

JOINT DESTRUCTION AFTER GLUCOCORTICOIDS ARE WITHDRAWN IN EARLY RHEUMATOID ARTHRITIS

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SUMMARY

Objective. Prednisolone reduced the progression of joint destruction over 2 yr in early, active rheumatoid arthritis. The response to discontinuation of prednisolone under double-blind conditions is now reported.

Methods. A randomized, double-blind, placebo-controlled trial of prednisolone 7.5 mg daily in addition to routine medication over 2 yr in 128 patients with early rheumatoid arthritis, using radiological progression (changes in the Larsen score) and the development of erosions as primary outcome measures. Study medication was blindly discontinued and follow-up maintained for a further year. Other assessments included disability, joint inflammation, pain and the acute-phase response.

Results. Similar results were obtained when all available radiographs were included for each year of assessment (maximum 114) and when only patients with radiographs at all time points were included (75 patients). In these 75, the mean progression in the prednisolone group was 0.21 Larsen units in year 1, 0.04 units in year 2 and 1.01 units in year 3 ($P = 0.587$, 0.913 and 0.039 for change within each year, respectively). The equivalent placebo group means were 2.34, 1.00 and 1.63 Larsen units ($P = 0.001$, 0.111 and 0.012; difference between groups: 2.13, 0.96 and 0.67 units, $P = 0.082$, 0.02 and 0.622). The percentage of hands which had erosions at each time point was: prednisolone group: 27.8, 29.2, 34.7 and 39.2; placebo group: 28.2, 48.7, 59.0 and 66.5. There was little evidence for a flare in clinical symptoms after discontinuation of prednisolone.

Conclusion. Joint destruction resumed after discontinuation of prednisolone. This corroborates the previously reported therapeutic effect and challenges current concepts of disease pathogenesis.

KEY WORDS: Rheumatoid arthritis, Disease-modifying drugs, Erosions, Corticosteroids, Randomized controlled trial.

RHEUMATOID arthritis is a major cause of disability, leading to joint destruction and loss of locomotor function [1]. Preservation of the articular surfaces is a therapeutic priority, but success in this endeavour has been elusive [2, 3]. We have previously reported the protective effect of 7.5 mg of prednisolone per day on joint erosions in the hand and wrist in patients with early rheumatoid disease [4]. This effect persisted for 2 yr, while symptomatic benefit lasted only a few months, raising the possibility that these two aspects of rheumatoid arthritis are related to different pathological mechanisms. We now report on the response of these patients to discontinuation of the study medication under double-blind conditions.

PATIENTS AND METHODS

Full details of the methods of the study have been published previously [4]. Patients aged 18-69 yr with rheumatoid arthritis of <2 yr duration and currently active disease [defined as six or more painful joints, three or more joints with active synovitis, early morning stiffness for >20 min and an erythrocyte sedimentation rate (ESR) >28 mm/h, plasma viscosity >1.72 or C-reactive protein (CRP) >10 mg/l] took part. Prednisolone 7.5 mg and identical placebo tablets were prepared and labelled specifically for this study. Randomization was in blocks of six subjects within each centre, 13 centres took part and (except in

an emergency) the patient codes were not broken until after the analysis at 36 months. Physicians managing each patient were free to prescribe any treatment, except systemic corticosteroids. After 2 yr, the study medication was reduced to alternate-day treatment for 2 weeks, then every third day treatment for 2 weeks, and was then discontinued. Both patient and physician therefore remained blind as to the treatment the patient had received. Double-blind follow-up was maintained for a further year, and is the subject of this report.

The primary outcome variables were progression of radiological damage in hand radiographs taken at entry and after 1, 2 and 3 yr, and the appearance of erosions in hands which had no erosions at baseline. All available radiographs were viewed jointly by the same experienced radiologist and rheumatologist using the same light for all films. To ensure similar conditions for assessing radiographs within each patient, and to avoid the possibility of bias which might develop over the several sittings required to read and score the radiographs, their presentation was in randomly ordered blocks of 30. All identifying markings were covered. In the initial analysis of response to treatment over 2 yr [4], 0, 1 and 2 yr films from 10 randomly selected patients were included in each block. Each hand was classified as erosive or non-erosive and each joint was then scored by the method of Larsen [5], which grades the degree of joint damage on a scale from 0 (radiologically normal joint) to 5 (maximum degree of joint destruction) with reference to a standard atlas of radiographs. Both assessments were made by consensus between observers and were recorded on

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coding sheets. The Larsen score is the summation of all the joint scores in both hands taken together. In the follow-up analysis of radiographs (which was performed 14 months after the initial readings), the 2 yr films were re-scored with the 3 yr films to allow for the possibility of changes in reader sensitivity to identifying radiographic features. Readings were performed in the same way as previously, but the blocks of 30 films contained 2 and 3 yr films for 15 randomly selected patients.

Secondary outcomes were assessed every 3 months. They included changes in disability (measured by the Health Assessment Questionnaire [6]), joint inflammation (measured by an articular index of tender and swollen peripheral joints weighted for joint size [7]), pain over the previous 24 h (using a visual analogue scale [8]), and the acute-phase response (measured either by the ESR, CRP or plasma viscosity, depending on the centre). Records of other treatments and adverse reactions (including measurement of weight and blood pressure) were also kept.

Statistical analysis employed the χ^2 test to compare proportions and Student's *t*-test to compare means [9]. Larsen scores were subject to log transformation [$\log_{10}(\text{score} + 1)$] before comparison between groups to take account of their skewed distribution. Year 3 readings were adjusted to take account of changes in reader sensitivity as reported below. Overall group mean scores were compared, but a more detailed and exact analysis of radiographic change was conducted on those patients for whom films were available for all four time points. The difference in the logarithms between examinations was calculated for each subject. The means of these differences in the two treatment groups were compared and their 95% confidence intervals (CI) determined using Student's *t*-test [9].

Data on secondary outcome variables are presented for the patients for whom films were available for all four time points to allow direct comparison with radiographic changes. Because different centres used different methods for measuring the acute-phase response, the values were standardized to enable combination of the data. *Z*-scores [9] (standard normal deviates) were calculated by taking all available values for each patient and re-expressing them as the number of standard deviations from the mean of those values. For each time point, the mean and standard deviation of these standardized scores were calculated to derive group values.

All statistical tests were two tailed and $P = 0.05$ was taken as the significance level.

RESULTS

The 128 patients enrolled in the study had moderately severe joint inflammation and were typical of patients entering studies of specific anti-rheumatoid therapy [4]. All had a disease duration reported as <2 yr, the mean was a little over 1 yr. Eleven patients did not have subsequent hand radiographs because they were lost to follow-up (three because they were withdrawn with other medical conditions and eight

because they moved away or declined to take study medication). These patients and three others for whom the initial radiographs were lost have been excluded from the analysis. Treatment was discontinued in six patients (two in the placebo group and one in the prednisolone group for hypertension and weight gain, and one each in the placebo group for diabetes, starting corticosteroids and declining further medication). These patients were subsequently followed and included in their initial treatment groups. Thus, 114 radiographs were available at year 0 (53 prednisolone, 61 placebo), but only 110 (53 and 57), 109 (51 and 58) and 96 (44 and 52) were available in subsequent years.

Re-reading the 2 yr radiographs at the same time as the 3 yr radiographs resulted in adjustments for changes in reader sensitivity as follows: in the prednisolone group, the proportion of hands identified as erosive in year 3 was reduced by a factor of 0.81, and in the placebo group by a factor of 0.98 (difference 0.17, 95% CI 0.04–0.31). In the prednisolone group, the year 3 Larsen score for each patient was reduced by a factor of 0.81 and in the placebo group by a factor of 0.98 (difference 0.17, 95% CI 0.04–0.30). These adjusted scores for year 3 were used in all subsequent comparisons and statistical analysis.

The comparison of radiological progression in all the available radiographs is shown in Table I. This shows significant benefits for the prednisolone-treated patients at all time points after the initiation of study treatment. There appears to be an increase in the difference between the groups during the third year, after study medication has been discontinued.

The 75 patients who had radiographs available for all four time points provide a more detailed comparison both within patients and between treatment groups. The characteristics of these patients are shown in Table II

TABLE I
Progression of joint damage in all available radiographs

	Year			
	0	1	2	3
Proportion (%) of erosive hands				
Prednisolone	30.2	31.1	33.3	37.6
Placebo	30.3	43.9	56.0	67.3
<i>P</i> (χ^2)	0.2498	0.0420	0.0003	0.0000
95% CI				
Prednisolone	8.73	8.81	9.15	10.52
Placebo	8.15	9.11	9.03	9.43
Mean* Larsen score				
Prednisolone	1.39	1.57	1.72	2.39
Placebo	1.57	3.18	4.48	7.13
<i>P</i> (<i>t</i> -test)	0.7318	0.0466	0.0067	0.0009
95% CI				
Prednisolone	1.13	1.14	1.15	1.16
Placebo	1.15	1.17	1.18	1.17
Difference between groups				
Erosions	0.1	12.7	22.7	29.6
Larsen score	0.18	1.61	2.76	4.75

*Antilog of mean after log transformation.

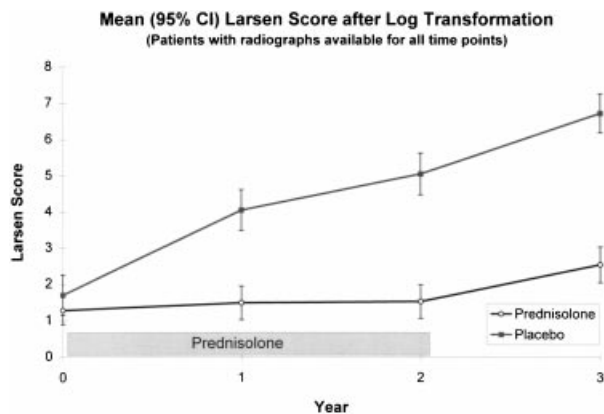


FIG. 1.—Mean (95% CI) Larsen score after log transformation for 75 patients with radiographs at all time points.

and compared with the patients excluded from this analysis. There were no significant differences between prednisolone- and placebo-treated patients, nor between patients included and excluded from the analysis. In particular, the proportions of erosive hands and Larsen scores at baseline were not significantly different.

The overall progression of Larsen scores is shown in Fig. 1 and Table III. In the placebo group, there was steadily progressive joint destruction. In the prednisolone-

alone-treated patients, there was very little change in the first 2 yr, but a significant increase during year 3, after withdrawing prednisolone treatment. This increase was not significantly different from that in the placebo group during year 3, although by the end of the follow-up period the prednisolone patients still had a much lower Larsen score than the placebo patients (2.29 vs 6.98, $P = 0.003$). The changes in Larsen score were principally in identifying grade 2 joint changes, and few scores of grade 1 contributed to the total scores.

The percentage of hands which had erosions at each time point in the prednisolone group was 27.8, 29.2, 34.7 and 39.2. There was no significant difference between each consecutive time point. Rather, there seemed to be a slowly increasing proportion of erosive hands which did not alter dramatically after discontinuation of glucocorticoid therapy. The change over the full 3 yr of follow-up was 11.4% (95% CI 4.1–18.7). In the placebo group, the equivalent figures were 28.2, 48.7 and 59.0 and 66.5. The difference between each time point was statistically significant ($P < 0.05$) and the pattern follows that which might be expected in these patients [10]. The change over the full 3 yr of follow-up was 38.3% (95% CI 27.5–49.1).

Clinically, the 75 patients analysed here reflect the broad picture of the response of all the patients entered into the original study and reported previously. There

TABLE II
Baseline characteristics of the patients included and excluded from the analysis

	Included in this analysis			Included in initial study but not in this analysis
	Prednisolone group	Placebo group	All patients	
Number	36	39	75	53
Age* (yr)	48.3 (9.4)	50.1 (10.1)	49.2 (10.7)	49.3 (9.8)
Proportion female (%)	61	77	69	57
Latex positive (%)	94	85	90	83
Previous SARD† (%)	9	17	12	10
Articular index* (0–534)	218 (102)	212 (125)	215 (115)	210 (122)
Pain score* (0–3)	1.35 (0.74)	1.56 (0.77)	1.46 (0.76)	1.34 (0.77)
Disability score* (0–3)	1.21 (0.68)	1.35 (0.72)	1.28 (0.70)	1.16 (0.71)
Standardized**				
acute-phase response*	0.27 (3.11)	–0.77 (4.62)	–0.30 (4.02)	–0.65 (3.37)
Weight* (kg)	69.9 (10.3)	66.8 (15.9)	68.3 (13.5)	70.9 (11.7)
Systolic BP* (mmHg)	129 (16)	132 (21)	130 (19)	130 (17)
Diastolic BP* (mmHg)	80 (14)	82 (13)	81 (13)	82 (9)
Log-transformed Larsen score*	0.359 (0.452)	0.423 (0.597)	0.397 (0.519)	0.336 (0.429)
Proportion with erosions (%)	28	28	28	36

*Mean (s.d.).

†Specific anti-rheumatoid drug.

**See Patients and methods.

There are no statistically significant differences between groups at $P < 0.05$.

TABLE III
Changes in Larsen score in 75 patients with radiographs at all time points

Larsen score	Year			P (t -test) within groups		
	1	2	3	Year 1	Year 2	Year 3
Prednisolone	0.21	0.04	1.01	0.587	0.913	0.039
Placebo	2.34	1.00	1.68	0.001	0.111	0.012
P (t -test) between groups	0.082	0.020	0.622			

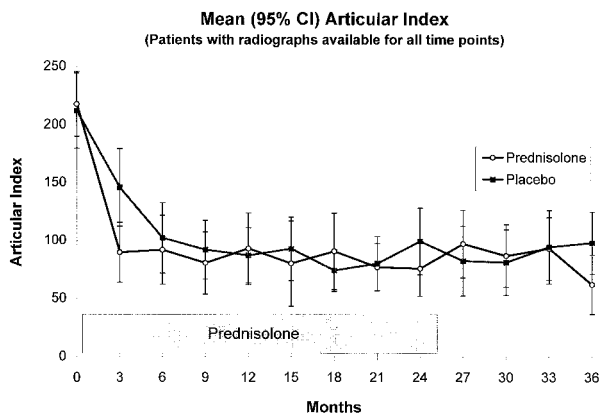


FIG. 2.—Mean (95% CI) articular index for 75 patients with radiographs at all time points.

was an early additional benefit for the steroid-treated patients for pain, disability and joint inflammation compared to that in the placebo patients, but there were no significant differences between the groups in any of the clinical measures after 9 months. A specific analysis of changes between 24 and 27 months, immediately following withdrawal of trial medication, is shown in Table IV. The only evidence for a flare in clinical symptoms is a relative increase in the articular index in the prednisolone-treated patients, but the difference between the two groups is due primarily to a (possibly chance) reduction in the joint inflammation in the placebo group (Fig. 2). Neither group showed any significant change in their pain assessments at 30, 33 or 36 months compared to that at 24 months, and there were no significant differences between the groups in this respect. There was no significant change in the Z-scores for acute-phase response in the third year either within or between groups.

There was no change in the proportion of patients taking various anti-rheumatoid drugs during the third year in either group (Table V). In addition, there was no difference in the outcome measurements amongst the placebo group whether they received anti-rheumatoid drugs or not, and the proportion of co-prescribed drugs was the same in patients included and excluded from the X-ray analysis (data not shown).

A small number of patients were treated with systemic glucocorticoids by their managing physician (Table VI). Overall, five of the original prednisolone group patients and six of the original placebo group

patients were taking physician-prescribed glucocorticoids by the end of the 3 yr study period. The patients in the prednisolone group were commenced on this treatment at some time during the 6 months following withdrawal of study treatment.

Both groups of patients increased their weight during the 36 months of the trial. There was no significant difference between groups for change in weight at 2 yr; however, in the third year the prednisolone group lost an average of 3.1 kg after prednisolone withdrawal (95% CI 1.9–4.3), whereas the placebo group continued to increase weight by 1.5 kg (95% CI 0.3–2.7). There were no significant changes in blood pressure.

DISCUSSION

Joint destruction in rheumatoid arthritis, measured here by the Larsen index and the proportion of hands with erosions, is arguably the most important objective parameter to modify with treatment [3]. We have already shown that fixed daily doses of 7.5 mg of prednisolone for 2 yr will significantly reduce progression of the Larsen index and the proportion of hands which develop their first erosions in patients with early disease [4]. This double-blind radiographic follow-up study has shown that after prednisolone withdrawal there is significant deterioration in the Larsen index, even though the majority of patients continued to take specific anti-rheumatoid treatment. This reinforces the conclusion that prednisolone is able to suppress erosive progression, but suggests it is only able to do so if it continues to be taken. It is possible that the co-prescribed drugs have reinforced the effect of glucocorticoids, but the design of this trial did not address that issue.

There is no suggestion from the results that there is an 'overshoot' of radiographic progression once glucocorticoids are withdrawn. Rather, the rate of progress runs a little less than and approximately parallel to that of the first year of placebo treatment, and shows that glucocorticoid treatment postpones the progression in Larsen score which would otherwise have occurred. At the end of the 3 yr follow-up, patients who had been treated with prednisolone for 2 yr still had significantly lower Larsen scores than did placebo-treated patients.

The development of erosions in hands which had no erosions at baseline was suppressed during prednisolone treatment and progressed at a much slower rate than in the placebo-treated patients. In the year following with-

TABLE IV
Changes in clinical variables after treatment discontinuation

	Prednisolone group			Placebo group			Difference between groups <i>P</i>
	24 months	Change 24–27 months	95% CI for change	24 months	Change 24–27 months	95% CI for change	
Pain score	0.90	0.05	−0.1 to 0.2	0.105	0.050	−0.109 to 0.209	0.095
Disability score	0.89	−0.025	−0.19 to 0.14	1.033	−0.12	−0.282 to 0.042	0.409
Articular index	76.1	5.9	−17.5 to 28.3	99.6	−28.6	−53.2 to −4.0	0.041
Acute-phase response	9.4	−2.5	6.6 to 1.8	10.8	−1.3	−4.0 to 1.4	0.625

TABLE V
Proportion (%) of patients taking various anti-rheumatoid drugs during the study

	0-24 months				24-36 months				Change from 24 to 35 months			
	Pred	Plac	Diff	95% CI of Diff	Pred	Plac	Diff	95% CI of Diff	Pred	Plac	Diff	95% CI of Diff
NSAID	75	83	-9	-27 9	71	76	-5	-25 15	3	7	-4	-9 1
I.m. gold	8	6	2	-9 13	8	6	2	-10 14	0	0	0	-3 3
D-Penicillamine	32	32	0	-21 21	38	35	3	-19 25	-6	-3	-3	-13 7
Sulphasalazine	27	34	-7	-28 14	30	27	3	-18 24	-3	7	-10	-13 -7
Methotrexate	2	7	-5	-15 5	9	11	-2	-16 12	-7	-4	-3	-14 8
Hydroxychloroquine	1	1	0	-4 4	0	0	0	0 0	1	1	0	-2 2
Other SARD	3	4	-1	-9 7	0	7	-7	-15 1	3	-3	6	5 7
Other drugs	46	66	-20	-44 2	55	77	-21	-43 1	-9	-11	2	-14 18

Pred, prednisolone; NSAID, non-steroidal anti-inflammatory drug; Plac, placebo; SARD, specific anti-rheumatoid drug; Diff, difference.

TABLE VI
Patients treated with glucocorticoids by their managing physician

	Treatment group	Number of patients entered	Months in study													
			0	3	6	9	12	15	18	21	24	27	30	33	36	
All entrants	Prednisolone	61											3	7	6	5
	Placebo	67		3	2	2	2	2	3	3	3	3	6	5	5	6
This analysis	Prednisolone	36											2	5	5	5
	Placebo	39							1	1	1	1	2	1	3	4

drawal of prednisolone, only a further 5% of hands became erosive, which was not significantly different from the rate on treatment. This raises the possibility that treatment for 2 yr with prednisolone may have a longer lasting effect in the prevention of onset of erosions. A recent randomized controlled trial of 155 patients treated with higher doses of prednisolone, but for only 6 months [11], has also shown a reduction in the rate of radiological progression, with some stronger evidence that the benefits of prednisolone may persist after treatment is withdrawn. A longer term radiographic follow-up of patients after the end of treatment would be worthwhile. We have not calculated the number of 'erosive patients' by combining the presence of erosions in both hands because we have no information about erosions at other joint sites such as the feet.

Many clinicians are concerned about the possibility of a deleterious flare in clinical signs and symptoms after glucocorticoid treatment is withdrawn. The clinical assessments in this study did not show any consistent deterioration at 27 or 30 months following glucocorticoid withdrawal at 24 months, but a small number of patients were started on treatment with glucocorticoids by their managing physician during this time or in the following 3 months. This suggests that the way in which treatment was scaled down (alternate days for 2 weeks and every third day for 2 weeks) was clinically acceptable to most patients. Many investigators noticed that there were some patients who experienced worse symptoms for a shorter period than 3 months, but this was not formally assessed in this study. The total number of patients on treatment with systemic glucocorticoids was similar in the prednisolone and placebo groups at the end of the follow-up period.

An important finding in this study is that the symp-

toms (pain, disability) and signs (articular index) of joint inflammation did not change after withdrawal of glucocorticoid treatment, but joint damage did progress. This mirrors the finding in the original study [4] where symptomatic improvement from glucocorticoids lasted for only a short time, but suppression of radiographic progression lasted throughout the 2 yr of treatment. Although the radiographic results relate only to the hand, these findings argue in favour of the existence of two pathological processes taking place within the joint— inflammation and joint destruction—which respond differently to treatment.

Eleven previous studies have been published which contribute evidence on the effects of glucocorticoids in rheumatoid arthritis (Table VII). Eight [4, 11-14, 17, 18, 20] are randomized controlled trials and one [16] is a longer term follow-up of one of these studies. Six of these eight are trials of daily oral glucocorticoids which point to a reduction in erosive progression. The two studies which do not support such a conclusion [17, 20] were tests of monthly i.v. infusion of methyl-prednisolone for 6 or 12 months. The results of the present study, which show that erosive progression recommences once glucocorticoid treatment is withdrawn, reinforce these findings. How long glucocorticoids might best be prescribed for the treatment of relatively early rheumatoid arthritis cannot be determined from this study, and the control of erosive progression will need to be balanced against the potential long-term risk of adverse reaction, recently reviewed by Saag *et al.* [21]. Measurements of bone mineral density (BMD) in the lumbar spine and femoral neck by dual-energy X-ray absorptiometry have been reported for 24 patients in this study during the treatment phase [22]. After 1 yr, BMD was reduced

TABLE VII
Trials of glucocorticoids in rheumatoid arthritis

Study	Ref.	Year	No. of patients	Treatment (mg/day)	Comparator	Duration (months)	RCT*	Radiographic result	Comments
MRC	12	1954	61	Cortisone 80	Aspirin 4.5 g/day	12	Yes	Not assessed	Withdrawal flares
ERC	13	1955	100	Cortisone 69	Aspirin 4 g/day	12	Yes	Non-significant but higher porosis and erosion scores in aspirin group	Erosion score could have been refined. If cut-off taken at moderate to severe scores, cortisone did far better
MRC	14	1959	77	Prednisolone 12 for year 1, 10 for year 2	Aspirin	36	Yes	Less after 1 and 2 yr	Prednisolone probably held advantage into third year
Berntsen	15	1961	183	Hydrocortisone 25-100	Analgesics, i.m. gold	>60		No difference (steroid group had better functional outcome)	Poorly matched, different doses and formulations, steroid group worse at start
West	16	1967	74	Prednisolone < 15	Aspirin	84		Less progression	10 mg better than 7.5 mg.
Liebling	17	1981	10	Methylprednisolone 1 g/month	Placebo	6	Yes	No difference	Publication not readily accessible
Harris	18	1983	18	Prednisolone 5	Placebo	10	Yes	Less progression in steroid group (and better functional outcome)	Very few patients
Million	19	1984	103	Prednisolone 10.3	No steroids	120		Less erosions	Broad treatment comparison with contamination between groups
Hansen	20	1990	97	Methylprednisolone 1 g i.v. monthly	i.v. saline	12	Yes	No difference in erosion scores	
Kirwan	4	1995	128	Prednisolone 7.5	Placebo	24	Yes	Reduced erosive progression	
Boers	11	1997	155	Sulphasalazine 2000 Prednisolone 60 → 7.5 then methotrexate 7.5 mg weekly	Sulphasalazine 2 g/day	28	Yes	Reduced erosive progression	

*RCT, randomized, controlled trial.

by 3.1 and 0.4% in these sites in the prednisolone patients, and by 1.4 and 2.3% in the placebo group. During the second year of treatment, both groups reduced their spinal bone mass further (prednisolone 3.1%, placebo 4.8%) and in the femoral neck the placebo group tended to lose more bone (prednisolone 4.0%, placebo 6.3%). This small pilot study indicated no dramatic fall in BMD related to the use of low-dose glucocorticoids in these patients, but a sample size in excess of 200 would be required to demonstrate a significant difference between the groups at year 1 with 80% power given the variance in measurements.

Whether treatment with fixed, low-dose prednisolone should be introduced at an earlier stage of treatment, continued for an additional 1 or 2 yr (as might be suggested from these results) or given for less severe disease needs to be tested, particularly in relation to potential prognostic indicators of those patients most likely to develop erosions [23].

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APPENDIX

The Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group Participants and Study Centres: M. Byron (Stoke Mandeville Hospital, Aylesbury), R. Jacoby (Princess Elizabeth Hospital, Exeter), P. A. Dieppe (Bristol Royal Infirmary, Bristol), A. Kirk (Amersham Hospital, Amersham), C. J. Eastmond (City Hospital, Aberdeen), J. R. Kirwan (Bristol Royal Infirmary, Bristol, Study Coordinator), P. Hollingworth (Southmead Hospital, Bristol), C. Moran (Christchurch Hospital, Christchurch), D. M. Reid (City Hospital, Aberdeen), J. Halsey (Lancaster Moor Hospital, Lancaster), A. J. Swannell (City Hospital, Nottingham), P. Hickling (Mount Gould Hospital, Plymouth), D. Yates (Taunton and Somerset Hospital, Taunton). Additional investigators: C. Cooper (Bristol Royal Infirmary, Bristol), E. George (Bristol Royal Infirmary, Bristol). Non-recruiting study advisor: J. Jessop (University Hospital of Wales, Cardiff). Pharmacist: D. Forbes (Bristol Royal Infirmary, Bristol). Radiologist: I. Watt (Bristol Royal Infirmary, Bristol).