

## Scientific papers

# Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: a longitudinal study

P N SAMBROOK,<sup>1,3</sup> M L COHEN,<sup>3</sup> J A EISMAN,<sup>1,2</sup> N A POCOCK,<sup>2</sup>  
G D CHAMPION,<sup>3</sup> AND M G YEATES<sup>2</sup>

From the <sup>1</sup>Garvan Institute of Medical Research and the Departments of <sup>2</sup>Nuclear Medicine and <sup>3</sup>Rheumatology, St Vincent's Hospital, Darlinghurst, NSW, Australia

**SUMMARY** Low dose corticosteroids are effective in suppressing synovitis in rheumatoid arthritis (RA), but there remains concern about their side effects, particularly osteoporosis. To examine the effects of low dose corticosteroids on bone loss in RA bone mineral density (BMD) was measured in the lumbar spine and hip for up to two years in 15 patients treated with these agents (mean dose prednis(ol)one 6.6 mg/day), 15 patients not receiving them, and 15 age matched controls. The initial BMD at both skeletal sites was significantly reduced in both patient groups compared with controls. The mean change in bone density was 0.2, 0.1, and -0.1% a year in the spine and -2.0, -1.9, and -1.0% a year in the hip respectively for the three groups. These rates of bone loss were not significantly different between groups at either site. These findings suggest that low dose corticosteroid treatment in RA is not associated with an increased risk of osteoporosis.

Standard teaching on the use of corticosteroids in rheumatoid arthritis (RA) is that they should be considered as a treatment of 'last resort', generally reserved for patients with severe disease refractory to other agents.<sup>1,2</sup> A recent survey of corticosteroid use in one hospital clinic, however, suggests actual clinical practice may be considerably different, with up to 30% of patients with RA taking low dose corticosteroids.<sup>2</sup> Moreover, corticosteroids are effective in suppressing synovitis,<sup>3</sup> and recently it has been suggested that the 'disease modifying' potential of low dose corticosteroids should be investigated if such doses could be shown to be acceptable in relation to potential adverse effects.<sup>4</sup>

One of the side effects of most concern with corticosteroids is the risk of inducing generalised osteoporosis in patients who may already be 'at risk' for this problem. The role of corticosteroids in causing osteoporosis in RA is unclear, however, and two recent studies using dual photon absorptiometry to examine axial bone mass have suggested that treatment with low dose corticosteroids does not significantly increase the risk of osteoporosis in patients with RA.<sup>5,6</sup>

Probably any effect of corticosteroids on bone mass would be both time and dose dependent. Thus there may be problems in attempting to determine a longitudinal effect from a cross sectional study. Therefore we examined the effect of low dose corticosteroids on bone loss in women with RA, treated or not treated with these agents, by performing longitudinal measurements of bone mass.

## Patients and methods

Women with definite or classical RA<sup>7</sup> seen consecutively in the department of rheumatology at St Vincent's Hospital were asked to participate. Informed consent was obtained from each subject, and the study received ethics committee approval. A full medical history and examination were performed, and in patients receiving corticosteroids cumulative and mean dose during the period of follow up were determined. Patients receiving hormone replacement therapy were excluded from the study. To assess disease severity we recorded each patient's functional class using the criteria of Steinbrocker *et al.*<sup>8</sup> An attempt was made to match each patient receiving corticosteroids by age and disease duration with patients not receiving corticosteroids. A further control group comprising healthy female volunteers matched for age was also studied.

Accepted for publication 5 December 1988.

Correspondence to Dr P N Sambrook, Garvan Institute of Medical Research, St Vincent's Hospital, Darlinghurst, NSW 2010, Australia.

Bone mineral density (BMD) was measured in the lumbar spine and femoral neck by dual photon absorptiometry on two to seven occasions in each patient over approximately two years. Bone mineral density was determined with a Lunar DP-3 dual photon absorptiometer (Lunar Radiation Corporation, Madison, Wisconsin, USA) using a gadolinium-153 source (44 keV, 100 keV, 40 GBq). Scans were made of three lumbar vertebrae and the right proximal femur. The BMD ( $\text{g}/\text{cm}^2$ ) was derived by dividing the bone mineral content of each region by the projected bone area. The radiation dose to the skin with this method is less than  $100 \mu\text{Gy}$ . For the lumbar spine scan the radiation dose to the ovaries in women is less than  $200 \mu\text{Gy}$ . The coefficient of variation with this method in our laboratory was 1.4% with cadaveric vertebrae and 2.6% in normal volunteers.

The BMD data were fitted to a linear regression against time to calculate rates of loss in each patient group. In subjects where BMD was measured on only two occasions the rate of loss was calculated as  $(\text{final BMD} - \text{initial BMD}) \times 100 / (\text{initial BMD} \times \text{interval between measurements})$ . Differences between groups were assessed by an analysis of variance. The chance of a type II error was also calculated.

## Results

Serial measurements of bone density were performed in 15 women with RA receiving prednis(ol)one (mean daily dose 6.6 mg, range 3–10 mg), 15 women with RA not receiving corticosteroids, and 15 healthy women. Femoral neck BMD measurements were not possible in two patients (one receiving and one not receiving corticosteroids) because of previous bilateral hip replacements. Table 1 shows the clinical details of the three groups. There was no significant difference in age between any group or in disease duration between groups with RA, although there was a trend for patients treated with corticosteroids to have more severe disease, judged by functional class.

Analysis of variance showed the initial BMD in patients with RA was significantly reduced compared with controls. In the lumbar spine:  $F=3.7$ ,  $p=0.033$  and Fisher's test therefore showed that initial BMD in both RA groups was significantly reduced compared with controls. In the femoral neck:  $F=5.84$ ,  $p=0.006$  with Fisher's test showing again that initial bone BMD in both RA groups was significantly reduced compared with controls.

The mean duration of follow up for BMD measurement was 2.02 years (range 1.09–2.53). Figure 1 shows the mean and 95% confidence

Table 1 Clinical details. Values are given as mean (SEM)

	RA <sup>†</sup> with CS <sup>†</sup>	RA no CS	Controls
Age	54.7 (3.1)	54.5 (3.0)	54.3 (3.0)
Disease duration	14.7 (2.4)	10.5 (1.5)	—
Functional class			
I	3	6	—
II	8	9	—
III	4	—	—
Initial BMD <sup>†</sup>			
Lumbar	0.99 (0.15)*	0.99 (0.16)*	1.12 (0.14)
Femoral	0.71 (0.09)*	0.73 (0.14)*	0.84 (0.09)

\*Significantly reduced ( $p<0.05$ ) compared with controls.

<sup>†</sup>RA=rheumatoid arthritis; CS=corticosteroids; BMD=bone mineral density.

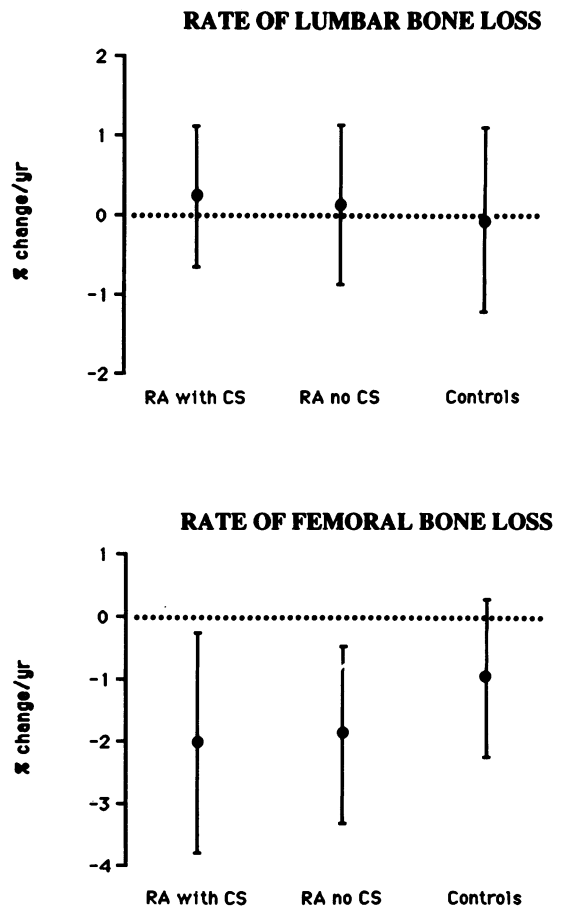


Fig. 1 Mean and 95% confidence intervals for change in bone mineral density over time expressed as percentage change per year. RA=rheumatoid arthritis; CS=corticosteroids.

intervals for change in BMD over time expressed as percentage change per year. Although the mean rates of bone loss from the femoral neck appeared to be greater in patients with RA (2%/year *v* 1.9 *v* 1.0 for corticosteroids *v* no corticosteroids *v* controls), there was no statistically significant difference in rates of loss at either site between any group. Type II error calculations were performed to determine the chance of having missed a significant difference between groups. For example, in the lumbar spine if a rate of loss of 1% per year was assumed for the control subjects and a rate double this assumed to be a clinically important difference for patients treated with corticosteroids—that is, 2%/year, the power of the study (1- $\beta$ ) to detect such a difference was greater than 90%. In the femoral neck the power to detect such a difference was lower at 74% because of the larger variance in the observed rates of loss.

## Discussion

A demonstration that low dose corticosteroids have little effect on the risk of osteoporosis in RA would have important therapeutic implications. Previous studies of the relation between corticosteroids and bone mass in RA, however, have been discrepant, with some workers suggesting that corticosteroids play a significant part,<sup>9-13</sup> but others failing to confirm this.<sup>14-16</sup> Many of these studies can be criticised for the methods used to assess osteoporosis and the clinical relevance of the site measured. Studies using radiological techniques<sup>9 13 15</sup> are too insensitive to assess osteopenia accurately. Quantitative techniques such as single photon absorptiometry measure only appendicular sites such as the radius,<sup>10 12 13</sup> where bone loss may reflect predominantly local disease. Similarly, measurement of total body calcium or total body bone mineral<sup>11 13 16</sup> provides no information on the relative contributions of localised and generalised bone loss. Assessment of bone mineral at clinically important fracture prone sites, such as the spine and hip, requires direct measurement by either dual photon absorptiometry or computed tomography.

Two recent studies have used the sophisticated technique of dual photon absorptiometry to examine axial bone mass in patients with RA treated with low dose corticosteroids. In the first study no difference in lumbar spine bone density could be shown between patients treated with low dose prednisolone (mean daily dose 8.9 mg) and normal controls.<sup>5</sup> In the second study BMD of the lumbar spine and hip in 44 women with RA who had received low dose prednisolone (mean daily dose 8 mg) was not significantly reduced compared with that in 40 patients who had not received these drugs.<sup>6</sup> A

subsequent study of male patients with RA receiving higher doses of prednisolone (mean daily dose 10.5 mg) did show a significant reduction in lumbar BMD compared with those not taking them.<sup>17</sup> These findings suggest there may be a dose-response relation, with doses of prednisolone below 8 mg/day being relatively safe but doses above 10 mg/day producing clinically important bone loss.

Because there may be problems associated with attempting to investigate a temporal process by a cross sectional study the present longitudinal study was performed. These data confirm our previous findings<sup>6</sup> and suggest that low dose corticosteroids do not increase bone loss above the rates seen in patients with RA not receiving them. In the femoral neck rates of bone loss in both patient groups were marginally greater than in the control group and greater than reported rates of age related bone loss.<sup>18</sup> This may reflect localised hip disease or reduced mobility, though the differences between groups were not statistically significant.

It has been suggested that a period of rapid bone loss occurs soon after corticosteroids are started.<sup>19</sup> In our study the patients were already receiving corticosteroid treatment before the first BMD measurement so it might be that an early phase of more rapid loss had been completed at the time of entry to the study. There was no significant difference between the two patient groups in their initial BMD, however, though BMD in both groups was significantly reduced compared with that in the control subjects, so it is unlikely that an early period of more rapid bone loss had occurred. The mechanisms for this reduction in initial BMD in both patient groups include reduced mobility and various disease related mechanisms, as we have recently shown.<sup>17 20</sup>

These data support the concept that low dose corticosteroids do not produce a clinically important increase in bone loss in the spine or hip in RA and hence are not associated with an increased risk of osteoporosis. It is noted that these data relate only to low dose treatment, and probably higher doses will produce clinically important bone loss. As corticosteroids can be useful in specific clinical situations in RA—for example, while awaiting the effects of slow acting disease modifying drugs or in patients with severe refractory disease, concern about inducing osteoporosis with low dose treatment seems not to be of clinical relevance.

## References

- 1 Hart F D, ed. *Drug treatment of the rheumatic diseases*. 3rd ed. London: Williams and Wilkins, 1987.
- 2 Byron M A, Mowat A G. Corticosteroid prescribing in rheumatoid arthritis—the fact and the fiction. *Br J Rheumatol* 1985; **24**: 164-6.

- 3 Masi A T. Low dose glucocorticoid therapy in rheumatoid arthritis: Transitional or selected add-on therapy? *J Rheumatol* 1983; **10**: 675-8.
- 4 Byron M A, Kirwan J R. Corticosteroids in rheumatoid arthritis: Is a trial of their 'disease modifying' potential feasible? *Ann Rheum Dis* 1986; **45**: 171-3.
- 5 Verstraeten A, Dequeker J. Vertebral and peripheral bone mineral content and fracture incidence in postmenopausal patients with rheumatoid arthritis. *Ann Rheum Dis* 1986; **45**: 852-7.
- 6 Sambrook P N, Eisman J A, Champion G D, Pocock N A, Yeates M G, Eberl S. Osteoporosis in rheumatoid arthritis: safety of low dose corticosteroids. *Ann Rheum Dis* 1986; **45**: 950-3.
- 7 Ropes M W, Bennett G A, Cobb S, Jacox R, Jessar R A. 1958 Revision of diagnostic criteria for rheumatoid arthritis. *Bull Rheum Dis* 1958; **9**: 175-6.
- 8 Steinbrocker O, Traeger C H, Batterman R C. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1949; **140**: 659-62.
- 9 Saville P D, Kharmosh O. Osteoporosis of rheumatoid arthritis: influence of age, sex and corticosteroids. *Arthritis Rheum* 1967; **10**: 423-30.
- 10 Mueller M N, Jurist J M. Skeletal status in rheumatoid arthritis. *Arthritis Rheum* 1973; **16**: 66-70.
- 11 Reid D M, Kennedy N J S, Smith M A, Tohill P, Nuki G. Total body calcium in rheumatoid arthritis: effects of disease activity and corticosteroid treatment. *Br Med J* 1982; **285**: 330-2.
- 12 de Deuxchaisnes C N, Devogelaer J P, Esselinckx W, *et al.* The effect of low dosage glucocorticoids on bone mass in rheumatoid arthritis: a cross-sectional and a longitudinal study using single photon absorptiometry. *Adv Exp Med Biol* 1984; **171**: 209-39.
- 13 Als O S, Gotfredson A, Christiansen C. The effect of glucocorticosteroids on bone mass in rheumatoid arthritis patients. *Arthritis Rheum* 1985; **28**: 369-75.
- 14 McConkey B, Frazer G M, Blich A S. Osteoporosis and purpura in rheumatoid disease: prevalence and relation to treatment with corticosteroids. *Q J Med* 1962; **31**: 419-27.
- 15 Buchanan W W, Samuels B M, Jasani M K, *et al.* Do oral corticosteroids cause osteoporosis in rheumatoid arthritis? *Ann Rheum Dis* 1970; **29**: 560-1.
- 16 Kennedy A C, Boddy K, Williams E D, *et al.* Whole body elemental composition during drug treatment of rheumatoid arthritis: a preliminary study. *Ann Rheum Dis* 1979; **38**: 137-40.
- 17 Sambrook P N, Eisman J A, Champion G D, Pocock N A, Eberl S, Yeates M G. Determinants of axial bone loss in rheumatoid arthritis. *Arthritis Rheum* 1987; **30**: 721-8.
- 18 Riggs B L, Wahner H W, Seeman E, *et al.* Changes in bone mineral density of the proximal femur and spine with aging. *J Clin Invest* 1982; **70**: 716-23.
- 19 Gennari C. Glucocorticoids and bone. *Bone and Mineral Research, Holland* 1985; **3**: 213-32.
- 20 Sambrook P N, Eisman J A, Champion G D, Pocock N A. Sex hormone status and osteoporosis in postmenopausal women with rheumatoid arthritis. *Arthritis Rheum* 1988; **31**: 973-8.