The presence of adverse advents was documented by the treating physician.

Radiographs of the wrists, hands, and forefeet at 0, 12, and 24 months were assessed according to the criteria of Kellgren (25), by 2 rheumatologists who reviewed the radiographs together and were blinded to the treatment group. Erosions and joint space narrowing were each scored on a 5-point scale (0 = no abnormalities, 1 = doubtful abnormalities, 2 = mild but definite abnormalities, 3 = moderate erosions or joint space narrowing, and 4 = severe destructive lesions and/or ankylosis, or total loss of joint space). The total number of affected joints was defined as the number of joints having erosions and/or joint space narrowing (score ≥2). The maximum possible number of affected joints was 50, resulting in a maximum possible radiologic score of 200.

**Effects on bone.** Patients with concurrent illnesses that might affect bone mass were not included in this evaluation. The following factors with possible influence on bone mass measurements were determined at entry: body mass index (BMI; kg/m²), degree of osteophytosis in the lumbar spine (26), and physical activity (27). Physical activity was also scored at the end of the study, and the mean value was used for analysis.

Bone mass measurements were made at 0, 6, 12, and 24 months by dual-energy x-ray absorptiometry (DXA)
The short-term precision error in bone mineral density (BMD) during daily spine phantom measurements was 0.40%, while no significant time trend was observed (mean ± SD = 0.02 ± 0.07% per year). The short-term precision error for hip BMD using a hip analysis. In our opinion, BMC is preferable to BMD for the repositioning of the patient between measurements; the turer of the densitometer, expressed as standard deviation phantom was

A control group of 21 age- and sex-matched patients (8 male, 13 female; mean age 65 years, range 60–79) with miscellaneous noninflammatory conditions, recruited from the rheumatology outpatient clinic, was also studied after informed consent was obtained. The female patients in all 3 groups had been postmenopausal for more than 5 years.

The following biochemical parameters of bone metabolism were measured in RA and control patients at the start of the study and in RA patients also at 6, 12, and 24 months: serum alkaline phosphatase, osteocalcin (by radioimmunoassay) (30), and parathyroid hormone (PTH) (by immunoradiometric assay; Incstar, Stillwater, MN) (31), and creatinine, calcium, and hydroxyproline (52) in a 2-hour morning urine sample (second void). Alkaline phosphatase, creatinine, and calcium were measured by standard automated laboratory methods. After the evening meal of the preceding day, only water and medication, excluding the calcium tablet, were allowed.

Statistical analysis. The two main study questions were whether a regimen starting with prednisone as the initial second-line drug was as effective as a regimen starting with chloroquine, and whether bone loss was higher during treatment with prednisone compared with chloroquine. Based on previous studies with chloroquine in early RA, an improvement of at least 40% in the swollen joint count in the chloroquine group was expected (33). With an α level of 5% and a β level of 10%, a sample size of 22 patients per study arm is necessary to detect a difference of 1.4% in bone mass loss between groups.

The analysis was based on the intention-to-treat principle. Comparisons of outcome parameters were made within the groups and between the groups with repeated-measures (mixed-model) analysis of variance. In this manner, the available data on patients not completing the study are included in the analysis. Comparisons at single time points were made with Student’s t-test or the Mann-Whitney U test, as appropriate. The relation of several factors to bone mass loss was tested with Pearson’s product-moment correlation and multiple regression analysis.

RESULTS

Outcome. At study entry, the 2 groups were comparable with regard to demographic and clinical characteristics (Tables 1 and 2 and Figure 1), except for a higher proportion of females and a higher percentage of patients with an elevated serum IgM rheumatoid factor titer in the prednisone group. Most patients were in an early stage of the disease: 91% were enrolled in the study less than 18 months after RA was diagnosed. None of the patients had previously been treated with oral corticosteroids. Two patients in each group had been previously treated with 1 DMARD.

Table 1. General characteristics at study entry, in rheumatoid arthritis patients treated with prednisone or chloroquine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prednisone group (n = 28)</th>
<th>Chloroquine group (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (range)</td>
<td>69 (60–77)</td>
<td>70 (60–84)</td>
</tr>
<tr>
<td>% females</td>
<td>71</td>
<td>43</td>
</tr>
<tr>
<td>Disease duration in months, mean (range)</td>
<td>11 (3–106)</td>
<td>10 (3–120)</td>
</tr>
<tr>
<td>% with elevated IgM rheumatoid factor titer</td>
<td>86</td>
<td>63</td>
</tr>
</tbody>
</table>

Table 2. Radiographic scores at study entry and at 24 months, in rheumatoid arthritis patients treated with prednisone or chloroquine

<table>
<thead>
<tr>
<th></th>
<th>Prednisone group</th>
<th>Chloroquine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entry 24 months</td>
<td>Entry 24 months</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
<td>6.8 ± 6.9</td>
<td>8.0 ± 8.9</td>
</tr>
<tr>
<td>Erosion score</td>
<td>4.8 ± 6.5</td>
<td>4.6 ± 7.3</td>
</tr>
<tr>
<td>No. of affected joints</td>
<td>2.8 ± 3.3</td>
<td>3.7 ± 4.7</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD.
Four patients died during the study, all in the chloroquine group. The causes of death were rheumatoid pericarditis, pneumonia, lung cancer, and gastric cancer, and were considered not to be related to the chloroquine treatment.

A similar percentage of patients in both groups completed 2 years of treatment with the drug to which they were originally assigned. In the prednisone group, 12 patients (43%) prematurely discontinued prednisone as single therapy, 9 because of failure and 3 because of adverse events, i.e., cushingoid features in all 3. Three patients who discontinued prednisone as single therapy later switched from chloroquine to gold treatment, and 1 subsequently switched to sulfasalazine treatment. The mean daily dosage of prednisone was 11.4 mg (range 7.9–13.8 mg) over the first 6 months, 8.2 mg (range 3.3–13.8 mg) over the second 6 months, 6.3 mg (range 0–11.7 mg) over the second year, and 8 mg (range 3.3–11.9 mg) over the whole 2-year period. After 2 years, 24 patients were still taking prednisone.

The mean daily dosage at 2 years in patients still taking prednisone was 7.1 mg (range 2.5–10 mg).

In the chloroquine group, 11 patients (39%) prematurely discontinued the study treatment. The reasons were lack of efficacy in 4 patients, adverse events in 5, and death in 2 (the other 2 patients who died had already discontinued chloroquine, because of lack of efficacy in 1 and an adverse event in the other). The adverse events that led to chloroquine discontinuation were nausea and/or rash. Eight patients started gold treatment after discontinuation of chloroquine, of whom 3 were later treated with sulfasalazine. The first 3 patients who were started on the chloroquine regimen could not tolerate the 300-mg/day loading dose. Thus, for subsequent patients, the loading phase of chloroquine was changed to 100 mg once daily in the first week and 100 mg twice daily in the second week. Thereafter, the original schedule was followed. Of all patients randomized to receive chloroquine, 10 (36%) could not tolerate the full loading dose. Over the 2
years, DMARDs (including prednisone) were prescribed 43 times for patients in the prednisone group and 39 times for patients in the chloroquine group.

Marked improvement relative to baseline was reported by 90% of the patients in the prednisone group at 1 month, but this decreased to 46–61% at 3, 12, and 24 months. In the chloroquine group, marked improvement was reported by 50–62% of the patients at each time point after baseline. The changes over time in the HAQ and the disease activity parameters are shown in Figure 1. Within the groups, there was a significant improvement of all 4 parameters between baseline and 24 months ($P < 0.01$).

An improvement of at least 30% in both the RAI and the swollen joint count between 0 and 24 months was found in 50% of the patients in the prednisone group and 46% of those in the chloroquine group. The course of the parameters over time was not significantly different between the groups, except for the ESR ($P < 0.01$). At individual time points, the only significant differences between groups were a lower swollen joint count and lower ESR in the prednisone group versus the chloroquine group at 1 month ($P < 0.01$).

Bone mass. Complete bone mass measurements were obtained in 27 patients in the prednisone group (96%), 20 patients in the chloroquine group (71%), and 21 patients in the control group (100%). The reasons for not measuring bone mass were primary hyperparathyroidism in 1 patient in the prednisone group, and death ($n = 4$), refusal ($n = 2$), testicular atrophy after orchitis ($n = 1$), and treatment with anti-androgens for carcinoma of the prostate ($n = 1$) in the chloroquine group. Femoral neck BMD could not be measured in 1 prednisone-treated patient because of bilateral arthroplasty; therefore, hip BMD was measured in 26 patients in this group. Vitamin D supplements were given to 7 patients in the prednisone group, 9 in the chloroquine group, and 4 in the control group. The frequency of definite osteophytes in the lumbar spine (score of ≥2) was 59% in the prednisone group, 60% in the chloroquine group, and 88% in the control group. Z scores were between −0.5 and 0.5 in the prednisone and chloroquine groups and −1 in the control group.

The course of spine BMC and hip BMD over time is depicted in Figure 2. In the control group there was a 2.3% increase in mean spine BMC (95% confidence interval [95% CI] 0.4–4.1%) and a 0.7% decrease in mean hip BMD (95% CI −1.2–2.5%) over the 2 years. In the chloroquine group there was a 1.8% decrease in spine BMC (95% CI −1.4–5.4%) and a 4.8% decrease in hip BMD (95% CI 2.5–7.1%) over the 2 years. The difference in the course of bone mass
PREDNISONE VS. CHLOROQUINE IN RA

Table 3. Bone metabolism parameters in rheumatoid arthritis (RA) patients treated with prednisone, RA patients treated with chloroquine, and control patients*

<table>
<thead>
<tr>
<th>Group, parameter</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (n = 27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>58 ± 25</td>
<td>39 ± 11†</td>
<td>42 ± 15†</td>
<td>49 ± 17†</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>3.7 ± 1.8</td>
<td>2.8 ± 1.3†</td>
<td>2.3 ± 1.0†</td>
<td>2.5 ± 0.9†</td>
</tr>
<tr>
<td>PTH</td>
<td>1.7 ± 1.3†</td>
<td>2.2 ± 1.2</td>
<td>2.5 ± 2.1†</td>
<td>2.6 ± 1.1†</td>
</tr>
<tr>
<td>Ca/Cr</td>
<td>0.51 ± 0.39</td>
<td>0.50 ± 0.32</td>
<td>0.48 ± 0.20</td>
<td>0.47 ± 0.28</td>
</tr>
<tr>
<td>HOP/Cr</td>
<td>31 ± 16†</td>
<td>22 ± 17†</td>
<td>18 ± 17†</td>
<td>18 ± 10†</td>
</tr>
<tr>
<td>Chloroquine (n = 20)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>ALP</td>
<td>66 ± 15†</td>
<td>61 ± 17</td>
<td>61 ± 15</td>
<td>63 ± 15</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>3.8 ± 1.1</td>
<td>3.6 ± 1.7</td>
<td>4.5 ± 2.3</td>
<td>3.8 ± 2.0</td>
</tr>
<tr>
<td>PTH</td>
<td>2.0 ± 1.9</td>
<td>2.9 ± 2.2†</td>
<td>3.7 ± 1.8†</td>
<td>3.8 ± 4.2</td>
</tr>
<tr>
<td>Ca/Cr</td>
<td>0.39 ± 0.25</td>
<td>0.26 ± 0.16</td>
<td>0.45 ± 0.45</td>
<td>0.29 ± 0.18</td>
</tr>
<tr>
<td>HOP/Cr</td>
<td>29 ± 9†</td>
<td>25 ± 11</td>
<td>27 ± 8</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Control (n = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>46 ± 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>3.2 ± 1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>3.2 ± 2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca/Cr</td>
<td>0.34 ± 0.20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOP/Cr</td>
<td>17 ± 5</td>
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</tbody>
</table>

* Values are the mean ± SD. ALP = alkaline phosphatase; PTH = parathyroid hormone; Ca/Cr = urinary calcium/creatinine ratio; HOP/Cr = urinary hydroxyproline/creatinine ratio.
† P < 0.01 versus baseline.
‡ P < 0.01 versus controls.

between the control group and the chloroquine group was significant both for the spine and for the hip (P < 0.01 and P < 0.05, respectively). In the prednisone group there was a 3.6% decrease in spine BMC (95% CI 1.1–6.2%) and a 6.3% decrease in hip BMD (95% CI 4.2–8.4%) over the 2 years. Nearly all the loss of spine BMC in this group occurred within the first 6 months, whereas the rate of BMD decrease in the hip was constant over time. In the second year the rates of bone loss at both sites were similar in both RA groups (Figure 2). The loss of spine BMC and hip BMD at 24 months was 1.8% greater and 1.5% greater in the prednisone group than in the chloroquine group. The course of the bone mass was not significantly different between these 2 groups of RA patients.

Bone metabolism. The biochemical parameters of bone turnover were measured in the same patients from whom bone mass measurements were obtained. At entry, the values in the prednisone group and the chloroquine group were similar (Table 3). Bone turnover was higher in RA patients than in control patients, as suggested by a higher alkaline phosphatase level in serum and a higher urinary hydroxyproline/creatinine ratio (HOP/Cr). During followup, the serum alkaline phosphatase and osteocalcin levels decreased significantly in the prednisone group but not in the chloroquine group. Serum PTH increased significantly in both groups. The urinary calcium/creatinine ratio (Ca/Cr) remained unchanged in both groups, as did the HOP/Cr ratio in the chloroquine group. HOP/Cr decreased significantly in the prednisone group.

Features possibly related to bone mass loss. Univariate correlations of the rates of bone mass loss over 2 years with sex, BMI, disease duration, osteophyte score, Z score, physical activity score, mean HAQ score, mean RAI, mean swollen joint count, baseline Ca/Cr, and HOP/Cr, and (in the prednisone group) the mean prednisone dose over 2 years were tested. Significant (P < 0.01) correlations between the various factors and bone loss in the spine were not found. The highest correlation was with the mean prednisone dose (r = 0.41, P = 0.03). For bone loss in the hip, significant correlations with the mean HAQ score (r = 0.51), the mean physical activity score (r = -0.37), the mean swollen joint count (r = 0.41), and the mean prednisone dose (r = 0.60) were found. The rates of bone loss in the 2 treatment groups were then compared in a multiple regression model, correcting for the differences between the groups in sex distribution, Z score, osteophyte score, physical activity, mean swollen joint count, and baseline Ca/Cr and HOP/Cr. The differences in rates of bone mass loss in
the spine and hip between the 2 groups remained similar in the multiple regression model. An independent relationship with bone mass loss in the spine was found for the swollen joint count, and with bone mass loss in the hip for the swollen joint count and physical inactivity.

**Fractures.** Four symptomatic fractures occurred in 4 patients (all women). In the first year, 1 patient in the chloroquine group had a hip fracture. In the second year, 2 prednisone-treated patients had a thoracic vertebral crush fracture and 1 prednisone-treated patient fractured an elbow. The patients with fractures had Z scores between -0.5 and 0.5, and their values for bone turnover parameters at baseline were in the same range as those for patients without fractures.

**DISCUSSION**

This study compares the efficacy of prednisone and chloroquine as the initial treatment of RA in dosages that are widely used in clinical practice. The main conclusion is that the antiarthritic effect and the progression of radiographic signs of joint destruction are similar in both groups. The patients treated with prednisone had a greater loss of bone mass in the spine and the hip after 2 years, although the differences were not statistically significant.

A clinical advantage of prednisone over chloroquine was lower disease activity at 1 month in the patients treated with prednisone. During the remaining period of the study, however, the parameters of disease activity did not differ significantly between the patient groups, which was reflected by the fact that similar numbers of patients were considered to need another DMARD. Although the sample size may not have been large enough to demonstrate a small difference between the treatment groups, it is unlikely that even a much larger study would demonstrate a clinically significant difference.

These results indicate that in the long-term treatment of active elderly-onset RA, a regimen starting with low-dose prednisone followed by chloroquine, gold, and sulphasalazine has no more antiinflammatory properties than a regimen starting with chloroquine. Changes in functional capacity, as well as the progression of radiologic abnormalities, were the same in both groups. Modification of radiologic progression of joint destruction in RA during chloroquine therapy was not found previously (35), and it can be concluded that prednisone also lacks such an effect. This result is in contrast with the findings of earlier studies on corticosteroids in the treatment of RA, which showed either no (8,9) or decreased (10) radiographic progression. It should be noted that in these earlier studies slightly higher prednisone dosages were used.

Concerning the dosage of chloroquine, it is of interest that many patients did not tolerate a dosage of >100 mg/day. It is also notable that 4 deaths occurred during chloroquine treatment, although there was no obvious relationship between the treatment and the deaths. In this clinical trial setting, chloroquine resulted in an unsatisfactory response in 29% of patients, whereas in clinical practice the likelihood of discontinuing antimalarial drugs after 2 years is 50% or more (12,36). It appears that regimens including other therapies in addition to chloroquine or prednisone are required for optimal control of RA in most patients.

The relatively small differences in bone mass loss between the groups did not reach statistical significance. This may be explained by the relatively small number of patients studied, the higher variance in the amount of bone loss than was previously found (34), and the relatively low mean dosage of prednisone. However, the well-described association of prednisone therapy with osteoporosis (16), and the fact that a higher bone mass loss in both the spine and the hip relative to baseline was found at all time points in the prednisone group compared with the chloroquine group, suggest that the loss of bone mass was indeed higher in the patients treated with prednisone. The loss of bone mass in the spine in the patients treated with prednisone occurred mainly within the first 6 months of treatment, as has been found previously (34,37–39). In the present study a dose effect cannot be excluded, since the prednisone dosage was higher in the first half-year of treatment than in later periods. It is not likely that the difference in bone mass loss between the groups would have become significant if the study had lasted longer, since the loss during the second year was equal in both groups.

The loss of trabecular bone in the vertebrae of RA patients may in reality be greater than was actually found, since BMC measurements by DXA can be influenced by growing osteophytes, as evidenced by an increase in BMC over time in the control group with a high frequency of osteoarthritis of the spine. In a study using quantitative computed tomography, which measures the trabecular BMD inside the vertebrae, an 8.2% decline of BMD was found after 20 weeks of treatment with prednisone at a mean dosage of 7.5 mg/day (39).

The biochemical data show a sustained de-
crease of bone formation, a parallel decrease of bone resorption, and an increased serum PTH level in the patients treated with prednisone. The rates of bone mass loss in this group suggest that bone formation is relatively more depressed than bone resorption. Other prospective studies of bone metabolism during prednisone therapy have also demonstrated depressed bone formation (40-42), but results of bone resorption parameters and of serum PTH levels were variable (37,40-42). The decrease in bone resorption may in part be juxtaarticular (43). The only change over time in the parameters of bone metabolism in the chloroquine group was an increase in serum PTH, which may be a consequence of impaired calcium absorption due to chloroquine (44,45). A negative calcium balance induced by chloroquine may have attenuated the differences in bone loss between the groups.

Three fractures occurred in the prednisone group and 1 in the chloroquine group. As expected in these small patient groups, the difference was not significant. The patients with fractures were all female, but they did not differ from the patients without fractures with respect to other risk factors measured. Bone mass loss in this study was related to physical inactivity, disease activity, and prednisone dose. Although the differences in bone mass loss between the groups were small, they should not be ignored, since even a small decrease in bone density is associated with an increased risk for fractures (46).

An alternative design for the present study could have been to compare combined prednisone and chloroquine with chloroquine alone. In an attempt to reproduce the results of earlier studies, which contain evidence for an effect of prednisone on radiographic progression (2,4,8,9), we chose to study the effect of prednisone in sufficiently high doses as the only initial second-line drug. Prednisone was more efficacious than chloroquine in the treatment of elderly-onset RA in the first month, when the highest doses were used. The long-term effects of both drugs on disease activity, functional capacity, and radiographic progression were similar. The results of the present study suggest that long-term prednisone therapy leads to a higher loss of bone mass. It has been shown that the bone mass loss induced by a short period of prednisone therapy is reversible (39). Therefore there are arguments to support the use of prednisone in the initial treatment of active RA, alone or in combination with other drugs, and to minimize its use in long-term treatment.

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