

Low-Dose Prednisone Therapy for Patients with Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Amalia A. van Everdingen, MD; Johannes W.G. Jacobs, MD, PhD; Dirk R. Siewertsz van Reesema, MD; and Johannes W.J. Bijlsma, MD, PhD

Background: Oral glucocorticoids combined with disease-modifying antirheumatic drugs are beneficial and retard radiologic joint damage in rheumatoid arthritis.

Objective: To investigate the clinical efficacy, disease-modifying properties, and side effects of low-dose glucocorticoids as monotherapy for previously untreated patients with early active rheumatoid arthritis.

Design: 2-year randomized, double-blind, placebo-controlled clinical trial.

Setting: 2 outpatient rheumatology clinics.

Patients: 81 patients with early active rheumatoid arthritis who had not been treated with disease-modifying antirheumatic drugs.

Intervention: 41 patients were assigned to 10 mg of oral prednisone per day, and 40 were assigned to placebo. Nonsteroidal anti-inflammatory drugs were allowed in both groups. After 6 months, sulfasalazine (2 g/d) could be prescribed as rescue medication.

Measurements: Clinical variables were assessed at baseline and every 3 months; radiologic studies were performed every 6 months. Adverse effects were documented every 3 months.

Results: In the first 6 months, the prednisone group showed more clinical improvement than the placebo group. This effect was not seen after 6 months except in grip strength and the 28-joint score for tenderness. Use of additional therapies was significantly less common in the prednisone group, particularly in the first 6 months. More than 65% of those who completed the study were not taking sulfasalazine. After month 6, radiologic scores showed significantly less progression in the prednisone group than in the placebo group. No clinically relevant adverse effects were observed, except for a higher incidence of osteoporotic fractures in the prednisone group.

Conclusions: Prednisone, 10 mg/d, provides clinical benefit, particularly in the first 6 months, and substantially inhibits progression of radiologic joint damage in patients with early active rheumatoid arthritis and no previous treatment with disease-modifying antirheumatic drugs. Because of their limited disease-modifying effects, glucocorticoids should be combined with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.

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For author affiliations, current addresses, and contributions, see end of text.

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Drug treatment for rheumatoid arthritis usually consists of a combination of a nonsteroidal anti-inflammatory drug (NSAID) and a disease-modifying antirheumatic drug (for example, sulfasalazine, methotrexate, gold salt, or a combination). New biological agents, such as tumor necrosis factor- α blocking agents and interleukin-1 receptor antagonists, appear promising (1, 2). Glucocorticoids have had a special place in the treatment of rheumatoid arthritis since the publication of the report by Hench and coworkers showing that cortisone dramatically alleviated the symptoms of rheumatoid arthritis by inhibiting inflammation (3). This period of enthusiasm in the 1950s was followed by a long period in which glucocorticoids were applied cautiously for rheumatoid arthritis because of their many side effects and the recognition that inhibition of in-

flammation is not necessarily associated with retardation of joint damage (4).

Ongoing research on glucocorticoids in rheumatoid arthritis focused on both inflammation and joint damage. Some recent studies showed that glucocorticoids reduced the progression of joint damage when added to therapy with disease-modifying antirheumatic drugs. These findings suggested that glucocorticoids might also have disease-modifying properties. If this could be confirmed, glucocorticoids might be used more often, especially since potential serious adverse effects of glucocorticoid therapy are more easily managed today (5). Secondary osteoporosis is inhibited by potent bisphosphonates, and gastrointestinal complications of glucocorticoid therapy, especially in combination with NSAIDs, can be reduced by misoprostol, proton-pump

inhibitors, or cyclooxygenase-2 selective NSAIDs. As yet, disease-modifying properties of low-dose glucocorticoids as monotherapy for patients with early rheumatoid arthritis have not been investigated. The aim of our study was to investigate the clinical efficacy, disease-modifying properties, and side effects of low-dose glucocorticoids as monotherapy for previously untreated patients with early active rheumatoid arthritis.

METHODS

Patients

From October 1992 through October 1995, all consecutive outpatients at the rheumatology departments of the Deventer and Zutphen Hospitals, the Netherlands, who were at least 18 years of age and had early previously untreated rheumatoid arthritis (disease duration < 1 year) that satisfied classification criteria were invited to participate in the study (6). To be included, patients had to have active disease, which was defined as the presence of at least two of the following three criteria: 1) early-morning stiffness lasting 30 minutes or longer, 2) 28-joint score for tenderness and 28-joint score for swelling of 3 or more, and 3) Westergren erythrocyte sedimentation rate of 28 mm or higher after 1 hour (7, 8). Exclusion criteria were contraindications to prednisone or NSAIDs, active gastrointestinal problems, serious complicating diseases, severe hypertension, hemorrhagic diathesis, treatment with cytotoxic or immunosuppressive drugs, alcohol or drug abuse, and psychiatric or mental problems. Informed consent was obtained from all patients before participation. Of the 118 eligible patients, 37 declined to participate (Figure 1).

Intervention

Pharmacy personnel at Deventer Hospital used a computer-generated randomization procedure to randomly assign the 81 participating patients, in blocks of 10, to one of two treatment groups. One group received two tablets of prednisone, 5 mg, once daily at breakfast, and one group received placebo. The pharmacology department at Deventer Hospital prepared and labeled the prednisone and placebo tablets, which were identical in shape and color, and distributed them to patients in unlabeled boxes. Only the pharmacist could access the allocation table. Both groups of patients received 500 mg of elementary calcium in the evening.

The code of randomization was broken after 2 years of treatment, and the prednisone dosage was tapered. Surplus tablets of the study medication were counted at every visit, and adherence was satisfactory (96%). Use of NSAIDs was not regulated. Local glucocorticoid injections were permitted only when absolutely necessary. Physical therapy and additional use of paracetamol were allowed. After 6 months, sulfasalazine (2 g/d) could be prescribed as rescue medication. The decision to add sulfasalazine was made on clinical grounds (activity of rheumatoid arthritis).

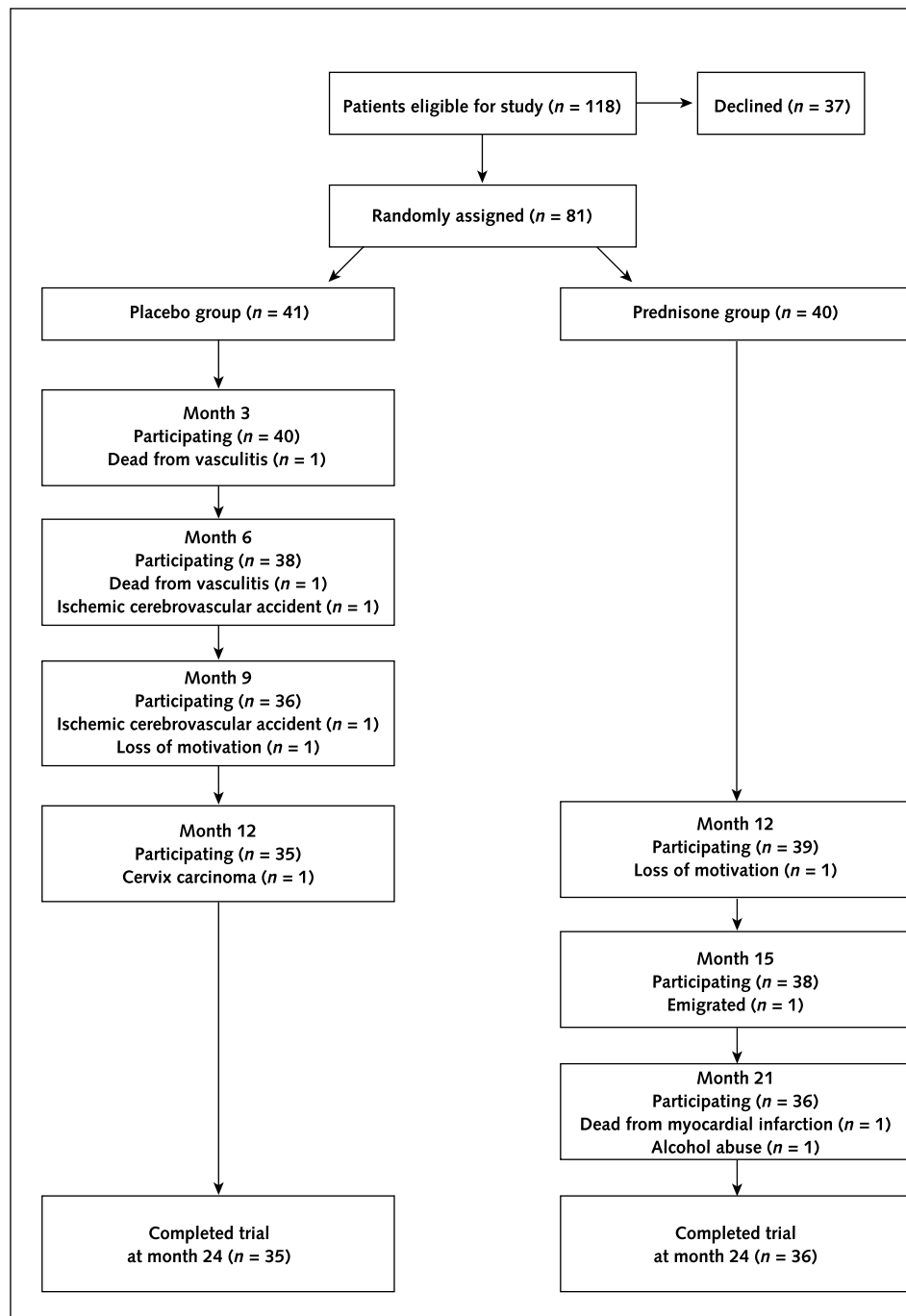
Design and Setting

The ethics committees of the University Medical Center Utrecht and the Deventer and Zutphen Hospitals approved the trial. The study was considered ethically acceptable when it was designed (1989–1991); later, however, it became clear that irreversible joint damage is an early feature of rheumatoid arthritis. With our present knowledge, it would probably be considered unethical to compare the effects of prednisone and placebo in patients who did not receive a disease-modifying antirheumatic drug for at least 6 months. In our study, sulfasalazine could be prescribed as rescue medication only after 6 months to avoid obscuring the effects of prednisone monotherapy.

Measurements

All clinical outcome measurements, except those for disability and radiologic outcomes, were performed at baseline and every 3 months. Disability, which was assessed with the Health Assessment Questionnaire, and radiologic outcomes were measured every 6 months. Early-morning stiffness was recorded in minutes (maximum, 720 minutes). Morning pain and general well-being were assessed on a horizontal visual analogue scale ranging from 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score. Swelling and tenderness were assessed with the 28-joint score (7, 8). Grip strength was measured in kPa with a vigorimeter (range, 0 to 200 kPa); the mean of three measurements was calculated for each hand. Disability was assessed with a validated Dutch version of the Health Assessment Questionnaire (Vragenlijst Dagelijks Functioneren) (9), which had a range of 0 to 3 (0 represented the best score [no problems], and 3 represented

Figure 1. Trial profile.



the worst score). Serum C-reactive protein level was measured in mg/L.

To investigate the possible sparing effect of the trial medication, we recorded the use of NSAIDs and anal-

gesics, the frequency of intra-articular corticosteroid injections, and the use of physiotherapy. The patients recorded the use of NSAIDs, analgesics, and physical therapy in standardized patient diaries. To calculate the

use of NSAIDs and to compare different NSAIDs, we arbitrarily chose naproxen as a reference. One thousand mg of naproxen was defined as 1 unit and was considered to be approximately equivalent to 600 mg of azapropazone, 100 mg of diclofenac, 200 mg of flurbiprofen, 1600 mg of ibuprofen, 100 mg of indomethacin, 200 mg of ketoprofen, 15 mg of meloxicam, 1000 mg of nabumetone, 20 mg of piroxicam, and 600 mg of tiaprofenic acid. Every 3 months, the first author recorded use of intra-articular corticosteroid injections.

Radiologic outcome measures were erosions, joint space narrowing, and the total score for both (range, 0 to 448). The total score is the sum of the erosions and narrowing scores in 44 joints in the hands and feet, assessed on plain radiography and scored with the van der Heijde modification of the Sharp method (10, 11). Radiologic outcome measures also included the number of patients with erosive disease in each group and the number of radiologically affected joints per patient.

Radiographs were taken at entry and every 6 months. An assistant prepared the radiographs to be read, and all identifying patient data on the radiographs were concealed from the readers. The readers had no knowledge of patient identity when they scored the radiographs. Radiographs were read in random patient order and were scored for each patient in temporal order. Scoring in temporal order clearly has advantages, as a comparative study has shown (11). However, with this method, scores can either be stable or increase; a decrease (indicating improvement) is not possible. The first author and an independent radiologist viewed all available radiographs at one center. When the readers' total scores for individual cases differed by 25% or more, agreement was reached through discussion. Joint damage was defined as a score that exceeded 0. To correct for possible differences between the two treatment groups in the number of patients who developed little or no joint damage, we also analyzed data only from patients who developed joint damage. Furthermore, radiologic damage was also analyzed with a cutoff point of 4 modified Sharp units. A score of 0 to 3 was interpreted as no damage, and scores of 4 or greater were interpreted as joint damage. This cutoff point seems to reflect clinically relevant change (12) and was also used in our study to define erosive rheumatoid arthritis.

At the start of the study and every 3 months for 2

years, standardized lists were used to document adverse effects. We noted the occurrence of infections and the use of antibiotics; the latter was checked at the patient's pharmacy. For hypertension, the first author used a single device to measure blood pressure in mm Hg. For steroid diabetes, serum glucose level was measured in mmol/L. Hyperglycemia was defined according to the World Health Organization standard: postprandial, a glucose level of at least 11.0 mmol/L (198 mg/dL), and fasting, at least 6.6 mmol/L (119 mg/dL). Urinary glucose level was measured by using a semiquantitative method (dipstick). A value less than 2.7 mmol/L (49 mg/dL) was considered negative, a value of 2.7 to 5.5 mmol/L (50 to 99 mg/dL) was considered a trace, a value of 5.6 to 16.6 mmol/L (100 to 299 mg/dL) was considered 1+, a value of 16.7 to 54.9 mmol/L (300 to 989 mg/dL) was considered 2+, and a value of 55 mmol/L or greater (≥ 990 mg/dL) was considered 3+. To assess weight gain, body weight in kg was determined with a standardized scale. Gastrointestinal bleeding, ulcers, and peptic symptoms were documented, and the decision to perform gastroscopy was made clinically. Skin disorders were documented, and additional dermatologic expertise was requested when necessary. Hemogram and laboratory variables for kidney and liver function were assessed to monitor for hematologic and biochemical abnormalities. For eye disorders, symptoms and abnormalities were documented; when necessary, additional ophthalmologic expertise was requested. Neuropsychological disorders were recorded.

To assess for osteoporosis, we obtained a radiograph of the spine at baseline and every 6 months for 24 months. We examined vertebrae Th12 through L5. The first author and an independent rheumatologist scored the vertebrae blind, according to the method of Kleerekoper (13). This method is based on naked-eye inspection of the vertebrae and comparison of each vertebra with the vertebrae below and above. If an abnormal shape is noticed, the anterior, middle, and posterior heights of that particular vertebra are measured with a ruler. The mean of the heights measured by the two authors was used. The scoring system is as follows: 0 (normal shape and dimensions), 1 (only endplate deformity, middle height, $<85\%$), 2 (anterior wedge deformity, anterior height, $<85\%$), and 3 (compression deformity, all 3 heights, $<85\%$) (13).

Statistical Analysis

All statistical analyses evaluating the effect of treatment were performed according to the intention-to-treat principle. For the 10 patients who withdrew during the study, the outcomes of the last measurements were carried forward, with the exception of the radiologic scores. For radiologic scores, missing data were estimated by using individual progression, as indicated by available scores; if the last measurements had been carried forward, the protective effect of medication on the joints would have been overestimated. Also, “on treatment” analyses were performed to validate the procedures used to estimate the missing data. For radiologic joint damage, which is in itself a cumulative score, and the secondary outcome measures (disability and grip strength), mean differences in changes from baseline between the two groups were tested at 24 months with two-sided *t*-tests or the Mann–Whitney U-test, where appropriate. For the other outcome measures, changes from baseline over time (24 months) were compared by using the change from baseline in the area under the curve (AUC) as a summary measure. This was done because baseline variables between the two groups favored the prednisone group, although the differences were not statistically significant (Table 1) (14). We divided the values for the change in AUC by the number of assessments at follow-up. Since the interval between assessments is identical (3 months), this makes the values for the change in AUC identical to the mean value of the changes occurring in each 3-month interval at follow-up. Therefore, the values for changes in AUC are easily interpretable.

The values for the change in AUC in both groups and the means of radiologic scores for each group at different points in time were tested for statistically significant differences by using unpaired two-sided *t*-tests or Mann–Whitney U-tests, where appropriate. We calculated the number of patients in each group who had clinically relevant improvement. Clinically relevant improvement was defined as at least 20% improvement in the 28-joint scores for swelling and tenderness and at least 20% improvement in at least two of the four following variables: pain, general well-being, Health Assessment Questionnaire score, and C-reactive protein level. In repeated-measurement analyses of variance, the clinical outcome measurements were used to analyze the relationship between time (disease course) and the effect

Table 1. Baseline Characteristics of the 81 Patients with Early Rheumatoid Arthritis*

Characteristic	Prednisone Group (n = 40)	Placebo Group (n = 41)
Age, y	60 ± 14	64 ± 12
Male/female, n/n	17/23	12/29
IgM rheumatoid factor, nt	29	31
Erosive disease, n‡	16	15
Early-morning stiffness, min	100 ± 62	117 ± 71
Morning pain, mm§	28 ± 20	34 ± 25
General well-being, mm§	31 ± 23	41 ± 23
28-Joint score for swelling	7.3 ± 3.7	8.6 ± 4.3
28-Joint score for tenderness	8.9 ± 5.7	8.6 ± 5.0
Grip strength, kPa	49 ± 24	47 ± 24
Disability score	0.8 ± 0.6	1.0 ± 0.7
C-reactive protein level, mg/L	11 ± 18	20 ± 28
Radiologic score for hands and feet¶	11 ± 11	15 ± 21
Hypertension, n**	5	11
Chronic obstructive pulmonary disease, n	1	2
History of documented peptic ulcer, n	1 (>10 years ago)	0
Peptic symptoms treated with medication, n	4	1
Cardiovascular disease, n	1 (coronary bypass)	0

* Values presented with a plus/minus sign are the mean ± SD. No statistically significant differences were seen between groups.

† Rheumatoid factor status was considered positive when the IgM rheumatoid factor level was ≥25 IU/mL. This cutoff point yielded a false-positive test result for <5% of the general population.

‡ A Sharp–van der Heijde erosion score of ≥4 was considered erosive, and a score of 0 to 3 was considered nonerosive.

§ Measured with the visual analogue scale. Morning pain and general well-being in the previous 48 hours were calculated on a scale from 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score.

|| Measured with a Dutch version of the Health Assessment Questionnaire (9). Scores ranged from 0 to 3, with 0 representing the best score (no problems) and 3 representing the worst score.

¶ Erosions and joint space narrowing were assessed by using the van der Heijde modification of the Sharp method (10, 11). Scores ranged from 0 (no damage) to 448 (maximum score for erosions and joint space narrowing in hands and feet).

** These patients were normotensive with medication at the start of the study.

of the medication (prednisone) on the clinical status of the patient. This allowed us to determine whether patients in the prednisone group showed improvement sooner than patients in the placebo group. To determine whether outcome measurements, patients’ characteristics, side effects, and additional therapies statistically significantly differed between groups, we used unpaired, two-sided *t*-tests or Mann–Whitney U-tests, where appropriate, for the means and Fisher exact tests for proportions. Changes from baseline within groups were tested with paired *t*-tests or Wilcoxon signed-rank tests, where appropriate. All analyses were performed with the Number Cruncher Statistical System 97 (NCSS Statistical Software, Kaysville, Utah).

Table 2. Effects of Prednisone Treatment in Patients with Early Rheumatoid Arthritis*

Variable	Prednisone Group (n = 40)	Placebo Group (n = 41)	95% CI for the Difference	P Value
Changes from baseline				
12 months				
Radiologic damage	8 ± 13	15 ± 15		0.008
Grip strength, <i>kPA</i>	13 ± 21	-1 ± 19	5 to 23	0.002
Functional disability†	0.1 ± 0.6	0.1 ± 0.6		>0.2
24 months				
Radiologic damage	16 ± 23	29 ± 26		0.007
Grip strength, <i>kPA</i>	13 ± 19	4 ± 24	0 to 19	0.05
Functional disability†	0.1 ± 0.7	0.0 ± 0.6		>0.2
Change in AUC at 24 months‡				
Early-morning stiffness, <i>min</i>	-43 ± 69	-28 ± 78		>0.2
Morning pain, <i>mm</i> §	-5 ± 17	1 ± 22	-2 to 15	0.14
General well-being, <i>mm</i> §	-1 ± 24	0 ± 18		>0.2
28-Joint score for swelling	-2 ± 4	-1 ± 4	-1 to 2	>0.2
28-Joint score for tenderness	-2 ± 4	0 ± 5	1 to 5	0.01
C-reactive protein level, <i>g/L</i>	-1 ± 15	-0 ± 24		>0.2
Individual patient improvement, <i>n/n (%)</i>				
At 12 months	13/40 (33)	10/41 (24)	-0.1 to 0.3	>0.2
At 24 months	12/40 (30)	9/41 (22)	-0.1 to 0.3	>0.2
Cumulative use of additional therapy				
Patients receiving physiotherapy, <i>n/n</i>				
At 6 months	7/40	12/41	-0.3 to 0.1	>0.2
At 24 months	12/40	19/41	-0.4 to 0.0	0.17
Physiotherapy sessions, <i>n</i>				
At 6 months	108	308		
At 24 months	701	771		
Patients receiving intra-articular corticosteroid injections, <i>n/n¶</i>				
At 6 months	2/40	11/41	-0.4 to -0.1	0.01
At 24 months	8/40	12/41	-0.3 to 0.1	>0.2
Injections, <i>n</i>				
At 6 months	2	21		
At 24 months	17	43		
Patients taking paracetamol, <i>n/n**</i>				
At 6 months	23/40	23/41	-0.2 to 0.2	>0.2
At 24 months	25/40	24/41	-0.2 to 0.3	>0.2
Paracetamol tablets, <i>n</i>				
At 6 months	772	2546		
At 24 months	4237	8334		

* Values presented with a plus/minus sign are the mean ± SD. Unpaired two-sided *t*-tests were used for normal distribution of the data, and Mann–Whitney U-tests were used for non-normal distribution; in the latter cases, no 95% CIs for the difference are given. AUC = area under the curve.

† Measured with a Dutch version of the Health Assessment Questionnaire. Scores ranged from 0 to 3, with 0 representing the best score (no problems) and 3 representing the worst score (9).

‡ The values for the change in AUC were divided by the number of assessments at follow-up, making them identical (since the interval between assessments [3 months] is identical) to the mean value of the changes occurring in each 3-month interval at follow-up. This was done to simplify interpretation of the data.

§ Measured with the visual analogue scale. Morning pain and general well-being in the previous 48 hours were assessed on a scale of 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score.

|| Improvement is defined as ≥20% improvement in the 28-joint score for swelling and the 28-joint score for tenderness and ≥20% improvement in ≥2 of the 4 following variables: visual analogue scale score for pain, visual analogue scale score for general well-being, disability score, and C-reactive protein level.

¶ A corticosteroid injection was defined as 40 mg of triamcinolone acetonide or equivalent.

** The use of nonsteroidal anti-inflammatory drugs is reported in Figure 2. Two patients in each group used additional analgesics (pentazocine, 50 mg; tramadol, 50 mg; or dextropropoxyphene, 150 mg).

RESULTS

Thirty-seven of 118 patients declined to participate in the study for the following reasons: a wish to become pregnant, concern about the side effects of glucocorticoids, the inconvenience of visits to the hospital outpatient department and frequent monitoring, and unwillingness to take the 50% risk for receiving placebo.

Patients who declined to participate had a mean age (±SD) of 48 ± 12 years. Twenty-five were women, 28 had IgM rheumatoid factor, and 14 had erosive changes on radiographs of the hands or feet. Compared with study participants, patients who declined participation were younger and more likely to be women. Patient characteristics at the start of the study are shown in

Table 1. No statistically significant differences were seen between the two groups. All patients were white except for 2 patients in the prednisone group.

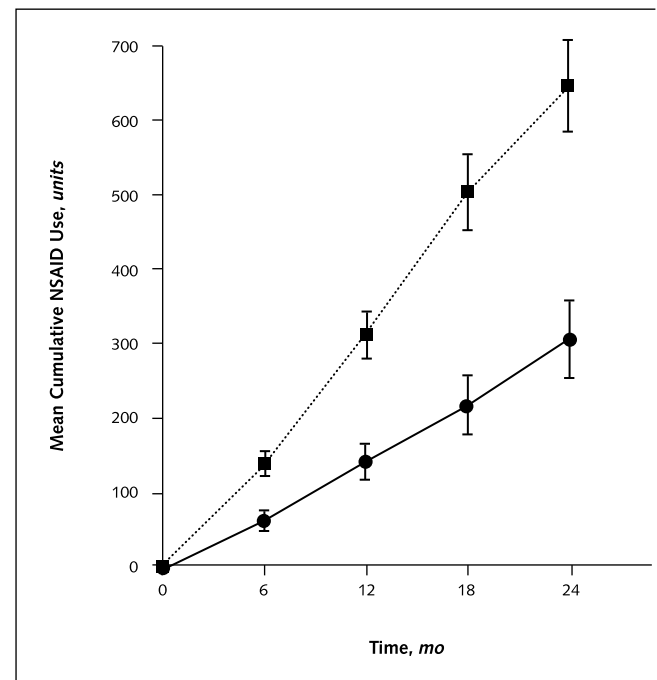
Ten patients withdrew from the study, 4 in the prednisone group and 6 in the placebo group (Figure 1). Patients in the prednisone group withdrew because of emigration (1 patient at 15 months), loss of motivation (1 patient at 12 months), alcohol abuse (1 patient at 21 months), and death from myocardial infarction (1 patient at 21 months). Patients in the placebo group withdrew because of cervix carcinoma (1 patient lost to follow-up at 12 months), ischemic cerebrovascular accidents that were attributed to arteriosclerosis (1 patient at 6 months and 1 patient at 9 months), loss of motivation (1 patient at 9 months), and rheumatoid arthritis vasculitis (1 patient who died at 3 months and 1 patient who died at 6 months despite aggressive immunosuppressive therapy). Of the 10 patients who withdrew, 1 patient in the prednisone group (alcohol abuse) and 1 in the placebo group (loss of motivation) received sulfasalazine as rescue medication at 15 and 6 months, respectively. No patients left the study because of adverse effects related to the study medication. After 6 months, 39 of the 71 patients who completed the study (20 in the placebo group and 19 in the prednisone group) received sulfasalazine as additional antirheumatic therapy.

Clinical Efficacy

For most clinical variables, the changes from baseline favored the prednisone group at 12 and 24 months but did not differ significantly between the two groups. Exceptions were grip strength and the 28-joint score for tenderness; for these variables, a larger, statistically significant improvement was seen in the prednisone group compared with the placebo group (Table 2). A statistically significant interaction of time and medication was seen for three clinical variables: pain, 28-joint score for tenderness, and grip strength. Plots of these variables in time showed that this was due to more rapid improvement during the first 6 months in the prednisone group than in the placebo group (data not shown). Individual patient improvement was 33% in the prednisone group and 24% in the placebo group at 12 months and 30% and 22%, respectively, at 24 months (Table 2).

Overall use of physiotherapy was significantly lower in the prednisone group than in the placebo group, es-

Figure 2. Cumulative mean use of nonsteroidal anti-inflammatory drugs (NSAIDs) in units.



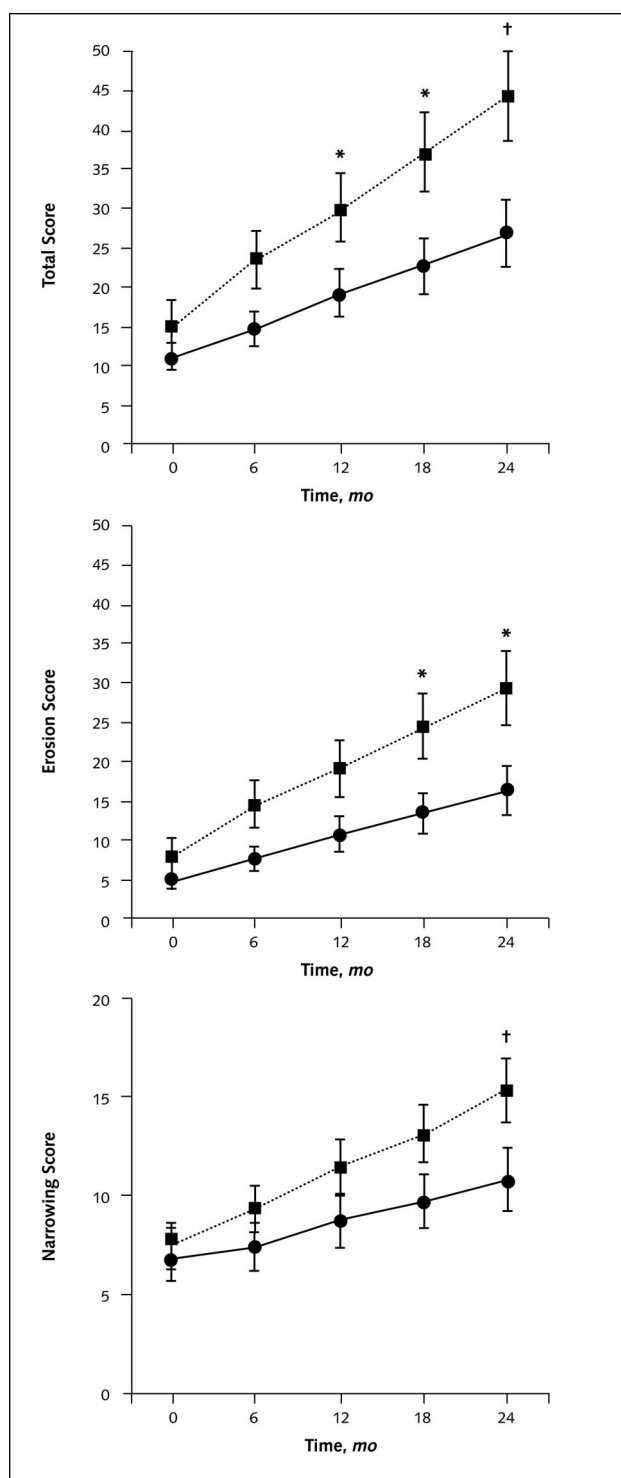
One unit = 1000 mg of naproxen or the equivalent dose of another NSAID. At follow-up at all points in time, statistically significant differences were seen between the two groups ($P < 0.001$ [Mann-Whitney U-test]). The solid line indicates the prednisone group; the dotted line indicates the placebo group. Error bars represent the standard error.

pecially in the first 6 months. At 24 months, the difference in the total number of sessions of physiotherapy was not as pronounced but continued to favor the prednisone group. In the first 6 months, 2 intra-articular corticosteroid injections were administered in the prednisone group and 21 were administered in the placebo group. The total number of intra-articular injections given in the prednisone group at 24 months was 40% lower than that in the placebo group. A total of 772 paracetamol tablets were taken in the first 6 months in the prednisone group compared with 2546 in the placebo group. At 24 months, use of paracetamol in the prednisone group was 49% lower than that in the placebo group. The overall use of NSAIDs over 24 months was also considerably lower in the prednisone group than in the placebo group (Figure 2).

Disease-Modifying Properties

Fifty patients (24 in the prednisone group [60%] and 26 in the placebo group [63%]) had nonerosive

Figure 3. Radiologic scores over time for both erosions and joint space narrowing in hands and feet (*top*), erosions alone (*middle*), and joint space narrowing alone (*bottom*).



disease at the start of the study. At 24 months, 30% of patients in the prednisone group and 22% in the prednisone group still had nonerosive disease. At baseline, the mean total score for radiologic outcome measures (the combination of the scores for joint space narrowing and erosions) was slightly higher for the placebo group than for the prednisone group, although the difference was not statistically significant (Table 1). From month 12 on, radiologic scores showed significantly less progression in the prednisone group than in the placebo group. Mean changes (\pm SD) from baseline in modified Sharp scores were 8 ± 13 and 15 ± 15 at 12 months for the prednisone and placebo groups, respectively ($P = 0.008$; effect size, 0.52) and 16 ± 23 and 29 ± 26 , respectively, at 24 months ($P = 0.007$; effect size, 0.56) (Table 2).

Radiologic scores over time are shown in Figure 3. At 12 months, the total mean score (\pm SD) for radiologic damage was 19 ± 19 for the prednisone group and 30 ± 28 for the placebo group ($P = 0.04$). At 24 months, the scores were 27 ± 28 and 44 ± 37 , respectively ($P = 0.02$) (Figure 3, *top*). The mean score for erosions at 12 months was 11 ± 13 in the prednisone group and 19 ± 23 in the placebo group ($P = 0.08$). At 24 months, the scores were 16 ± 20 compared with 29 ± 30 , respectively ($P = 0.04$) (Figure 3, *middle*). The mean scores for joint space narrowing were 9 ± 9 in the prednisone group and 11 ± 9 in the placebo group at 12 months ($P = 0.06$) and 11 ± 10 and 15 ± 10 , respectively, at 24 months ($P = 0.02$) (Figure 3, *bottom*). The mean total numbers of affected joints per patient in the prednisone group and the placebo group were 10 ± 7 and 13 ± 8 at 12 months ($P = 0.05$) and 12 ± 9 and 16 ± 9 at 24 months ($P = 0.047$), respectively. Similar differences in all radiologic scores between the two groups were found by “on treatment” analyses ($n = 71$), analyses only of patients developing joint damage, and analyses of radiologic damage with a cutoff point of 4 (0 to 3, no damage; ≥ 4 , joint damage) (data not shown).

All scores are means and are based on the van der Heijde modification of the Sharp method (10, 11). Solid lines indicate the prednisone group; dotted lines indicate the placebo group. Error bars represent the standard error. * $P = 0.04$; † $P = 0.02$.

Adverse Effects

We compared body weight, serum glucose levels, and blood pressure at the start of the study and after 24 months of treatment. In the prednisone group, the mean body weight (\pm SD) increased significantly from baseline, from 77 ± 19 kg to 80 ± 20 kg ($P = 0.001$). In the placebo group, no statistically significant change was seen. Also in contrast to the placebo group, the mean serum glucose level (\pm SD) increased significantly in the prednisone group, from 5.1 ± 0.6 mmol/L to 5.9 ± 1.9 mmol/L (92 ± 11 mg/dL to 106 ± 34 mg/dL) ($P = 0.01$). Hyperglycemia, as defined by the World Health Organization, developed in 2 patients in the prednisone group and 1 in the placebo group. The other variables did not change significantly in either group. At the start of the study, 1 patient in each group had one vertebral fracture (from Th12 to L5). After 24 months, the number of new vertebral fractures was higher in the prednisone group than in the placebo group. Five patients in the prednisone group had new fractures in the spine; of these 5 patients, 3 had a single fracture and 2 had two fractures. The patient in the prednisone group with a fracture at baseline did not develop new fractures. In the placebo group, 2 patients had new vertebral fractures. One was the patient with a fracture at baseline who developed another fracture; the other patient developed three fractures. Except for one osteoporotic fracture of the pelvis in the prednisone group, no osteoporotic fractures outside the spine (forearms, ribs, pelvis, or hips) were seen (Table 3).

Other adverse effects are shown in Table 3. There were minor infections in both groups. Patients in the prednisone group had no serious skin infections, but erysipelas was seen five times in 4 patients in the placebo group. The numbers of infections in the respiratory, gastrointestinal, and urinary tracts were approximately equal in the two groups. Three patients (1 in the prednisone group and 2 in the placebo group) developed peptic ulcer disease with bleeding, which was confirmed by gastroscopy. The numbers of patients with newly developed hypertension during the study were approximately equal (7 in the prednisone group and 6 in the placebo group). At the start of the study, 11 patients in the placebo group and 5 in the prednisone group were normotensive because of medication for essential hypertension, and they remained stable during the study. In the prednisone group, 1 patient (76 years of age) died

Table 3. Adverse Effects and Complications

Adverse Effect or Complication	Events in the Prednisone Group (n = 40)	Events in the Placebo Group (n = 41)
	<i>n</i>	
Infections treated with antibiotics, <i>n/n</i> *		
Skin	0	5 (4 patients)
Respiratory tract	13 (11 patients)	13 (9 patients)
Intestinal tract†	1	2
Urinary tract	3 (2 patients)	2
Gastrointestinal		
Stomatitis‡	0	1
Nausea/vomiting	2	2
Peptic symptoms leading to gastroscopy	7	3
Ulcer with bleeding on gastroscopy	1	2
Diarrhea	0	2
Cardiovascular		
Newly developed hypertension	7	6
Angina pectoris	3	3
Myocardial infarction§	1	0
Ischemic cerebrovascular accident	0	2
Arterial occlusion in legs	0	1
Calf vein thrombosis	0	2
Heart rhythm disorders	1	2
Congestive heart failure	1	1
Ankle edema	1	0
Skin (excluding infections)		
Ulcer cruris	3	2
Exanthema	2	1
Petechiae	1	1
Ophthalmologic		
Glaucoma	1	0
Cataract	1	1
Vitreous humor hemorrhage¶	1	0
New osteoporotic fractures**		
Vertebral	7 (5 patients)	4 (2 patients)
Peripheral (pelvis)	1	0
Miscellaneous		
Impotence††	0	2
Depression	1	2
Concentration disorders	0	1
Cervix carcinoma‡‡	0	1
Medication-dependent diabetes mellitus	2	1
Systemic vasculitis§§	0	2

* The number of infections not treated with antibiotics, such as the common cold, was similar in both groups.

† No cultures were taken.

‡ Stomatitis was caused by allergy, probably to a nonsteroidal anti-inflammatory drug used, according to the patient's dermatologist.

§ Cause of death. The patient was 76 years of age.

|| Cause of withdrawal from the study. The patients were 72 and 73 years of age.

¶ Probably not related to the study medication.

** Vertebral fractures Th12 to L5, assessed according to the Kleerekoper method (13). At the start of the study, one patient in each group had a vertebral fracture.

†† Impotence was not included in the standardized diary but was spontaneously reported by these two patients.

‡‡ Cause of withdrawal from the study.

§§ Cause of death. The patients were 62 and 78 years of age.

after 21 months of a myocardial infarction (confirmed at autopsy). During the study, 3 patients (2 in the prednisone group and 1 in the placebo group) developed

diabetes mellitus, which was managed with oral antidiabetic agents and diet; no insulin treatment was needed. Except for infections, the two groups had an equal number of adverse effects affecting the skin, which were well controlled with conservative treatment. Serum aminotransferase levels were elevated in 1 patient in the prednisone group and 1 in the placebo group; values were less than two times the upper limit of normal. Mean serum creatinine concentration did not increase during the study in either group. No other biochemical or hematologic abnormalities were seen during the study. One patient in the prednisone group had glaucoma that was well controlled with conservative treatment, and 1 patient in each group had a cataract. One patient in the prednisone group had a hemorrhage in the vitreous humor in the right eye that caused partial loss of vision, but this complication was probably unrelated to the study medication. No disorders of the central nervous system were observed. For patients with newly developed depressive symptoms (1 in the prednisone group and 2 in the placebo group), no medication was needed.

DISCUSSION

The Medical Research Council and Nuffield Foundation trials in the mid-1950s and mid-1960s suggested a possible disease-modifying role for glucocorticoids. It is difficult to interpret the results of these trials, however, because of the heterogeneity of the patient groups, the long duration of disease at the start of the studies, confounding by indication, and multiple concomitant therapies. In 1995, in a double-blind, placebo-controlled study of 128 patients with early rheumatoid arthritis (average disease duration, 1.3 years), Kirwan demonstrated a significant reduction in progression of radiologic joint damage in the hands when glucocorticoids were added to antirheumatic treatment (15). Patients received prednisone (7.5 mg/d) or placebo for 2 years in addition to NSAIDs (95% of patients) and disease-modifying antirheumatic drugs (71% of patients). After 2 years, both the total number of new erosions and the number of patients with erosions were significantly lower in the glucocorticoid group. Clinical variables improved only during the first year of therapy. Kirwan concluded that a fixed daily dose of 7.5 mg of prednisone given as adjuvant therapy for early active rheumatoid arthritis retards radiologic progression of

joint destruction. However, only hands were evaluated for the radiologic score. In a 1998 follow-up study by Hickling and coworkers (16), joint destruction resumed after the prednisone dosage was tapered and therapy was discontinued.

In 1996, Saag and associates (17) reviewed the literature systematically and performed a meta-analysis of the effectiveness of low-dose glucocorticoids in rheumatoid arthritis. Glucocorticoids seemed to be at least as effective as other therapies in improving disease activity. However, data were limited because the treatment episodes were relatively short (7 months on average) and glucocorticoids were given late in the disease course, often in combination with disease-modifying antirheumatic drugs.

In a randomized study of early rheumatoid arthritis, Boers and colleagues (18) compared the effect of sulfasalazine monotherapy with that of combined therapy with prednisone, methotrexate, and sulfasalazine. Prednisone was started at an initial dosage of 60 mg/d, which was tapered in six steps over 6 weeks to 7.5 mg/d, and was withdrawn at week 28. The combined therapeutic regimen slowed radiologic damage significantly more than sulfasalazine alone at weeks 28, 56, and 80. Haagsma and coworkers (13) and Dougados and associates (19), however, found no differences in effect between sulfasalazine and the combination of sulfasalazine and methotrexate in patients with rheumatoid arthritis. Therefore, the difference in effectiveness between combination therapy and sulfasalazine in the study by Boers and colleagues was probably due to the effect of prednisone. In addition, the combined therapy offered better disease control. In contrast to our present study, the cohort of patients with rheumatoid arthritis in the study by Boers and colleagues was younger and had more active disease. Patients received prednisone at an initial dosage of 60 mg/d, which was tapered; treatment was stopped at 28 weeks. During that 1-year study, the effect of combination therapy on progression of joint destruction persisted after 28 weeks but clinical remission ended in most patients.

Our study is unique because it did not include concomitant therapy with disease-modifying antirheumatic drugs at study entry. We were therefore able to assess the effects of steroids on joint damage independent of disease-modifying antirheumatic drugs. In our study, most patients taking low-dose prednisone needed less

additional therapy and showed temporary improvement in most disease variables when compared with the placebo group, although the differences were not statistically significant for all variables. This may be due to more intensive use of additional therapies, including NSAIDs, in the control group (Table 2 and Figure 2). The clinical improvement seen in the studies by Kirwan (15) and by Boers and colleagues (18) lasted longer, for more than 6 months but less than 1 year, at which point the treatment groups no longer differed from the control groups. Compared with prednisone as monotherapy, combination of glucocorticoids with disease-modifying antirheumatic drugs or biological agents in early active rheumatoid arthritis might prolong the clinical benefit. The remarkable retardation of radiologically detected joint destruction in our study was similar to that observed in the studies by Kirwan (15) and by Boers and colleagues (18). The difference between the two groups in our study even increased gradually until the end of the second year. We do not advocate use of glucocorticoids as monotherapy, however. In our opinion, glucocorticoids, because of their limited disease-modifying effects, should be combined with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.

In our study, glucocorticoid-induced osteoporosis was a major side effect. We prescribed calcium supplementation for all patients, but if we were performing this study today, we would use more intensive treatment, such as bisphosphonates. This would probably result in fewer signs and symptoms of osteoporosis.

Glucocorticoids suppress a wide variety of nonspecific inflammatory responses (such as cell trafficking and prostaglandin production), as well as specific immune processes, with emphasis on cytokine modulation. At a cellular level, glucocorticoids inhibit the access of leukocytes to inflammatory sites; modulate the functions of leukocytes, endothelial cells, and fibroblasts; inhibit the production and functioning of a variety of proinflammatory cytokines while enhancing the production of anti-inflammatory mediators; and suppress the synthesis of cartilage-degrading metalloproteases by fibroblasts and articular chondrocytes. Taken together, these effects induce the marked clinical amelioration of rheumatoid arthritis (21) and may also explain the protection of bone and cartilage against inflammation-induced degradation, which in turn may explain the drugs' disease-modifying properties.

In conclusion, low-dose prednisone alleviates symptoms of rheumatoid arthritis and has disease-modifying properties. Further investigation of long-term low-dose glucocorticoid therapy in rheumatoid arthritis that examines not only symptoms but especially joint damage and functional outcome is needed.

From University Medical Center Utrecht, Utrecht; Deventer Hospital, Deventer; and Zutphen Hospital, Zutphen, the Netherlands.

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Requests for Single Reprints: Johannes W.G. Jacobs, MD, Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, F02.127, Box 85500, 3508 GA Utrecht, the Netherlands; e-mail, j.w.g.jacobs@azu.nl.

Current Author Addresses: Dr. van Everdingen: Department of Rheumatology, Deventer Hospital, Box 5001, 7400 GC Deventer, the Netherlands.

Dr. Jacobs: Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, F02.127, Box 85500, 3508 GA Utrecht, the Netherlands.

Dr. Siewertsz van Reesema: Department of Rheumatology, Deventer Hospital, Box 5001, 7400 GC Deventer, the Netherlands.

Dr. Bijlsma: Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, F02.127, Box 85500, 3508 GA Utrecht, the Netherlands.

Author Contributions: Conception and design: A.A. van Everdingen, J.W.G. Jacobs, D.R. Siewertsz van Reesema, J.W.J. Bijlsma.

Analysis and interpretation of the data: A.A. van Everdingen, J.W.G. Jacobs, D.R. Siewertsz van Reesema, J.W.J. Bijlsma.

Drafting of the article: A.A. van Everdingen, J.W.G. Jacobs, D.R. Siewertsz van Reesema.

Critical revision of the article for important intellectual content: A.A. van Everdingen, J.W.G. Jacobs, D.R. Siewertsz van Reesema, J.W.J. Bijlsma. Final approval of the article: A.A. van Everdingen, J.W.G. Jacobs, D.R. Siewertsz van Reesema, J.W.J. Bijlsma.

Provision of study materials or patients: A.A. van Everdingen, J.W.G. Jacobs.

Statistical expertise: A.A. van Everdingen, J.W.G. Jacobs.

Obtaining of funding: A.A. van Everdingen, J.W.J. Bijlsma.

Administrative, technical, or logistic support: A.A. van Everdingen, J.W.G. Jacobs, J.W.J. Bijlsma.

Collection and assembly of data: A.A. van Everdingen, J.W.G. Jacobs.

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