Low-dose glucocorticoids in early rheumatoid arthritis: discordant effects on bone mineral density and fractures?
Abstract
To investigate the incidence of osteoporotic fractures and effects on bone of low-dose glucocorticoid (GC) in a group of previously untreated patients with early active RA we performed a double blind, randomised, placebo-controlled clinical trial. The study duration was 2 years, with an open follow-up during the third year. Patients were randomly allocated to receive 10 mg prednisone or placebo.

Non-steroidal anti-inflammatory drugs (NSAIDs) were allowed in both groups. After 6 months sulphasalazine (2 gr daily) could be prescribed as rescue therapy in both groups. Except for 500 mg calcium supplement daily, no specific preventive measures were taken.

At the start of the study and every 6 months, X-rays of the twelfth thoracic and of all lumbar vertebrae were scored using the Kleerekoper method, and every year biochemical parameters of bone metabolism and bone mineral density (BMD) were assessed.

In the prednisone group there was a higher incidence during the study of lumbar vertebral fractures than in the placebo group: 7 vs 4 respectively. This difference did not reach statistical significance however, probably because of the small numbers. One patient of the prednisone group suffered an osteoporotic fracture of the pelvis. In the 2-year study and the subsequent follow-up year, no other peripheral fractures were seen in either group. No significant changes from baseline in BMD of the hips and lumbar spine were seen in either group during the study and the follow-up year: BMD values in both groups did not differ significantly during the whole study. No correlation between changes in serum osteocalcin and BMD was observed.

Low-dose prednisone for patients with early active previously untreated RA seems also to increase the risk of fractures independent of the BMD.
INTRODUCTION

In rheumatoid arthritis (RA) periarticular as well as generalised bone loss is an early feature of the disease with an increased risk of fractures of 1.5 to 2.1. Bone formation is normal or reduced and bone resorption is increased in RA patients compared to healthy controls. Bone loss is the result of this uncoupling between bone formation and resorption. The aetiology of generalised bone loss in RA is multifactorial. Inflammation with circulating cytokines and hypogonadism as well as general factors such as decreased physical and weight-bearing activity, age, vitamin D status, hormonal status and physical impairment play a role.

Another risk factor for osteoporosis is treatment with glucocorticoids (GC); in general this therapy doubles the risk of fractures. However there is still debate as to whether low-dose GC treatment of an active inflammatory disease also results in the development of osteoporosis and an increased risk of fractures. In contrast to the negative effects on bone, low-dose GC treatment of patients with RA reduces disease activity and joint damage and enhances mobility, effects that are anti-osteoporotic. Therefore, the positive effects of low-dose GC treatment of patients with RA on disease activity and joint damage may counterbalance the negative effects on bone. In various studies the incidence of clinical manifestations of vertebral fractures was significantly higher in patients with RA treated with GC compared to RA patients without GC. However, interpretation of the results of other studies is difficult because of confounding factors such as the administration of prednisone only to patients with more active disease (allocation bias).

The aim of our study, in which prednisone therapy was randomly allocated (thus excluding allocation bias for prednisone) was to investigate the effects on bone and the risk of fractures of low-dose prednisone in patients with early active previously untreated RA.

PATIENTS AND METHODS

Patients

From October 1992 through October 1995 eighty-one out of 118 eligible consecutive outpatients of the Departments of Rheumatology of the Deventer and Zutphen Hospitals, who were at least 18 years of age, had early previously untreated RA (disease duration less than one year), and satisfied the 1986 ARA-classification, were enrolled in the study. Inclusion criteria were: active disease defined as (at least 2 out of 3): 28 joint score for tenderness and 28 joint score for swelling of 3...
or more, Westergren erythrocyte sedimentation rate (ESR) 28 mm after one hour or higher and early morning stiffness lasting 30 minutes or longer. Exclusion criteria were contraindications for the use of prednisone and/or NSAID’s, serious concomitant diseases, active gastrointestinal problems, severe hypertension, haemorrhagic diathesis, treatment with cytotoxic or immunosuppressive drugs, alcohol or drug abuse and severe psychiatric or mental problems.

Informed consent was obtained from all subjects prior to participation. Of the 118 eligible patients, thirty-seven refused to participate.

**Intervention**

The 81 participating patients were randomly allocated in blocs of 10 subjects by the Pharmacy of the Deventer Hospital to one of two groups for treatment for two years: 1) two tablets of 5 mg prednisone once daily at breakfast (=10 mg), 2) placebo tablets in the same way. The Pharmacology Department prepared and labelled the prednisone and placebo tablets, which were identical in shape, taste and colour. Both groups of patients received 500 mg elementary calcium in the evening to retard GC-induced osteoporosis as was the normal procedure at that time (study designed in 1989-91). According to current knowledge patients would now be treated with bisphosphonates and/or vitamin D and 1000 mg elementary calcium.

The code of randomisation was broken after 2 years of treatment. Dosage was then tapered off for patients receiving prednisone. At every visit the surplus tablets of the study medication were counted; compliance was satisfactory (96%). Use of NSAID’s was free. Local CS injections were permitted only if unavoidable. Physical therapy and additional use of paracetamol were allowed and recorded every 3 months. After 6 months sulphasalazine (2 gr. daily) could be prescribed as rescue medication. The decision to add sulphazalazine was based on clinical grounds only (activity of RA).

**Design, setting**

This prospective, double-blind, randomised, placebo-controlled trial was approved by the Ethics Committees of the University Medical Center Utrecht and the Deventer and Zutphen Hospitals. At the time the study was designed (1989-91), the study design was considered ethically acceptable; later it became clear that irreversible joint damage in RA is an early feature of the disease. With our present knowledge comparison of the effects of prednisone and placebo in patients who did not
TABLE 1

Baseline characteristics of the 81 patients with early RA (number of patients (n) or means and standard deviations). There were no statistically significant differences between the two groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prednisone Group (n = 40)</th>
<th>Placebo Group (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>60 (14)</td>
<td>64 (12)</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>17 / 23</td>
<td>12 / 29</td>
</tr>
<tr>
<td>IgM rheumatoid factor positive ‡ (n patients)</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Patients with erosive disease (n)</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>28 Joint score for swelling</td>
<td>7 (4)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>28 Joint score for tenderness</td>
<td>9 (6)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Vas pain in mm¶</td>
<td>11 (18)</td>
<td>20 (28)</td>
</tr>
<tr>
<td>HAQ*</td>
<td>0.8 (0.6)</td>
<td>1.0 (0.7)</td>
</tr>
<tr>
<td>CRP in mg/L</td>
<td>28 (20)</td>
<td>34 (25)</td>
</tr>
<tr>
<td>Serum creatinine in umol/L#</td>
<td>81 (15)</td>
<td>80 (12)</td>
</tr>
<tr>
<td>Serum 25-OH vitamin D@</td>
<td>72 (35)</td>
<td>61 (21)</td>
</tr>
</tbody>
</table>

‡ RF status was considered positive when the IgM-RF was 25 IU/ml or more, a cut-off point resulting in a false-positive test for less than 5% of the general population.
¶ VAS (visual analogue scale) for morning pain and general wellbeing referred to the previous 48 hours on a scale ranging from 0 -100 mm, 0 representing the best (no problems) and 100 the worst score.
* A Dutch version of the HAQ (VDF, Vragenlijst Dagelijks Functioneren), its score ranging from 0-3, 0 representing the best (no problems) and 3 the worst score.28
# Serum creatinine: normal ≤ 110 male; ≤ 90 female.
@ Normal range: 25-150 nmol/L; only one patient (in the prednisone group) had a subnormal value (23 nmol/L).

receive a DMARD for at least six months would probably be considered unethical. In our study sulphasalazine as rescue medication could be prescribed only after 6 months in order not to obscure the effects of prednisone monotherapy.

Measurements

At the start of the study and every 3 months for three years, variables on disease activity and adverse effects were assessed: the results are reported elsewhere.7 In this report, baseline values of joint scores, visual analogue scale (VAS) pain (0-100 mm), the HAQ score and serum C-reactive protein are shown in Table 1.

At the start of the study and every 6 months radiographs of the lower thoracic and lumbar spine were made and assessed according to the method of Kleerekoper.13
The vertebrae (Th 12 through L 5) were scored by naked eye inspection and compared to the vertebrae below and above by two observers (AAvE, DH). The radiographs were prepared for reading by a houseman; data of the patients on the radiographs were blinded from the observers. The observers had no knowledge of the identity of the patients on the radiographs at the time of scoring. Radiographs were read in random patient order and scored for each patient in temporal order: 0 (normal shape and dimensions), 1 (only endplate deformity, middle height < 85%), 2 (anterior wedge deformity, anterior height < 85%) and 3 (compression deformity, all heights < 85%). The maximum score was 18.

At the start of the study and once every year bone mineral density (BMD) of the lumbar spine (L2-4) and collum femoris of both hips was measured by dual-energy X-ray absorptiometry (BMD in g/cm²) (Hologic QDR-4500A) with a cut-off point for changes from baseline >0.27 g/cm². BMD values were expressed as T-scores and changes from baseline. Osteocalcin in serum (mg/L; measured by OStK-Pr radioimmunoassay kit purchased from CIS BIO International, GIP-SUR-Yvette, Cedex France) and excretion of hydroxyproline in 24-hour samples of urine (um/24h/m²) on a hydroxyproline-poor diet, considered at the time of the study the most reliable markers of bone metabolism, were measured in addition to excretion of calcium and creatinine in 24h urine in mmol/24h.

At the start of the study and every 3 months serum creatinine in umol/L was assessed and at the start of the study also serum 25-OH vitamin D.

Statistical analysis

All statistical analyses to evaluate possible effects of treatment on bone were performed with patients ‘on treatment ’; ‘intention to treat ’ analysis with estimation of missing data by carrying the last measurement forward would have yielded a too positive result. For the 10 patients in the 2-year study and the 6 patients in the follow-up year who dropped out, the outcomes of clinical variables were estimated conservatively according to the method of last measurements carried forward. Outcome measurements were tested for statistically significant differences between the two groups using unpaired, two-sided T-tests or Mann-Whitney U tests, where appropriate, for the means and Fishers’ exact test for proportions.

Correlations were calculated between osteocalcin and BMD and between CRP and BMD using Pearson’s correlation coefficients.

All analyses were performed with the statistical package “Number Cruncher Statistical System” version 97 (Jerry Hintze, Kaysville, Utah).
TABLE 2

Bone mineral densities (T-scores) and fractures across time for patients with RA (prednisone vs. placebo)
Time in months, means (standard error of the mean, SEM), number of patients

<table>
<thead>
<tr>
<th>Time in months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-score Lumbar spine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-prednisone (n = 32)</td>
<td>-0.8 (0.3)</td>
<td>-1.0 (0.3)</td>
<td>-1.1 (0.3)</td>
<td>-1.1 (0.3)</td>
</tr>
<tr>
<td>-placebo (n = 33)</td>
<td>-0.7 (0.3)</td>
<td>-0.6 (0.3)</td>
<td>-0.6 (0.3)</td>
<td>-0.6 (0.3)</td>
</tr>
<tr>
<td><strong>T-score Femoral neck</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-prednisone (n = 32)</td>
<td>-1.8 (0.2)</td>
<td>-1.8 (0.2)</td>
<td>-1.9 (0.2)</td>
<td>-1.8 (0.2)</td>
</tr>
<tr>
<td>-placebo (n = 33)</td>
<td>-1.9 (0.2)</td>
<td>-1.9 (0.2)</td>
<td>-1.9 (0.2)</td>
<td>-1.9 (0.2)</td>
</tr>
<tr>
<td><strong>Cumulative number of Fractures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-prednisone</td>
<td>1</td>
<td>5</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>-placebo</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
| **Cumulative number of patients with fractures**
  (total number of patients) |      |      |      |      |
| -prednisone | 1 (40) | 4 (40) | 5 (36) | 5 (31) |
| -placebo   | 1 (41) | 2 (36) | 2 (35) | 2 (33) |

RESULTS

Patients’ characteristics at the start of the study are shown in Table 1: there were no statistically significant differences between groups. All patients were Caucasian except for two in the prednisone group: one Asian and one Mediterranean. Of the 118 patients 37 declined to participate in the study. They had the following characteristics: mean age 48 (SD 12) years; 25 were female; 28 patients had IgM-rheumatoid factor and 14 exhibited erosive changes on radiographs of the hands and/or feet. So, the group of non-participants consisted of relatively more female and younger patients compared to the study group.

Ten patients dropped out of the study: 4 in the prednisone group and 6 in the placebo group, details are described elsewhere. For 65 of the 71 patients all BMD measurements were available. No significant changes from baseline in BMD of the hips and lumbar spine were seen in either group nor significant differences between both groups, see Table 2.

At the start of the study there was one patient in each group with one vertebral fracture (Th12-L5). After 24 months, 5 patients in the prednisone group had new fractures in the lumbar spine: 3 patients had a single fracture and 2 had 2 fractures.
The one patient who had a fracture at the start did not develop new fractures. In the placebo group 1 patient had 3 new vertebral fractures and the one patient who had had a fracture at the start of the study had developed a new one. Except for one osteoporotic fracture of the pelvis, no other fractures (forearms, ribs or hip) were seen (Table 2). During the follow-up year no new vertebral fractures occurred in the placebo group. In the prednisone group 2 patients who already had vertebral fractures developed a new vertebral fracture.

The first patient entered the 2-year study in 1993; the last patient finished the study in 1998. In 1999 we were able to take radiographs of the thoracic and lumbar spine of 59 out of the 65 patients. There were no new fractures in the placebo group. In the prednisone group there was one thoracic vertebral fracture in a patient who was known to have a lumbar vertebral fracture: 2 patients who had had lumbar vertebral fractures had both developed one new lumbar fracture.

At the start of the study, only one patient (in the prednisone group) had a subnormal 25-OH vitamin D level: 23 (normal: 25-150 nmol/L).

There was a significantly lower serum osteocalcin level at 12 and 24 months in the prednisone group compared to the placebo group (p-value 0.05 and 0.007, respectively). There was also a significantly higher calcium excretion in samples of 24h urine at 24 months in the prednisone group (p-value 0.0008). No statistically significant differences were found for the excretion of hydroxyproline in samples of 24h urine.

No statistically significant correlations were found between serum osteocalcin and BMD and between serum CRP and BMD (data not shown).

**DISCUSSION**

In our 2-year placebo-controlled (and 1-year follow-up) study, which showed joint protective properties of low-dose prednisone for patients with early previously untreated active RA, we found more vertebral fractures in the prednisone group compared to the placebo group but this (clinically relevant) difference did not reach statistical significance, probably because of the small numbers. No clinically relevant nor statistically significant differences in BMD measurements were found between the group of patients treated with prednisone and the group on placebo. There was a higher disease activity in the placebo group compared to the prednisone group but no clear differences in clinical variables, probably because the use of NSAID’s was more than doubled in the placebo group compared to the placebo group to the prednisone group (details reported elsewhere). In inflammatory
diseases such as RA, there is a positive correlation between disease activity, bone turnover and rate of fractures, most of which are vertebral deformities.\textsuperscript{6} Probably in our study the negative effect of disease activity on bone that was higher in the placebo group counterbalanced the negative effect of prednisone in the prednisone group: hence no statistically difference between the two groups regarding BMD.

In recent literature the relationship between low-dose GC treatment, the development of low BMD and the risk of fractures is a subject of controversy. Most of these retrospective studies were performed with patients with longstanding RA and the results are controversial.\textsuperscript{8,14} We will go into these studies in short. In several studies on low-dose long-term GC treatment of postmenopausal RA patients, a higher incidence of fractures -especially of the vertebrae and femoral neck- compared to RA patients who did not receive GC and had a lower BMD was reported.\textsuperscript{9,15}

In a cohort of patients with a variety of diseases no difference was found in the relationship between changes in BMD and vertebral fractures between patients receiving GC and who were not on this therapy.\textsuperscript{16} In contrast, in other studies higher fracture rates than could be expected from the observed changes in BMD were reported,\textsuperscript{17,18} as in our study. However, there is a difference between the study population for those studies and our patients, all of whom had previously untreated, active early RA. The fact that our study, which was free of allocation bias, was indicative of a discrepancy between bone strength and BMD in patients on prednisone, seems to confirm the hypothesis that GC treatment may lead to fractures also via effects on bone other than a decrease in BMD, i.e. changes in bone strength and structure.\textsuperscript{19} For patients with a variety of diseases who are on long-standing GC treatment, the risk of fractures can be explained for only 40\% by the value of BMD, the other 60\% by other factors such as the risk of falling (5).

At the time of our study it was standard procedure only to provide a supplement of 500 mg elementary calcium daily for patients with RA treated with GC to prevent osteoporosis. After 1996 a number of well-conducted studies was published showing the efficacy of bisphosphonates in combination with calcium and vitamin D in preventing bone loss and even increasing BMD in patients treated with GC.\textsuperscript{20-23} Nowadays it is considered unethical to perform studies with GC without adequate prevention of osteoporosis.

Statistically significant differences were found between the two groups in serum osteocalcin levels and excretion of calcium in 24h samples of urine: lower serum osteocalcin and higher calcium excretion characterised the prednisone group. No
correlations were found in either group between bone markers, disease activity and the BMD. Our finding of a statistically significant decrease in serum osteocalcin and the excretion of calcium in 24h urine for the prednisone group compared to the placebo group contrasts with data in the literature. In a study of postmenopausal women with longstanding RA no significant differences in biochemical markers of bone turnover were observed between RA patients treated with low-dose GC and those receiving placebo.\textsuperscript{15} Another study did not find significant differences in excretion of calcium in 24h urine.\textsuperscript{24} In a similar study there were no differences in serum osteocalcin between the prednisone and placebo groups.\textsuperscript{25} Differences with respect to our study of early RA patients could possibly be explained by a different disease duration: the majority of other studies were performed with patients with longstanding RA.

At this time only one study on the effects of short-term low-dose GC on bone metabolism in patients with active RA has been published.\textsuperscript{8}

The hypothesis that the positive effects of GC on disease activity might counterbalance the negative effects on bone might explain the lack of correlation between disease activity (CRP) and bone marker (osteocalcin in serum).

In conclusion, in our study without allocation bias for prednisone, a discrepancy seems to be present between the lack of change in BMD and the increased albeit not statistically significant incidence of fractures in patients with early active RA treated with low-dose prednisone. Apparently mechanisms other than a decreased BMD are also responsible for diminished bone strength and an increased risk of fractures.

**REFERENCES**


