ORAL STEROIDS AS BRIDGE THERAPY IN RHEUMATOID ARTHRITIS PATIENTS STARTING WITH PARENTERAL GOLD. A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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SUMMARY

The efficacy of oral prednisone as bridge therapy in rheumatoid arthritis (RA) was studied. Forty patients starting aurothioglucose were randomized to receive either prednisone or placebo for 18 weeks. The dose was 10 mg/day in the first 12 weeks, 7.5 mg/day in weeks 13 and 14, 5 mg/day in weeks 15 and 16, and 2.5 mg/day in weeks 17 and 18. Patients were followed for 44 weeks. We found that disease activity was significantly lower in the prednisone group as early as week 1 and continued up to week 12. Response to prednisone was noticed in 60% of the patients. After tapering prednisone, a rebound deterioration was noticed at weeks 20 and 24 in 58% of the responders. No significant differences in X-ray progression were found between the two groups. We concluded that oral prednisone (10 mg/day) significantly reduces short-term disease activity in 60% of patients with active RA. The rebound deterioration after tapering the dose means that bridge therapy with prednisone using this dose-reduction scheme is not recommended.

KEY WORDS: Rheumatoid arthritis, Prednisone, Efficacy.

FOR almost 45 yr corticosteroids have played a role in the treatment of rheumatoid arthritis (RA). There was initial enthusiasm for this therapy because of the great symptomatic relief patients reported. But the observed adverse reactions with doses of 20–40 mg/day prednisone made physicians more reluctant in prescribing this medication. A new interest in oral steroids arose when treatment with lower doses of prednisone was proposed as 'bridge therapy' [1]. Patients who did not respond to non-steroidal anti-rheumatic drugs alone, and who were awaiting the effect of slow-acting anti-rheumatic drugs (SAARDs), could benefit from corticosteroid addition.

Although a common treatment regimen at present, there is only one controlled study published regarding low-dose oral prednisone efficacy in the treatment of RA [1]. In this study prednisone (5 mg/day) was added to other drugs [non-steroidal anti-inflammatory drugs (NSAIDs) or constant doses of gold salts or D-penicillamine] over 24 weeks. No statistically significant differences between the prednisone and the placebo groups were noted. At present there is not a single study reporting a significant treatment effect with low doses of oral prednisone, although it is commonly believed to be an effective drug. To fill this gap in the literature a randomized double-blind placebo-controlled trial was performed, in which prednisone and placebo were added to aurothioglucose, a parenteral gold compound.

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PATIENTS AND METHODS

Patients were selected from an out-patient population at the University Hospital Nijmegen between April 1988 and April 1991. All patients with definite or classical RA [2] were selected for this study when a treatment with parenteral gold was considered by the attending rheumatologist. Gold therapy generally was introduced when patients failed on at least one other SAARD (hydroxychloroquine, sulphasalazine, oral gold, methotrexate, azathioprine or D-penicillamine). Patients fulfilled at least three of the following five criteria: five or more tender joints, three or more swollen joints, erythrocyte sedimentation rate (ESR) > 28 mm/h, morning stiffness $\geq$ 60 min and a haemoglobin level below normal (age and sex specific) limits. Patients with diseases or medication that might affect bone mass were excluded from the study. An additional exclusion criterion concerned women who were less than 3 yr post-menopausal or had irregular cycles. These criteria were necessary for a part of the study focusing on bone mass [3]. Informed consent was given by all patients. The study was approved by the local ethics committee.

Intramuscular aurothioglucose (Auromyose[®]) was given with a test dose of 10 mg 1 week before starting, and 50 mg/week during the following 20 weeks. Thereafter 50 mg every 2–4 weeks was given. In case of adverse reactions the dose could be adjusted. NSAIDs in stable doses were permitted. Patients were randomly assigned to receive either placebo or prednisone. No block randomization or stratification was used. Both the patients and observers were unaware of the assigned treatment regimen. Prednisone was started with 10 mg/day for 12 weeks. The dose was gradually tapered according to the protocol with 2.5 mg/day

every 2 weeks, until they received 0 mg/day in weeks 19 and 20. Intra-articular injections with steroids were allowed, omitting the injected joint from further evaluation.

Clinical assessment were made by one observer (RL) between 1.00 and 4.00 pm. At weeks 0, 1, 2, 4 and thereafter every 4 weeks until week 44 the following variables were collected: disease activity score (DAS) [4], a composed index of disease activity containing Ritchie articular index (RAI), number of swollen joints, ESR and patient assessment of general health with a visual analogue scale (VAS 100 mm); patient assessment of pain (VAS 100 mm); morning stiffness (min); haemoglobin (mmol/l); thrombocytes ($10^9/l$); mean grip strength left and right hand (kPa). Functional capacity with a Dutch equivalent [5] of the Stanford Health Assessment Questionnaire (HAQ, ranging from 0 to 3) was measured at weeks 0, 12, 20 and 44. Hand and feet radiographs were made at weeks 0, 20 and 44. Joint erosions and joint space narrowing were independently scored by two observers with a modified Sharp method [6]. In cases of disagreement a consensus score was reached after re-evaluation of the radiographs. Response was defined as an improvement in DAS from baseline of more than twice the measurement error (1.08) [4], indicating a significant change in DAS in individual patients.

Statistical analysis

Differences between groups in categorical data were analysed with the chi-square or (with low cell numbers) Fisher's exact tests. Numerical data were analysed with *t*-tests and Wilcoxon rank sum tests. Within group differences were analysed with paired *t*-tests and Wilcoxon signed rank tests. Skewed distributions were, where possible, transformed to a normal distribution.

RESULTS

During the study period 55 patients were considered for treatment with aurothioglucose. Three patients were inadvertently not reported by their treating physician, nine patients refused to participate, one patient did not fulfil the inclusion criteria of active disease, and two patients were excluded because of irregular menstrual cycles. Forty patients were included and randomized to receive either prednisone ($n = 20$) or placebo ($n = 20$).

Patient characteristics at baseline

At the start no significant differences were apparent in patient characteristics between the two groups. Sex, age, disease duration and rheumatoid factor were equally distributed. All disease activity variables were comparable, as was X-ray score (Table I).

Course of treatment

At week 4 one patient in the placebo group refused further participation because of active disease, and was then treated with 10 mg prednisone. For analysis she remained in the original group (intention to treat). At 20 weeks gold was discontinued in eight patients (four

TABLE I
Patient characteristics at baseline

Variables	Gold + prednisone $n = 20^*$	Gold + placebo $n = 20^*$
Sex (male:female)	6:14	6:14
Age (yr)	57.0 (40.5, 60.5)	56.0 (41.5, 64.5)
Disease duration (months)	21.5 (12.5, 45.0)	29.5 (18.0, 47.5)
Rheumatoid factor positive	16/20	17/20
Previous DMARDs	17/20	18/20
Previous prednisone	1/20	0/20
Disease activity score	4.88 (4.52, 5.20)	4.97 (4.30, 5.41)
Functional capacity	0.69 (0.57, 1.21)	0.58 (0.42, 0.95)
X-ray total	11.0 (3.0, 35.5)	17.0 (8.5, 34.5)

*All values with parentheses are medians (interquartile ranges).

prednisone, four placebo) because of adverse reactions. Between weeks 20 and 44 another 12 patients discontinued gold treatment. The reasons were inefficacy (five prednisone, two placebo), and adverse reactions (four prednisone, one placebo). Mucocutaneous adverse reactions were seen in 12 patients (seven prednisone, five placebo), and one patient developed proteinuria (prednisone). One patient (placebo) developed an acute and irreversible pancytopenia, probably related to gold. She died as a consequence of pulmonary haemorrhages. The course of treatment is summarized in Table II. Intra-articular injections with corticosteroids were considered necessary in one prednisone-treated patient (one joint), and in four patients with placebo (six joints).

Change in disease activity variables

In Fig. 1 mean values of the DAS are shown for both groups during the 44 weeks of observation. In the prednisone group a fast improvement was noticeable. The differences between the two treatment groups were significant at weeks 1, 2, 4 and 8 for the DAS. A similar pattern was seen for the DAS components (data not shown).

At week 12 all disease activity variables (DAS, RAI, swollen joints, ESR, general health, pain, morning stiffness, haemoglobin, thrombocytes, mean grip strength and functional capacity) had improved significantly from baseline in the prednisone group. The placebo group improved significantly in almost all

TABLE II
Course of treatment

Group	Drugs	Week 0	Week 12	Week 20	Week 44
Prednisone	Prednisone	20	20	0	6
	ATG	20	19	16	7
	DMARD	0	0	1	9
	no DMARD	0	1	3	4
Placebo	Placebo	20	18	0	0
	Prednisone	0	1	0	2
	ATG	20	15	15	12
	DMARD	0	0	0	5
	no DMARD	0	4	4	2

ATG, aurothioglucose. Other DMARDs: methotrexate 11 (four in placebo group), sulphasalazine three (one in placebo group).

FIG. 1.—Mean disease activity scores (DAS) with 95% confidence intervals ($2 \times \text{S.E.M.}$). Gold + prednisone (—) and gold + placebo (---).

variables as well, but to a smaller degree. Improvement in DAS, RAI, ESR, morning stiffness, haemoglobin, grip strength and functional capacity was significantly greater in the prednisone group compared to placebo. With area under the curve (AUC) analysis, taking into account all measurements between weeks 0 and week 12, the existing difference was even more obvious. The difference in disease activity score was especially highly significant (Table III).

After week 12 the prednisone dose was gradually tapered during the next 6 weeks. Figures 1 and 2 show a marked exacerbation in the DAS and its components in the prednisone group during this period. The placebo group, however, was still showing a gradual decline in disease activity variables.

At week 20 only DAS, RAI and number of swollen joints remained significantly different from baseline in the prednisone group. In the placebo group however, a clear improvement was shown in all variables except haemoglobin. Decline in DAS and ESR was significantly greater in the placebo group. The area under the curve analysis for weeks 12–20 did not show any difference between the two groups (Table III). With an AUC analysis for the whole period (0–20) the

TABLE III

Disease activity variables: analysis of the area under the curve

Variables	Weeks 0–12* <i>P</i> -values†	Week 12–20* <i>P</i> -values†
DAS	3.62:4.58 0.0001	3.97:3.66 0.40
Ritchie articular index	9.4:14.1 0.07	12.6:7.5 0.31
Swollen joints	11.7:16.8 0.01	10.1:12.3 0.06
ESR	20.3:46.1 0.0001	22.0:33.8 0.15
General health	26.0:44.3 0.005	34.4:31.8 0.78
Pain	25.5:51.5 0.002	29.9:27.5 0.73
Morning stiffness	24.4:50.0 0.30	20.6:18.8 0.91
Haemoglobin	7.99:6.70 0.005	7.89:6.90 0.09
Thrombocytes	308.2:357.2 0.35	339.0:321.8 0.92
Grip strength	28.1:19.7 0.38	30.1:23.0 1.00

*Median values corrected for the length of the interval, prednisone: placebo.

†*T*-test (disease activity score) and Wilcoxon rank sum test.

TABLE IV
Individual treatment response

Week	Gold + prednisone*	Gold + placebo*	<i>P</i> -value†
1	8/19 (1.38)	0/19 (—)	0.003
2	8/20 (1.55)	0/19 (—)	0.003
4	12/20 (1.64)	0/19 (—)	0.000
8	14/20 (1.99)	4/20 (1.55)	0.001
12	13/20 (2.43)	8/19 (1.39)	0.15
16	13/20 (1.65)	8/18 (1.67)	0.20
20	7/20 (2.24)	13/19 (1.76)	0.04
24	7/17 (1.85)	12/16 (1.99)	0.05
28	11/19 (2.07)	12/17 (2.00)	0.43
32	11/19 (1.78)	8/15 (2.16)	0.79
36	13/17 (2.25)	7/15 (2.72)	0.08
40	12/17 (1.99)	11/16 (1.68)	1.00
44	14/20 (2.16)	13/19 (2.57)	0.92

Response is defined as a significant decrease in DAS from baseline (> 1.08). All values in parentheses are median changes in DAS from baseline in the response group.

*Number of responders/total.

†Chi-square test/Fisher's exact test comparing the number of responders in both groups.

DAS, number of swollen joints, and ESR were still significantly lower, and haemoglobin higher, in the prednisone treated group (data not shown).

At week 44 all clinical variables had improved significantly in both groups, except for haemoglobin in the placebo group. There were no significant differences in changes between prednisone and placebo. An AUC analysis for weeks 20–44 also showed no difference between the groups. AUC analysis over the whole period (weeks 0–44) demonstrated only a weak difference in ESR: the prednisone group had lower values.

Individual treatment response

Table IV shows the proportion of patients responding at several time intervals. The number of responders in the prednisone group was significantly higher than in the placebo group at week 1, 2, 4 and 8. At week 4 there were 12 responders (60%) in the prednisone group *vs* none in the placebo group. At weeks 20 and 24 the placebo group had more responders than the prednisone group. Of the original 12 responders at week 4, only five still exhibited a significant decline in disease activity score from baseline at week 20 (42%). In seven patients a rebound deterioration was noticed (58%). After week 24 the number of responders in both groups were comparable.

X-ray progression

Radiographs were taken at weeks 0, 20 and 44. At weeks 20 and 44 neither the progression in total joint damage, nor the progression in joint erosions or joint space narrowing were significantly different between the two groups (Table V). When dividing the groups into responders and non-responders, it was found that in the prednisone group responders at week 4 had significantly more X-ray progression at weeks 20 and 44 than non-responders ($P = 0.02$ and $P = 0.04$, respectively).

TABLE V
X-ray progression from baseline

	Week 20			Week 44		
	Gold + prednisone*	Gold + placebo*	Between groups†	Gold + prednisone*	Gold + placebo*	Between groups†
Joint erosions	2.0 (0.0, 4.0)	2.0 (1.0, 5.0)	$P = 0.48$	3.5 (0.0, 8.0)	5.0 (2.0, 10.0)	$P = 0.48$
Joint space narrowing	1.5 (0.0, 3.0)	0.0 (0.0, 2.0)	$P = 0.54$	2.0 (0.0, 5.0)	2.0 (0.0, 4.0)	$P = 0.84$
Total joint damage	3.0 (2.0, 7.5)	4.0 (1.0, 8.0)	$P = 0.99$	4.5 (2.0, 12.5)	7.0 (2.0, 12.0)	$P = 0.92$

*Median score (interquartile range).

†Significance testing with *t*-test.

DISCUSSION

Prednisone is a common treatment regimen in the management of patients with RA. Although it is recommended as an effective temporary therapy while awaiting the therapeutic benefits of slow-acting anti-rheumatic compounds [7], no clear evidence exists proving the efficacy of low-dose oral prednisone in reducing disease activity. Whether steroids have disease-modifying potential is another matter of discussion. Several authors have reviewed these questions and they arrive at different conclusions, probably as a result of insufficient objective evidence [7–11].

The study was carried out with the intention to treat analysis: all patients remained for analysis in the original treatment group. Only one patient in the placebo group changed to prednisone during the first 20 weeks of standardized treatment, and four patients in both groups discontinued gold because of adverse reactions before week 20. We do not believe that an analysis including these treatment violations will overestimate the efficacy of prednisone. After week 20 patients were followed without a standardized treatment protocol. Since treatment was individually adjusted it was not surprising that no differences were found at week 44 comparing the original treatment groups.

At week 44 more patients in the prednisone group had discontinued gold treatment than placebo-treated patients. The number of patients, however, is too small to draw any conclusions as to whether prednisone had an impact on gold response.

Only one placebo-controlled study on low-dose oral steroids has been published [1]. In this study 5 mg prednisone ($n = 18$) or placebo ($n = 16$) were added to other anti-rheumatic drugs during 24 weeks. Nearly all variables failed to show a significant difference between the two groups at week 24. After abrupt cessation of prednisone at week 24, disease activity markedly exacerbated. At week 32 the increase in most disease activity variables was significantly higher in the prednisone group. This rebound deterioration was suggested to indicate that low-dose oral steroids were effective, although almost no differences were noticeable during the first 24 weeks. The discrepancy with our findings might be explained by the lower doses they used. When the dose in our study was reduced to 5 mg at week 16, no differences with the placebo group remained. An alternative explanation is the fact that Harris *et al.* excluded from their analysis seven patients

withdrawn because of inefficacy, of whom five patients received placebo. With the intention to treat analysis a significant difference might have been found.

Results comparable with ours were found with intramuscular methylprednisolone pulse treatment (120 mg at weeks 0, 4 and 8) [12]. A fast improvement was noticed until 4 weeks after the last injection. Twelve weeks later disease activity variables in the methylprednisolone and the placebo group were within the same range. No rebound deterioration was found, probably as a result of the slow fall in serum levels by using an intramuscular depot regimen. There was no significant difference in increase of erosion score. Two controlled studies with intravenous methylprednisolone pulses (1000 mg) failed to show significant differences in clinical variables or X-ray progression with placebo [13, 14]. However, disease activity was measured 4 weeks after an injection, shortly before the next pulse was given. It is possible that disease activity was already rising by that time, and an early effect was missed. Based on several controlled and uncontrolled studies, two review articles concluded that methylprednisolone pulse therapy is an effective but short-lived treatment [15, 16].

Most studies are only reporting and testing overall group values. However, significantly different group values do not give an indication of how many patients in both groups actually show improvement. Therefore the individual response to prednisone was studied. Response to prednisone was assessed at week 4, since no patient in the placebo group responded at that time, excluding a possible gold response. Whereas in our study the prednisone group as a whole showed an impressive fast improvement, 40% of the patients in the prednisone group was classified as non-responder because of a non-significant change in DAS. This is in contrast with the general clinical impression that nearly all patients benefit from prednisone treatment.

The notable difference in disease activity during the first 12 weeks did not significantly influence X-ray progression as an outcome variable. No significant differences in erosions, joint space narrowing or total joint damage between the groups were found after 20 and 44 weeks. There are several possible explanations for this observation. First, the progression of joint damage was relatively low in both groups, and therefore may have already been reduced by gold without an additional disease-modifying effect of prednisone. Second, the mechanism by which prednisone reduces

inflammation may be different from the mechanism responsible for retarding joint destruction. A third possibility is a lack of power (type II error) to detect an existing difference in X-ray progression with 20 patients in each group.

The progression rate of joint destruction (at 24 and 44 weeks) in the prednisone group was found to be significantly higher for the responders (at week 4) than for the non-responders. This difference, however, is based on a small group of patients and the statistical significance disappears after correction for multiple testing.

We conclude that bridge therapy with low-dose prednisone decreases disease activity in 60% of patients with RA. Its action is fast, and already noticeable in the first week. However, a fixed gradual withdrawal of the prednisone dose produces a rebound deterioration of disease activity in seven of the initial 12 responders (58%). Prednisone did not reduce the progression rate of joint destruction. Another disadvantage may be the marked (reversible) bone loss observed even with these short courses of 10 mg prednisone [3]. The observed rebound deterioration means that bridge therapy with this dose regimenscheme is not to be recommended. Whether this rebound deterioration can be reduced with a more gradual withdrawal, as has been shown with intramuscular methylprednisolone, needs to be studied further.

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