

THE EFFECT OF GLUCOCORTICOIDS ON JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS

JOHN R. KIRWAN, M.D.,

AND THE ARTHRITIS AND RHEUMATISM COUNCIL LOW-DOSE GLUCOCORTICOID STUDY GROUP*

Abstract *Background.* Oral glucocorticoids are widely used to treat patients with rheumatoid arthritis, but their effect on joint destruction, as assessed radiologically, is uncertain.

Methods. We conducted a randomized, double-blind trial comparing oral prednisolone (7.5 mg daily for two years) with placebo in 128 adults with active rheumatoid arthritis of less than two years' duration. Except for systemic corticosteroids, other treatments could be prescribed. The primary outcome variables were the progression of damage as seen on radiographs of the hand after one and two years, as measured by the Larsen index, and the appearance of erosions in hands that had no erosions at base line. The radiographs were viewed jointly by a radiologist and a rheumatologist who were unaware of the treatment assignment and the time point at which the films were obtained.

Results. The statistical analysis of radiologically detected changes was based on 106 patients for whom there were films obtained at base line and two years later. After two years, the Larsen scores increased by a mean of 0.72 unit in the prednisolone group, indicating

very little change, and by 5.37 units in the placebo group, indicating substantial joint destruction ($P=0.004$). Of the 212 hands of these patients, 147 (69.3 percent) had no erosions at the start of the study. At two years, 15 of the 68 such hands in the prednisolone group (22.1 percent) and 36 of the 79 such hands in the placebo group (45.6 percent) had acquired erosions (difference, 23.5 percentage points; 95 percent confidence interval, 5.9 to 40.7; $P=0.007$). The patients in the prednisolone group had greater reductions than the patients in the placebo group in scores on an articular index and for pain and disability at 3 months; for pain at 6 months; and for disability at 6, 12, and 15 months (all $P<0.05$). There was no difference between groups in standardized scores for the acute-phase response. The adverse events were typical of those encountered with antirheumatoid drugs.

Conclusions. In patients with early, active rheumatoid arthritis, prednisolone (7.5 mg daily) given for two years in addition to other treatments substantially reduced the rate of radiologically detected progression of disease. (*N Engl J Med* 1995;333:142-6.)

RHEUMATOID arthritis causes the inflammation and progressive destruction of joints. Nonsteroidal antiinflammatory drugs help to control symptoms. Specific antirheumatoid drugs (such as gold salts, penicillamine, and methotrexate) suppress inflammation but increase the number of adverse reactions. Oral glucocorticoids have been used for over four decades to treat patients with rheumatoid arthritis, but their role and value have been debated.¹ Nevertheless, glucocorticoids are widely used; 24 percent of patients with rheumatoid arthritis at one British hospital were taking prednisolone daily,¹ and 15 percent of patients at a Dutch clinic were receiving corticosteroids.² Glucocorticoids provide symptomatic benefit³ and may prevent joint destruction.³⁻⁵ Studies of their effect on the radiographically detected progression of disease are difficult to interpret, because they have been poorly controlled^{6,7} or too short⁸ or have used unacceptably high doses of medication.⁷ We conducted a randomized, double-blind, placebo-controlled trial of a fixed daily dose of prednisolone (7.5 mg), in addition to other treatments, in patients with active rheumatoid arthritis.

METHODS

Study Design

The study protocol was approved by the hospital ethics committee at each participating center. From May 1989 through May 1991, consecutive patients 18 to 69 years of age who had had rheumatoid arthritis⁹ for less than two years that was currently active (defined by

the presence of ≥ 6 painful joints, ≥ 3 joints with active synovitis, and early-morning stiffness for >20 minutes and an erythrocyte sedimentation rate of >28 mm per hour, a plasma viscosity >1.72 , or a level of C-reactive protein >10 mg per liter) were invited to participate. A target size of 160 patients was calculated for the trial by extrapolation from the figures given by West,⁵ assuming a linear dose-response curve for the effect of prednisolone and a 90 percent power to detect a 50 percent reduction in the progression of joint erosion over two years.¹⁰ A record of those who declined to participate was kept, with their stated reasons.

Prednisolone (7.5 mg) and identical tablets of placebo were prepared and labeled specifically for the study by the pharmacy at the Bristol Royal Infirmary. The tablets were distributed to pharmacies at 13 participating centers. Randomization was performed in blocks of six subjects at each center, and except in an emergency, the randomization codes were not broken until after the main analysis. After providing written informed consent, eligible patients were assigned the next available study number at the center where they were recruited. They were instructed to take the assigned study medication each day. After two years, the dose was tapered, with treatment for two weeks on alternate days followed by treatment for two weeks every third day, and then discontinued. Throughout the study, their physicians were free to prescribe any other treatment for the patients except systemic corticosteroids.

Outcome Variables

The two primary outcome variables were the progression of damage as detected on radiographs of the hands at entry and one and two years later and the development of erosions on hands that had no erosions at base line. All available radiographs were sent to the coordinating center and viewed jointly by the same experienced radiologist and rheumatologist. The same light was used to view all the films. To ensure similar conditions for the assessment of each patient's radiographs and to avoid the possible development of bias over the several sittings required to read and score the radiographs, the films were viewed in randomly ordered groups of 30. Each group included the three films for each of 10 randomly selected patients. All markings that might identify the patients were covered. The condition of each hand was classified as erosive or nonerosive, and each finger or wrist joint was then scored by the method of Larsen et al.,¹¹ which grades joint damage on a scale from 0 (for a radiologically nor-

Address reprint requests to Dr. Kirwan at the University Department of Medicine, Bristol Royal Infirmary, Bristol BS2 8HW, United Kingdom.

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*The investigators and study centers participating in the Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group are listed in the Appendix.

mal joint) to 5 (for a joint with maximal destruction) with reference to a standard atlas of radiographs.¹¹ The assessments were made jointly by the two observers. The Larsen index (with scores ranging from 0 to 140) was subsequently calculated for each radiograph by adding the scores obtained for each finger and wrist joint.

Secondary outcomes were assessed every three months. They included changes in the degree of disability (as measured by the Health Assessment Questionnaire¹²), joint inflammation (as measured by an articular index of tender and swollen peripheral joints, weighted for joint size¹³), pain over the previous 24 hours (as assessed on a visual-analogue scale¹⁴), and acute-phase responses (as measured by the erythrocyte sedimentation rate, the level of C-reactive protein, or plasma viscosity, depending on the center). Records of other treatments, adverse reactions, weight, and blood pressure were also kept.

Statistical Analysis

The statistical analysis used the chi-square test to compare proportions and Student's t-test to compare means.¹⁰ Because of their skewed distributions, Larsen scores were log-transformed before the group comparisons were made. The difference in log values between the base-line and follow-up examinations was calculated for each patient. The means of these differences were compared between groups, and their 95 percent confidence intervals were determined by Student's t-test.¹⁰ Because different centers used different methods to measure acute-phase responses, the values were standardized so that the data could be combined. Z scores¹⁰ (standard normal variables) were calculated by taking all available values for each patient and expressing them again 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 a P value of 0.05 or less was taken to indicate statistical significance.

RESULTS

Of the 162 patients invited to participate in the study, 34 declined to do so, for the following reasons: concern about the adverse effects of corticosteroids (14 patients) or of medications generally (3), inconvenient location of the study center (4), unwillingness to receive placebo due to an anticipated need for corticosteroid therapy (4), too short an interval since diagnosis (1), and unspecified reasons (8). The remaining 128 patients were treated at 13 centers; the patients' characteristics are shown in Table 1. In general, the study patients had moderately severe joint inflammation. All had had their disease for less than two years (mean, slightly over one year). Eleven patients did not subsequently undergo radiography of the hands because they were lost to follow-up (one each was withdrawn with carcinoma of the lung, cerebral tumor, and a changed rheumatologic diagnosis, and eight moved away or declined to take the study medication). These patients and three others whose initial radiographs were lost were excluded from the analysis. Treatment was discontinued in six patients (two in the placebo group and

Table 1. Base-Line Characteristics of the 128 Study Patients According to Treatment Assignment.*

VARIABLE†	PREDNISOLONE	PLACEBO	ALL PATIENTS
No. of patients	61	67	128
Age (yr)	48.2±10.0	50.3±10.1	49.2±10.1
Sex (F/M)	38/23	44/23	82/46
Duration of disease (yr)	1.28±0.31	1.34±0.27	1.31±0.29
Previous specific antirheumatoid therapy (% of patients)‡	18	22	40
No. of patients with hand erosions§	18	20	38
Positive latex-agglutination test (% of patients)¶	88	89	89
Articular index	208±105	209±125	209±116
Pain score	1.36±0.71	1.54±0.75	1.44±0.75
Disability score	1.22±0.67	1.34±0.69	1.28±0.69
Plasma viscosity (mPa)	1.81±0.16	1.78±0.16	1.80±0.16
Weight (kg)	71.1±11.1	67.4±15.4	69.2±13.7
Blood pressure (mm Hg)			
Systolic	130±17	132±21	131±19
Diastolic	82±9	82±12	82±11
Log-transformed Larsen score	0.35±0.42	0.41±0.55	0.38±0.49

*Plus-minus values are means ±SD. Fourteen patients (six in the prednisolone group and eight in the placebo group) were excluded from the analysis because they did not have subsequent hand radiographs or because their initial radiographs were lost (see the Results section).

†Scores for joint inflammation were assessed by an articular index of inflamed joints¹³ and were expressed on a scale ranging from 0 (no joint inflammation) to 534 (all joints of the hands and wrists inflamed). Pain scores were derived from a visual-analogue scale¹⁴ that recorded the severity of pain over the previous 24 hours on a scale ranging from 0 (no pain) to 3.0 (worst possible pain). Disability scores were derived from the disability scale of the Health Assessment Questionnaire^{12,14} and were expressed on a scale ranging from 0 (no disability) to 3.0 (inability to perform most activities of daily living).

‡Refers to treatment with gold salts, penicillamine, or methotrexate.

§Includes 30 affected hands in the prednisolone group and 35 in the placebo group.

¶Denotes a serologic test in which antigen-coated particles of latex agglutinate with rheumatoid factors in a specimen of serum or synovial fluid.

||Assessed in 67 patients (33 in the prednisolone group and 34 in the placebo group; see the Results section) and measured in millipascals (mPa).

one in the prednisolone group because of hypertension and weight gain, and one each in the placebo group because of diabetes, the initiation of corticosteroid therapy, and a refusal of further medication); these six patients were subsequently followed and analyzed as part of their initial treatment groups. Of the remaining 114 patients, 11 did not appear for radiography at year 1, and 8 did not appear for radiography at year 2. In the prednisolone group, 49 patients had films for all three time points, whereas 54 patients had films only at entry and year 1 and 57 patients had films only at entry and year 2. The statistical analyses of changes on the films for years 1 and 2 were based on these 103 and 106 patients, respectively. Patients who declined to participate or were lost to follow-up were distributed evenly across the 13 participating centers.

The radiographically detected progression of rheumatoid arthritis during the study is shown in Figure 1. The base-line values show that a few patients with more severe damage were included in the placebo group, including one patient with an extremely high Larsen score. There was no significant base-line difference between groups, however, when the mean values were compared after log transformation ($P=0.48$) (Table 1) or by the Mann-Whitney test (median for placebo, 0 [interquartile range, 0 to 5]; median for prednisolone, 0 [0 to 4]; median difference, 0 [0 to 0]; $P=0.83$).

Disease progressed to a mean of 0.73 Larsen unit in the prednisolone group after one year and to a mean of

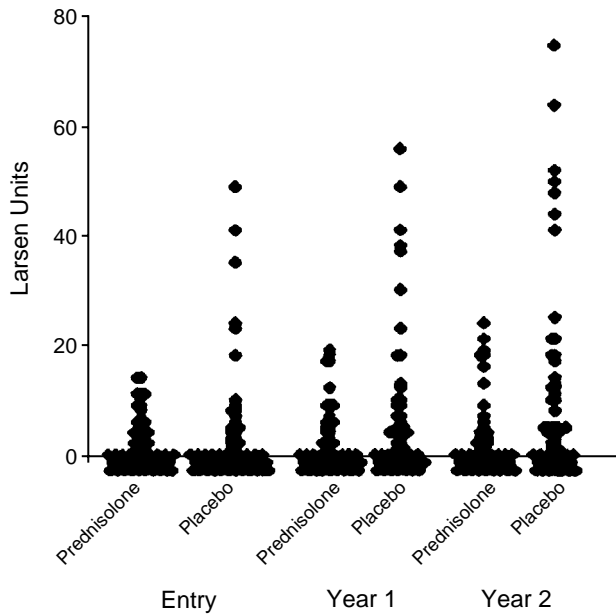


Figure 1. Scores on the Larsen Index during Treatment, According to Study Group.

The mean values at entry into the study and one and two years thereafter, expressed in Larsen units, were as follows: prednisolone group, 2.65, 3.38, and 3.37, respectively; placebo group, 6.23, 9.86, and 11.60; difference between groups, 3.58, 6.48, and 8.23. $P=0.479$, $P=0.033$, and $P=0.002$ for the respective group differences as calculated from log-transformed scores. The mean changes after one and two years were as follows: prednisolone group, 0.73 and 0.72, respectively; placebo group, 3.63 and 5.37; difference between groups, 2.90 and 4.65. $P=0.052$ and $P=0.004$ for the respective group differences as calculated from log-transformed scores.

0.72 Larsen unit after two years, indicating very little change in radiographically detected joint damage. In the placebo group, the mean progression of disease after one year was to 3.63 Larsen units and after two years to 5.37 Larsen units, indicating substantial joint destruction that was similar to the progression usually expected in early erosive disease. The statistical differences between groups in the changes in Larsen scores at one and two years were calculated from the changes in the log-transformed scores. The mean (\pm SD) changes in log-transformed scores after one year were as follows: prednisolone group, 0.02 ± 0.39 ; placebo group, 0.19 ± 0.48 ; difference, 0.17 (95 percent confidence interval, 0 to 0.34; $P=0.052$). The changes after two years were as follows: prednisolone group, 0.02 ± 0.43 ; placebo group, 0.30 ± 0.52 ; difference, 0.28 (95 percent confidence interval, 0.09 to 0.47; $P=0.004$).

In the group of 106 patients with radiographs obtained at both base line and two years, 147 of their 212 hands (69 percent) did not have erosions at the start of the study. In the group of 49 patients with radiographs for all three time points, erosions had developed after one year on 18 of 68 such hands in the prednisolone group (26 percent) and 30 of 79 such hands in the placebo group (38 percent), a difference of 18.9 percent (95 percent confidence interval, 1.7 to 35.7 percent; $P=0.018$). After two years, the comparable figures were

15 of 68 hands (22.1 percent) and 36 of 79 hands (45.6 percent), a difference of 23.5 percentage points (95 percent confidence interval, 5.9 to 40.7; $P=0.007$).

The clinical responses of the patients are summarized in Figure 2. The mean score for pain in the prednisolone group decreased from 1.35 units at base line to 0.88 unit after three months (a reduction of 0.47 unit), whereas the mean score for pain in the placebo group decreased from 1.52 units at base line to 1.18 units after three months (a reduction of 0.34 unit). The reduction in the placebo group was 25 percent less than that in the prednisolone group (95 percent confidence interval, 8 to 41 percent; $P<0.001$). Similarly, after three months the patients in the placebo group had 63 percent less reduction (95 percent confidence interval, 54 to 72 percent) in their disability scores than the patients in the prednisolone group (from 1.34 to 1.19, as compared with a reduction from 1.21 to 0.80; $P<0.001$) and 41 percent less reduction (95 percent confidence interval, 4 to 84 percent) in the articular index (from 209 to 142 in the placebo group, as compared with 208 to 97 in the prednisolone group; $P<0.05$). The prednisolone group also had a greater reduction in pain at 6 months and in disability at 6, 12, and 15 months. There was no difference between groups in standardized scores for the acute-phase response.

There were no significant differences between groups at each review in the proportion of patients treated with nonsteroidal antiinflammatory drugs (mean percentage, diclofenac, 23 percent; naproxen, 18 percent; aspirin, 15 percent; indomethacin, 12 percent; ibuprofen, 8 percent; piroxicam, 4 percent; and other agents, 15 percent) or with specific antirheumatoid drugs (intramuscular gold, 8 percent; penicillamine, 30 percent; sulfasalazine, 26 percent; methotrexate, 4 percent; and other agents, 3 percent). Nor did the proportion of patients who reported adverse reactions differ between groups at each review according to type of treatment (mean percentage, gold, 22 percent; penicillamine, 19 percent; sulfasalazine, 8 percent; methotrexate, 32 percent; and other agents, 10 percent). The adverse reactions reported included thrombocytopenia, rash, proteinuria, elevated serum aminotransferase levels, transient malaise, and altered bowel habits. These were in keeping with well-recognized patterns of adverse reactions to specific antirheumatoid drugs.¹⁵

DISCUSSION

Fixed daily doses of 7.5 mg of prednisolone, given in addition to other treatments for a two-year period, substantially reduced the rate of radiologically detected progression of disease in patients with early, active rheumatoid arthritis. The majority of the patients in this study also received specific antirheumatoid therapy, and this treatment was distributed equally between the prednisolone and the placebo groups. The evidence that treatment can interrupt the progression of joint damage in rheumatoid arthritis is sparse.^{16,17} Sigler et al.¹⁸ compared intramuscular gold with placebo in 32 patients and concluded that it reduced the rate of radiologically detected progression. This finding, which

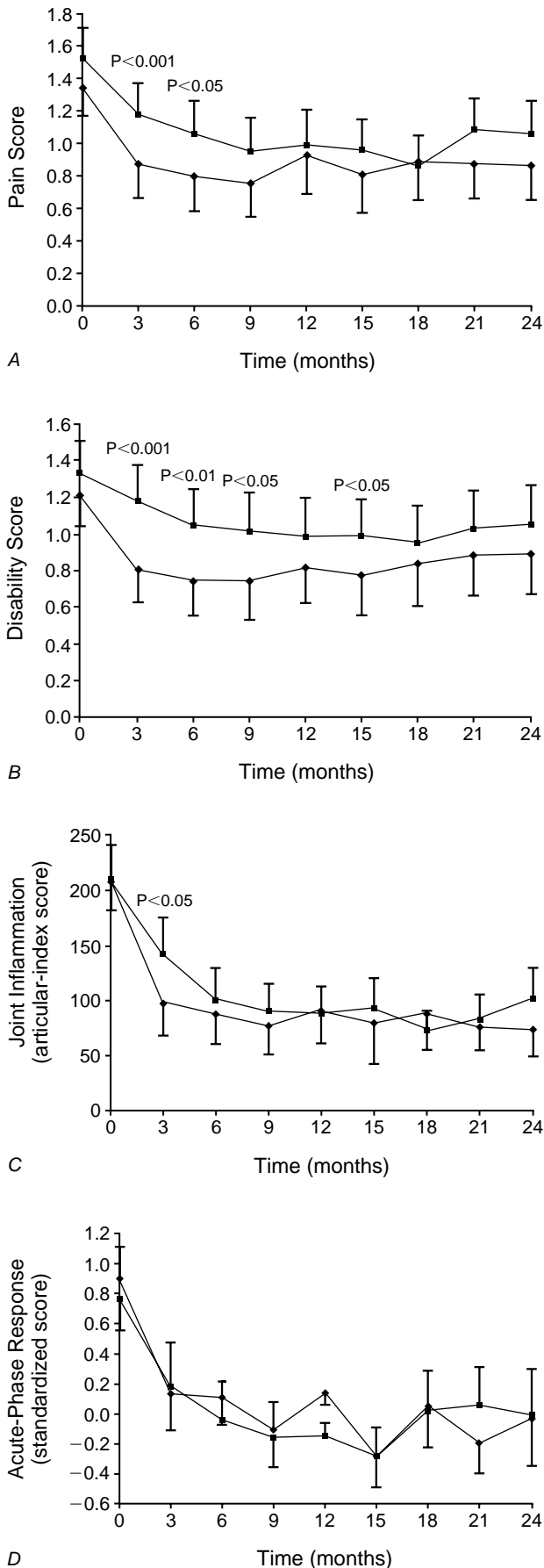


Figure 2. Changes in Clinical Variables during Treatment, According to Study Group.

Group means and 95 percent confidence intervals are shown for the prednisolone (◆) and placebo (■) groups. Pain scores (Panel A) were derived from a visual-analogue scale¹⁴ that recorded the severity of pain over the previous 24 hours on a scale ranging from 0 (no pain) to 3.0 (worst possible pain). Disability scores (Panel B) were derived from the disability scale of the Health Assessment Questionnaire^{12,14} and were expressed on a scale ranging from 0 (no disability) to 3.0 (inability to perform most activities of daily living). Scores for joint inflammation (Panel C) were assessed by an articular index of inflamed joints¹³ and were expressed on a scale ranging from 0 (no joint inflammation) to 534 (all joints of the hands and wrists inflamed). The acute-phase response (Panel D) was reported as a standardized score (the number of standard deviations from the mean) for each patient to allow a variety of methods to be used to measure the overall acute-phase response for the group (see the Methods section).

was in contrast with those of other studies of gold treatment,¹⁹ may have been due to the unconventional method of analysis and an imbalance in the severity of disease in the two study groups rather than to any pharmacologic action.¹⁶ The radiologic study of Luukkainen et al.²⁰ is often cited in support of the efficacy of gold, but it was an uncontrolled comparison of patients treated with several agents, including chloroquine and glucocorticoids, and it lacked defined criteria for the start of treatment.¹⁶

A more recent double-blind study of antirheumatoid drugs, with entry criteria similar to those we used, compared hydroxychloroquine with sulfasalazine²¹ in 50 patients. That study did not have a placebo group. Among the patients who originally had no erosions, 72 percent acquired them during treatment with hydroxychloroquine, and 36 percent did so during treatment with sulfasalazine. This difference was significant ($P < 0.02$), but the result in the sulfasalazine group was similar to that in our placebo group. The patients in our prednisolone group had little overall disease progression as measured by the Larsen index, and only 17 percent of patients who originally had no erosions acquired them during the first year. Our two-year results are consistent with those of earlier studies of glucocorticoids in patients with rheumatoid arthritis, such as the retrospective follow-up by West⁵ of the patients in the original Medical Research Council and Nuffield Foundation trial.^{3,4}

Most of the patients we studied had clinical improvement, as would be expected when patients with active rheumatoid arthritis begin a specific therapy. The addition of prednisolone accelerated this response, but as observed in earlier reports,^{3,4} this additional symptomatic benefit did not persist into the second year of treatment.

Four patients had adverse events that may have been attributable to corticosteroid therapy. Two events (hypertension in one patient and hypertension and weight gain in another) occurred in the prednisolone group, and two (diabetes and hypertension) occurred in the placebo group. There were no significant increases in weight or blood pressure in either group. The 7.5-mg

dose of prednisolone was chosen²² in the light of clinical experience and reported adverse effects²³ to provide the best chance of reducing radiologically detected progression while minimizing complications. A recent case-control study²⁴ has suggested, however, that even in low doses, corticosteroids may predispose patients with rheumatoid arthritis to fractures, infections, and gastrointestinal ulcers and bleeding. In that study the patients treated with corticosteroids had more severe disease than those in the control group. The possible induction of osteoporosis may be counterbalanced by increased physical activity or reduced joint inflammation in the treated patients.

Our findings have implications for the understanding of rheumatoid arthritis. We found that the development of erosions, clinical symptoms, and to some extent the acute-phase response can occur independently of each other after glucocorticoid treatment. The dissociation of these three aspects of the disease argues against combining them in a single measure²⁵ and challenges researchers to identify their differing control mechanisms.

We are indebted to Mrs. Sara Selley and Mrs. Shelagh Snow for their invaluable contributions to the administration of this study.

APPENDIX

The following investigators and study centers, all in the United Kingdom, participated in the Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study: M. Byron, Stoke Mandeville Hospital, Aylesbury; P. Dieppe, Bristol Royal Infirmary, Bristol; C. Eastmond, City Hospital, Aberdeen; J. Halsey, Lancaster Moor Hospital, Lancaster; P. Hickling, Mount Gould Hospital, Plymouth; P. Hollingworth, Southmead Hospital, Bristol; R. Jacoby, Princess Elizabeth Hospital, Exeter; A. Kirk, Amersham Hospital, Amersham; J. Kirwan, Bristol Royal Infirmary; C. Moran, Christchurch Hospital, Christchurch; D. Reid, City Hospital, Aberdeen; T. Swannell, City Hospital, Nottingham; and D. Yates, Taunton and Somerset Hospital, Taunton. *Additional investigators:* C. Cooper and E. George, both in Bristol. *Nonrecruiting study participants:* D. Forbes, Bristol Royal Infirmary; J. Jessop, University Hospital of Wales, Cardiff; and I. Watt, Bristol Royal Infirmary.

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