Randomized withdrawal of long-term prednisolone treatment in rheumatoid arthritis: effects on inflammation and bone mineral density

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Objective: Short-term, low-dose glucocorticoid (GC) treatment has anti-inflammatory and disease-modifying effects in rheumatoid arthritis (RA). However, scientific support for long-term, low-dose GC treatment, although widespread, is poor, and information on the effects on bone density is scarce. The aim of this study was to investigate how long-term GC treatment in RA affects inflammation as well as bone density, and also to investigate the feasibility of withdrawal of GC.

Patients and methods: Fifty-eight patients with RA treated with 5–7.5 mg prednisolone daily for at least 2 years were randomized either to withdraw or to continue GC treatment. The patients were followed prospectively for 2 years with respect to disease activity [using the Disease Activity Score calculated for 28 joints, (DAS28)], functional ability [using the Health Assessment Questionnaire (HAQ) score] and bone mineral density (BMD) of the lumbar spine and hip.

Results: Only 11 patients out of 26 randomized to stop GC treatment and available for outcome measures succeeded in stopping the GC medication within 1 year. Fifteen patients failed withdrawal of GC because of increased joint symptoms. A higher mean DAS28 during the study was associated with loss of bone mass in the trochanter. The group that continued with unchanged GC treatment did not deteriorate in BMD during the 2 years but in fact Z-scores improved significantly.

Conclusion: Our results indicate that low-dose GC treatment after several years has persisting anti-inflammatory effects in RA and no further negative impact on BMD. It thus seems to be more important to control disease activity than withdraw low-dose GC treatment in this population considering bone health.

Glucocorticoids (GC) have been used in the treatment of rheumatoid arthritis (RA) for about 50 years (1). The frequent long-term use of GC at doses between 5 and 10 mg of prednisolone per day is used to decrease disease activity. Such an effect of low-doses GC has, however, been demonstrated only for the first 6 months of treatment (2–4). Resistance to GC is a problem in treatment of inflammatory diseases and may cause the decrease in symptomatic relief sometimes seen (5). More recently, a potential disease-modifying role has been demonstrated for low-dose GC (4, 6, 7), but hitherto only in early RA. Consequently, scientific support is limited for the current widespread long-term treatment with low doses of GC (8).

Treatment with GC is generally associated with many side-effects, of which osteoporosis and fractures have the largest impact in terms of morbidity and mortality (9, 10). Also in RA, GC treatment has been associated with reduced bone mineral density (BMD) (11–13) and increased fracture risk (14–16). However, the dose of GC at which bone loss occurs in RA patients is uncertain. A dose of 5 mg daily or more has been considered a risk factor for the development of osteoporosis in a review (17), whereas in a meta-analysis the use of GC less than 10 mg daily for a shorter period than 1 year has been considered not to be associated with clinically important bone loss (18).

The effects of GC on bone structure are thought to be mediated by both osteoblasts and osteoclasts. GC treatment is known to reduce bone formation mediated by osteoblasts (19, 20), whereas reports of GC on osteoclasts and thus bone resorption are inconsistent (20). It is also unclear whether the GC-mediated effects on BMD occur mainly during the...
first year of treatment (20) or continue also during long-term therapy (21).

The interesting issue in RA is that not only treatment with GC may mediate loss of bone density but also that the inflammatory process itself may have the same effect. Inflammation in RA is associated with both reduced bone formation and increased bone resorption (21–24), where the latter appears to be the most important factor in RA-associated osteopenia (24, 25). Several cytokines and inflammatory mediators, including interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF) z are involved in this disease activity-associated bone resorption in RA (17, 25).

The potential dual effects of GC on bone in RA are illustrated by the observations that GC treatment inhibits production and release of the proinflammatory cytokines in RA (26). Any determination of the effects of GC treatment on bone density in RA thus has to take into account both the anti-inflammatory and the osteopenia-inducing properties of the treatment (27). This uncertainty is particularly evident in long-term treatment with GC in RA.

The aim of the present investigation was to analyse the risk–benefit of long-term (>2 years), low-dose GC treatment in RA with respect to disease activity and BMD. Patients on such treatment were randomized either to continue or to withdraw GC treatment and were thereafter followed prospectively for 2 years to analyse the feasibility and consequences of withdrawal.

**Patients and methods**

Fifty-eight patients with RA according to the American College of Rheumatology (ACR) criteria (28) attending the Rheumatology Clinic at Karolinska University Hospital in Sweden were enrolled in the study. The inclusion criteria were treatment with prednisolone 5–7.5 mg/day for at least 2 years prescribed because of articular but not systemic disease, with stable disease activity as well as unchanged dose of GC for at least 3 months and stable treatment with disease-modifying anti-rheumatic drugs (DMARDs). Patients with high disease activity were excluded, as we wanted to recruit a population in which attempts to taper GC doses would have been normally carried out. Fifty of the patients were treated with DMARDs, namely methotrexate (n=29), sulphasalazine (n=14), injectable gold (n=8), cyclosporin (n=5), chloroquine (n=2), penicillamin (n=1), podophyllin (n=3), and etanercept (n=1). Fourteen of these patients were treated with two DMARDs.

After baseline, the patients were randomized either to taper and discontinue GC (withdrawal group) or to continue GC treatment unchanged (treatment group). The tapering of prednisolone was very slow, with a 2.5 mg reduction in the total weekly dose once a week, and with permission to go slower if the patient had withdrawal symptoms. Patients who did not withdraw prednisolone within 12 months were considered as ‘withdrawal failures’. All patients were treated with a daily dose of 800 mg of calcium and 400 mg of vitamin D3. The patients were followed for 2 years after randomization.

The randomization was performed according to a minimization procedure (29) that balanced the two groups with respect to gender, age (older or younger than 50 years) and the presence or absence of osteoporosis according to the criteria of the World Health Organization (WHO) (30).

Eight patients in the withdrawal group were treated with oestrogens or bisphosphonates, and four patients were premenopausal. The corresponding figures for the treatment group were 13 and three. In five patients, three in the withdrawal group and two in the treatment group, the antiresorptive treatment was started at study entry due to a very low BMD.

All patients provided informed consent to the study and the ethical committee approved the study protocol.

**Disease activity measures**

The Disease Activity Score (DAS28), a composite index of disease activity calculated for 28 joints, was used to assess disease activity at baseline and every 3 months (31). DAS28 includes number of swollen joints, number of tender joints, the patients’ global assessment of disease activity measured on a visual analogue scale (VAS), range 0–100 mm, and the erythrocyte sedimentation rate (ESR). The mean DAS28 during the 2 years was calculated from the 3-monthly samples divided by the number of assessments.

The patients also completed the Swedish version of the Stanford Health Assessment Questionnaire (HAQ), a self-reporting instrument (32). This disability index comprises 20 questions, divided into eight subcategories, each consisting of 2–3 activities of daily life. The response to each question ranges from 0 (no difficulty) to 3 (unable to perform). The created score for the disability index ranges from 0 to 3, where a higher score indicates a higher degree of disability (33).

**BMD measurements**

BMD was measured by dual-energy X-ray absorptiometry (DXA) with a Lunar densitometer at the lumbar spine (L1 and L2–L4) with anterior–posterior...
view, and at the left hip (femoral neck, the trochanter region and Ward’s triangle). BMD was expressed as the number of standard deviations (SD) from the mean of young healthy people (the T-score), and as the number of SD from the mean of healthy age- and sex-matched people (the Z-score). Values were obtained from Lunar’s combined European/USA reference populations (34). Osteoporosis was defined as a T-score of more than 2.5 SD below the mean value for young adults according to the WHO definition (29).

Radiological examinations

Radiological examinations were performed at baseline on the hands, wrists and feet as well as at the lateral projections of the thoracic and lumbar spine according to the clinical routines of our departments. The presence of vertebral fracture was estimated according to routine clinical practice. Patients who’s X-rays showed at least one erosion were considered erosive.

Statistical analysis

Statistics were performed using the Statistica, StatSoft®, Scandinavian AB for Windows (version 6.0). Correlation matrices and Spearman rank order correlations were used for continuous data normally and not normally distributed, respectively. For comparisons between groups, Student’s t-test was used for normal distributed data and the Mann–Whitney U-test for data not normally distributed. For comparisons between two dichotomous variables, Pearson’s χ²-test or Fischer’s exact p-test was performed. For multivariate analyses, logistic or linear regression analyses were performed. For both, backward eliminations were performed until four variables remained.

Results

Patient characteristics

The patient characteristics are depicted in Table 1. The patients showed considerable variation in disease duration, disease activity and functional capacity as well as duration of previous GC treatment. The two study groups were, however, well balanced in these aspects.

Clinical data for patients during the 2-year prospective study

Five patients, one in the withdrawal group and four in the treatment group, died during the study, and one patient randomized to withdrawal of prednisolone...
declined further participation after some months. Thus, 52 patients were evaluable for outcome measures.

Of the 26 patients randomized to withdrawal of prednisolone and evaluable for outcome measures, 15 failed to be free of GC within 12 months because of increasing rheumatic symptoms. Eight of these 15 patients tapered the dose or withdrew the GC during the second year of the trial. The failure subgroup had on average a higher DAS28 during the 2 years compared with the treatment group (4.24 vs. 3.60, p = 0.015). The mean DAS28 for the success subgroup was 3.81, which did not differ from the treatment group (p = 0.31). The mean DAS28 every third month is shown in Figure 1 for each group separately. In the success subgroup, the mean DAS28 showed a large variance, with some patients preferring to continue without GC despite their active disease. The mean cumulative GC dose during the study was 414 mg in the success subgroup, 3306 mg in the failure subgroup and 4059 mg in the treatment group.

Patients who succeeded in GC withdrawal within the 12 months were younger than with the patients who failed to withdraw (p = 0.027), and premenopausal women were more successful than postmenopausal (p = 0.031). Logistic regression showed that age, and not premenopausal status, was primarily associated with successful withdrawal of GC (Table 2).

BMD and fractures at baseline
BMD was moderately reduced at all sites measured (Table 1). The largest proportion with osteoporosis according to the definition of the WHO (29) was found in Ward’s region (51%). Seventeen patients had a BMD value > −2.5 at all measured sites; that is, they did not have osteoporosis according to the WHO criteria (29).

The correlations between BMD expressed as Z-scores at the five different sites and disease specific and non-specific variables are shown in Table 3.

Table 2. Baseline patient characteristics of the 26 patients randomized to withdraw GC treatment or to continue treatment.

<table>
<thead>
<tr>
<th></th>
<th>GC withdrawn (n=11)</th>
<th>Failures (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50 (49–64)</td>
<td>63 (60–77)</td>
<td>0.027</td>
</tr>
<tr>
<td>Proportion of women</td>
<td>73</td>
<td>73</td>
<td>0.97</td>
</tr>
<tr>
<td>No. pre/postmenopausal women</td>
<td>4/4</td>
<td>0/11</td>
<td>0.031</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>14 (3–17)</td>
<td>10 (3–16)</td>
<td>0.98</td>
</tr>
<tr>
<td>Duration of CG treatment, years</td>
<td>3 (2.0–6.2)</td>
<td>5.8 (3.1–8.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>RF positive</td>
<td>82</td>
<td>87</td>
<td>0.73</td>
</tr>
<tr>
<td>Erosions on X-ray</td>
<td>82</td>
<td>94</td>
<td>0.36</td>
</tr>
<tr>
<td>DAS28</td>
<td>3.95 (2.6–5.2)</td>
<td>3.6 (2.6–4.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.44 (0.13–1.6)</td>
<td>1.13 (0.5–1.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Current and previous smokers</td>
<td>73</td>
<td>80</td>
<td>0.66</td>
</tr>
<tr>
<td>Patients on DMARDs</td>
<td>91</td>
<td>87</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Values are given as percentage or median (interquartile range).
Disease duration, duration of GC treatment, the presence of rheumatoid factor (RF), HAQ score and BMI showed significant correlations with BMD in univariate analyses. In multiple regression analyses BMI was independently correlated with BMD in the neck, Ward’s region, the trochanter and L1 and HAQ scores correlated independently with BMD in the neck, the presence of RF with BMD in the trochanter and disease duration with BMD in L2–L4. The duration of GC treatment thus did not correlate with BMD at any site measured.

At baseline, 47% of the patients had a vertebral fracture detectable on X-ray and/or had experienced a peripheral fracture. In multivariate analysis the influence of age, gender, duration of disease, HAQ, duration of GC treatment, RF and erosive disease were tested. Except for age (above or below 50), only the presence of RF was significantly correlated with fractures (p = 0.020), with an odds ratio (OR) of 14.5 [95% confidence interval (CI) for OR 1.4–14.6] of having suffered a fracture if RF was positive.

Change in BMD during the 2-year prospective study

There were no significant differences between the two study groups concerning changes in BMD during the 2-year follow-up. Of interest, all mean values of changes were positive, that is both groups had on average higher Z-scores at the end of the study. Further analysis demonstrated that this was the case for patients who withdrew GC treatment within 12 months and for the treatment group but not for patients who failed the withdrawal for which they had been randomized (Table 4).

Changes in BMD in the trochanter correlated to mean DAS28 (r = 0.32, p = 0.031), that is a higher mean DAS28 was associated with bone loss.

Table 3. Correlations between Z-scores and different variables known to impact BMD. Statistically significant regression coefficients are given.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Femur neck n=53</th>
<th>Ward’s region n=53</th>
<th>Trochanter n=53</th>
<th>L1 n=31</th>
<th>L2–L4 n=48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r²</td>
<td>−0.33</td>
<td>−0.43</td>
<td>−0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.015</td>
<td>0.013</td>
<td>0.021</td>
<td>0.86</td>
<td>0.40</td>
</tr>
<tr>
<td>Duration of treatment with GC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r²</td>
<td>−0.32</td>
<td>−0.3</td>
<td>0.05</td>
<td>0.57</td>
<td>0.96</td>
</tr>
<tr>
<td>p</td>
<td>0.019</td>
<td>0.028</td>
<td>0.024</td>
<td>0.80</td>
<td>0.29</td>
</tr>
<tr>
<td>RF Lower in RF positivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.030</td>
<td>0.050</td>
<td>0.024</td>
<td>0.80</td>
<td>0.29</td>
</tr>
<tr>
<td>DAS28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r²</td>
<td>−0.39</td>
<td>−0.38</td>
<td>−0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.006</td>
<td>0.006</td>
<td>0.050</td>
<td>0.31</td>
<td>0.63</td>
</tr>
<tr>
<td>HAQ score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r²</td>
<td>−0.39</td>
<td>−0.38</td>
<td>−0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.006</td>
<td>0.006</td>
<td>0.050</td>
<td>0.31</td>
<td>0.63</td>
</tr>
<tr>
<td>Smoking, pack years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.38</td>
<td>0.92</td>
<td>0.92</td>
<td>0.82</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r²</td>
<td>+0.41</td>
<td>+0.31</td>
<td>+0.34</td>
<td>+0.39</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.002</td>
<td>0.021</td>
<td>0.013</td>
<td>0.007</td>
<td>0.47</td>
</tr>
</tbody>
</table>

r², Spearman regression coefficient.

Table 4. Mean changes in BMD (Z-score) during the 2-year prospective study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients randomized to GC withdrawal</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Successful</td>
<td>Failures</td>
</tr>
<tr>
<td>Femur neck</td>
<td>+0.40*</td>
<td>−0.08</td>
</tr>
<tr>
<td>Ward’s region</td>
<td>+0.28</td>
<td>−0.23</td>
</tr>
<tr>
<td>Trochanter</td>
<td>+0.25</td>
<td>+0.13</td>
</tr>
<tr>
<td>L2–L4</td>
<td>+0.50*</td>
<td>+0.08</td>
</tr>
<tr>
<td>L1</td>
<td>+0.42*</td>
<td>+0.03</td>
</tr>
<tr>
<td>Total body</td>
<td>+0.36</td>
<td>+0.20</td>
</tr>
</tbody>
</table>

*The change in BMD from baseline to the 2-year follow-up is statistically significant.
The change in BMD during the study did not differ between patients with and without antiresorptive treatment.

Discussion

The present study shows that withdrawal of long-term GC treatment was difficult or impossible in a substantial proportion of the patients because of increased inflammatory activity. Our results thus indicate that GC after several years still had anti-inflammatory properties, in contrast to findings in the studies by and van Everdingen et al (4) and Kirwan (6), where the anti-inflammatory effect of GC decreased and eventually disappeared with time. In the extension study by Hickling et al (7), GC was blindly discontinued with little evidence of flare in clinical symptoms. Our study differs from these previous attempts to determine long-term effects of GC (4, 6) both by being a withdrawal study and by involving patients with late RA. The patients in our study had been judged to need GC due to the inadequate effect of DMARDs, and the start of GC was thus not due to recruitment to a trial. Thus, the results of our study are consistent with the clinical observation that GC treatment, once started in clinical practice, has a tendency to be chronic and is in fact the therapy least likely to be discontinued over a 5-year period (35).

The four premenopausal women randomized to discontinuation all succeeded in withdrawal. Premenopausal status was in our study associated with lower HAQ score but not with lower degree of inflammation. A milder course of RA in premenopausal women has been described previously (36, 37). However, the two men below the age of 50 and randomized to withdrawal also succeeded in stopping medication. Age rather than premenopausal status was associated with successful withdrawal according to the multivariate analysis.

The present RA population with long-term, low-dose GC treatment had, on average, modestly reduced BMD. The site with the largest proportion of osteoporosis was Ward’s region that is a site with predominantly trabecular bone.

Our study confirms several previous reports stating that disease severity has a major effect on BMD. Thus, the HAQ score, which mirrors both current degree of inflammation and cumulated structural damage, correlated with BMD in the three regions in the hip. Furthermore, RF-positive patients had, on average, lower BMD at the three measured sites in the hip as well as more fractures. The fact that DAS28 did not correlate with BMD was probably due to the cross-sectional design, which gives information on inflammation only at a single time point. Inflammation must persist over time to impact BMD, consistent with the finding that the mean DAS28 values during the study period correlated inversely with changes in BMD in the trochanter. Neither duration of disease nor duration of GC treatment correlated independently with BMD at any site.

The number of fractures was high in the present population. However, the proportion of patients who reported non-vertebral fractures did not differ from either cases (RA patients) or controls in a recently published study (38). Vertebral deformities as a finding on X-rays are fairly common. In a large population-based study of vertebral osteoporosis in 19 European countries, 8–20% of men and 6–21% of women aged 50 years or more had at least one vertebral deformity. The highest rates were found in the Scandinavian countries (39). In the present study there was no independent correlation between duration of GC treatment and fractures.

The only group in the present study that on average did not show an increase in BMD at all sites during the two observational years was the group that failed to withdraw GC treatment within 12 months. These patients had a higher mean DAS28 during the two study years than patients randomized to continuing treatment with GC. Higher disease activity was thus more deleterious for bone tissue than use of low-dose GC. The group that was randomized to continue GC treatment despite stable disease with low grade of inflammatory activity in general did not deteriorate in BMD during the study. In fact, the mean values of BMD (Z-scores) in the treatment group improved significantly in three out of the six sites measured. This finding is consistent with a meta-analysis concluding that long-term, GC-treated RA patients on average do not decrease in BMD (18). In another study of RA patients, BMD was measured with a mean interval of 6.6 years. Bone loss was less than expected and Z-scores, as in our study, improved. However, GC use was associated with increased bone loss (40). Patients on bone-active agents including calcium and vitamin D preparations were excluded in that study. Calcium and vitamin D supplementation has been shown to prevent bone loss in the lumbar spine and trochanter in RA patients treated with low-dose GC (41).

In contrast to our findings, a 2-year prospective observational study in Norway demonstrated bone loss in patients with and without GC treatment at follow-up. Patients with GC treatment were more severely affected by RA but multivariate analysis showed that GC was independently associated with bone loss in the hip (42). The different outcomes may be explained by the different study designs, that are an observational versus an intervention study.

Our treatment group had stable disease and relatively low inflammatory disease throughout the study and in clinical practice attempts to taper the GC
dose would probably have been made. However, the patients were recruited and followed before anti-TNF treatment became routine clinical practice. BMD is reported to improve during anti-TNF treatment in patients with RA (43) and our results would probably have been different if our populations had had a more modern treatment, and were given the opportunity to control inflammation effectively without GC treatment. However, these drugs are not available for all patients because of their high cost and adverse effects and for some RA patients because of their lack of effect. Until inflammation in RA patients can be effectively controlled in all patients with drugs other than GC, our results should thus be of relevance for clinical practice.

In conclusion, there were substantial difficulties in withdrawing GC treatment in RA patients with stable disease, indicating an anti-inflammatory effect still present after a median 4 years of treatment. Patients with stable disease and continuous low-dose GC did not deteriorate in BMD during the 2 years of observation but on the contrary had higher Z-scores at the end of the study. Supplementation with calcium and vitamin D probably contributed to the positive outcome in the control group. Taken together, our findings imply that tapering or withdrawal of GC treatment should not be performed at the cost of higher disease activity, at least not with regard to bone health.

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References


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