Low-dose glucocorticoids in early rheumatoid arthritis: Discordant effects on bone mineral density and fractures?

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Abstract

Objective

To investigate the incidence of osteoporotic fractures and effects on bone of low-dose glucocorticoid (GC) monotherapy 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.

Methods

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. This was a normal procedure at the time the study was designed (1989-1991). 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, expressed in T-scores) and bone mineral content (BMC, expressed in g/cm) were assessed.

Results

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 and BMC of the hips were seen in either group during the study and the follow-up year. In the lumbar spine, BMD in the prednisone group decreased although not statistically significantly during the whole study. No correlation between changes in serum osteocalcin and BMD was observed.

Conclusion

Low-dose prednisone monotherapy for patients with early active previously untreated RA seems to increase the risk of fractures not only by reducing the BMD but also by changes in bone strength and structure.

Key words

10 mg prednisone, early rheumatoid arthritis, bone mineral density, bone metabolism, fracture risk.

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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 (1-3). 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 (4, 5).

Another risk factor for osteoporosis is treatment with glucocorticoids (GC); in general this therapy doubles the risk of fractures (6). However there is still debate as to whether treatment of an active inflammatory disease with 10 mg prednisone also results in the development of osteoporosis and an increased risk of fractures. In contrast to the negative effects on bone, GC treatment of patients with RA reduces disease activity and joint da-mage and enhances mobility, effects that are anti-osteoporotic (7, 8). Therefore, the positive effects of GC treatment of patients with RA on disease activity and joint damage might partially counterbalance the negative effects on bone (3, 6, 7). 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 (9, 10). However, interpretation of the results of these 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 10 mg prednisone monotherapy 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 (11). Inclusion criteria were: active disease defined as at least 2 of the following: ≥3 in the 28 joint score for tenderness and the 28 joint score for swelling, Westergren erythrocyte sedimentation rate (ESR) after one hour ≥28 mm and early morning stiffness lasting 30 minutes or longer (12, 13). Exclusion criteria were contraindications for the use of prednisone and/or NSAIDs, 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, 37 refused to participate.

Intervention

The 81 participating patients were randomly allocated in blocks 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) two 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 1989-1991). 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. The 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%). NSAIDs were furnished to the study participants free of charge. Local GC 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 gm daily) could be prescribed as a rescue medication. The decision to add sulphasalazine was based on clinical grounds only (RA activity).

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. During the period in which the study was designed (1989-1991) and the initial period of the study (1992-1995), the design was considered ethically acceptable; later (beginning in 1993) 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 receive a DMARD for at least six months would be considered unethical. In our study sulphasalazine as a 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 of disease activity and adverse effects were assessed: the results are reported elsewhere (7). In this report, baseline values for joint scores, the visual analogue scale (VAS) for pain (0-100 mm), the HAQ score and serum C-reactive protein are shown in Table I.

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 (14). 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 medical resident; observers were blinded to the patients'data and identity 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 the bone mineral density (BMD) of the lumbar spine (L2-4) and collum femoris of both hips was measured by dual-energy X-ray absorptiometry (BMC in g/cm)(Hologic QDR-4500A) with a cut-off point for changes from baseline > 0.27 g/cm^2. BMD values were also expressed as T-scores and changes from baseline. Osteocalcin in the serum (mg/L; measured by a OStK-Pr radioimmunoassay kit purchased from CIS BIO International, GIP-SUR-Yvette, Cedex France) and excretion of hydroxyproline in 24-hour samples of urine (µmol/24h/m^2) 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 µmol/L was assessed and at the start of the study serum 25-OH vitamin D was measured.

Statistical analysis

All statistical analyses to evaluate possible effects of treatment on bone were performed with patients 'on treatment'; 'intention to treat'analysis with the 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 the clinical variables were estimated conservatively according to the method of the last measurements carried forward. Outcome measurements were tested for statistically significant differences between the two groups using unpaired T-tests or Mann-Whitney U tests where appropriate, for the means and Fishers' exact test for proportions. Changes from baseline within groups were tested for statistically significant differences with the paired T-test or the Wilcoxon rank test, where appropriate. Correlations were calculated between osteocalcin and BMD and between CRP and BMD using Pearson's correlation coefficients. All testing was two-sided; the level of significance was $p < 0.05$.

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

Results

The patients' characteristics at the start of the study are shown in Table I: 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. Therefore 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 furnished elsewhere (7). For 65 of the 71 patients all BMD and BMC measurements were available. No significant changes from baseline in the BMD and BMC of the hips were seen in either group, nor significant differences between the two groups (see Table II). In the prednisone group the BMD and BMC decreased from baseline although this change was not statistically significant. This resulted in a non-significant difference between the groups at the end of the study of about 0.5 in the T-score of the lumbar spine in favour of the placebo group.

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

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

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

‡ 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 well-being 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 (30).
# Serum creatinine: normal ≤ 110 for males; ≤ 90 for females.
@ Normal range:25-150 nmol/L; only one patient (in the prednisone group) had a subnormal value (23 nmol/L).

Table II. Bone mineral densities (T-scores), BMC in g/cm and fractures over time for patients with RA receiving prednisone vs. those receiving placebo [means (standard error of the mean), number of patients].

Time in months	0	12	24	36
T-score lumbar spine				
-prednisone (n=32)	-0.8 (0.3)	-1.0 (0.3)	-1.1 (0.3)	-1.1 (0.3)
-placebo (n=33)	-0.7 (0.3)	-0.6 (0.3)	-0.6 (0.3)	-0.6 (0.3)
T-score femoral neck				
-prednisone (n=32)	-1.8 (0.2)	-1.8 (0.2)	-1.9 (0.2)	-1.8 (0.2)
-placebo (n=33)	-1.9 (0.2)	-1.9 (0.2)	-1.9 (0.2)	-1.9 (0.2)
BMC lumbar spine				
-prednisone (n=32)	51 (2)	49 (2)	48 (2)	49 (2)
-placebo (n=33)	52 (3)	52 (3)	52 (3)	53 (3)
BMC femoral neck				
-prednisone (n=32)	2.8 (0.1)	2.8 (9.6)	2.8 (1.0)	2.8 (0.1)
-placebo (n=33)	2.6 (0.1)	3.2 (0.5)	2.7 (0.1)	2.7 (0.1)
Cumulative number of fractures				
-prednisone	1	5	8	10
-placebo	1	2	5	5
Cumulative number of patients with fractures (total number of patients)				
-prednisone	1 (40)	4 (40)	6 (36)	6 (31)
-placebo	1 (41)	2 (36)	2 (35)	2 (33)

patients had a single fracture, and two 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 developed a new one. Except for one osteoporotic fracture of the pelvis, no other non-vertebral fractures (forearms, ribs or hip) were seen (Table II). 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 1992; patients were included from 1992-1995 and the last patient finished the study in 1998. In addition, in 1999 we were able to take radiographs of the thoracic and lumbar spine of 59 out of the 65 patients. There were at that time no new fractures in the placebo group. In the prednisone group there was one new thoracic vertebral fracture in a patient who was known to have a lumbar vertebral fracture; 2 patients who had already had lumbar vertebral fractures both developed one new lumbar fracture. Therefore a total of 3 new fractures had developed.

At the start of the study only one patient (in the prednisone group) had a subnormal 25-OH vitamin D level of 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; at t=0, t=12 and t=24 it was 15.6 versus 14.2 (p = 0.9), 14.3 versus 18.3 (p = 0.05), and 15.5 versus 18.8 (p = 0.0007) mg/L respectively. There was also significantly higher calcium excretion in samples of 24 hr urine at 24 months in the prednisone group, at t=0, t=12 and t=24 it was 0.5 versus 0.4 (p = 0.2), 0.5 versus 0.4 (p = 0.2) and 0.6 versus 0.4 (p = 0.0008) mmol/24h respectively. No statistically significant differences were found in the excretion of hydroxyproline in samples of 24 hr urine, nor significant correlations between serum osteocalcin and BMD, nor between serum CRP and BMD (data not shown).

Discussion

In our 2-year placebo-controlled study with a 1-year follow-up, which showed the 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 involved. Neither clinically relevant nor statistically significant differences in BMD and BMC of

the hips were found between the group of patients treated with prednisone and the group on placebo. The BMD and BMC of the lumbar spine showed a decrease in the prednisone group compared to the BMD and BMC of the placebo group. Although this decrease did not reach statistical significance, it is in line with the lower osteocalcin levels at 12 and 24 months and the higher calcium excretion at 24 months in the prednisone group compared with the placebo group. In interpreting these results one should take into account the relatively small numbers but the lower BMD levels in the spine (T-scores) in the prednisone group (if real) compared with those in the placebo group only partially explain the higher occurrence of osteoporotic fractures in this group. The difference was about 0.5 SD, whereas the fracture rate was about doubled in the prednisone group; the latter would be more compatible with a decrease of 1.0 SD. In a small, but well-designed randomized trial, rapid reversible trabecular bone loss in the spine was observed in patients treated with prednisone (15). In a study with long-term prednisone treatment (15 mg/day for 1 month, with the dosage tapered thereafter) of elderly-onset RA comparing disease activity and bone mass, there was a non-significant excess bone loss of 1.8% in the spine and 1.5% in the hip in the prednisone group compared to the chloroquine group (16), a finding similar to our results.

The use of GC diminishes disease activity; the lack of clear differences in clinical variables between the prednisone group and the placebo group was probably due to the use of NSAIDs, which was about doubled in the placebo group compared to the prednisone group (details reported elsewhere) (7).

In inflammatory diseases such as RA, there is a positive correlation between disease activity, bone turnover and the rate of fractures, most of which are vertebral deformities (6). Although GC induce secondary osteoporosis, GC also reduce proinflammatory processes (cytokines), effects leading to osteoporosis. In this way, prednisone could partially counterbalance its negative effect on bone of patients in the prednisone group. In the 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 studies thus far have been retrospective and performed among patients with longstanding RA and the results are controversial (9, 17). We will briefly discuss these studies.

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 (10, 18).

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 patients who were not on this therapy (19). In contrast, in other studies higher fracture rates than could be expected from the observed changes in BMD were reported (20, 21), 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. Our study, which was free of allocation bias, was indicative of a discrepancy between bone strength and BMD in patients on prednisone. This 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 (22). For patients with a variety of diseases who are on long-standing GC treatment, only 40% of the risk of fractures can be explained by BMD; the other 60% are accounted for by other (known and unknown) 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 were 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 (23-26). Nowadays it is considered unethical to perform studies with GC without adequate measures to prevent osteoporosis.

Statistically significant differences were found between the two groups in serum osteocalcin levels and the excretion of calcium in 24 hr samples of urine: lower serum osteocalcin and higher calcium excretion characterised the prednisone group. However, no correlations were found in either group between bone markers, disease activity and the BMD. The fact that GC diminish disease activity might explain the lack of correlation between disease activity (CRP) and the bone marker of osteocalcin levels in the serum.

Our finding of a statistically significant decrease in serum osteocalcin and the increased excretion of calcium in 24 hr urine for the prednisone group compared to the placebo group contrasts with the data in the literature, except for one study in which significant lower osteocalcin levels were found in women receiving GC compared to controls (27). 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 (16). Another study in postmenopausal women with RA did not find significant differences in excretion of calcium in 24 hr urine (28). In a similar study there were no differences in serum osteocalcin between the prednisone and placebo groups as well (29). Differences with respect to our study of early RA patients could possibly be explained by the different disease durations: the majority of other studies were performed in patients with longstanding RA.

In a review on the effects of short-term and long-term low-dose GC therapy in patients with RA considerable bone loss was reported only in long-term therapy without anti-osteoporotic treatment (9). The hypothesis that the positive effects of GC on disease activity might counterbalance the negative effects on bone could explain the lack of correlation between disease activity (CRP) and the bone marker (osteocal-

cin in serum).

In conclusion, in our study without an allocation bias for prednisone, a discordance seems to be present between the non-statistically significant decrease in BMD and BMC of the spine and the clinically relevant, albeit not statistically significant, increase in the incidence of fractures in patients with early active RA treated with low-dose prednisone. Apparently mechanisms other than a decreased BMD also seem to be responsible for diminished bone strength and an increased risk of fractures.

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