Articles

Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis

Maarten Boers, Arco C Verhoeven, Harry M Markusse, Mart A F J van de Laar, René Westhovens, J Christiaan van Denderen, Derkjen van Zeben, Ben A C Dijkmans, André J Peeters, Piet Jacobs, Hans R van den Brink, Hubert J A Schouten, Désirée M F M van der Heijde, Annelies Boonen, Sjef van der Linden

Summary

Background The value of intensive combination therapy in early rheumatoid arthritis is unproven. In a multicentre, double-blind, randomised trial (COBRA), we compared the combination of sulphasalazine (2 g/day), methotrexate (7·5 mg/week), and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7·5 mg/day) with sulphasalazine alone.

Methods 155 patients with early rheumatoid arthritis (median duration 4 months) were randomly assigned combined treatment (76) or sulphasalazine alone (79). Prednisolone and methotrexate were tapered and stopped after 28 and 40 weeks, respectively. The main outcomes were the pooled index (a weighted change score of five disease activity measures) and the Sharp/Van der Heijde radiographic damage score in hands and feet. Independent health-care professionals assessed the main outcomes without knowledge of treatment allocation.

Findings At week 28, the mean pooled index was 1·4 (95% CI 1·2–1·6) in the combined treatment group and 0·8 (0·6–1·0) in the sulphasalazine group (p<0·0001). At this time, 55 (72%) and 39 (49%) patients, respectively, were improved according to American College of Rheumatology criteria. The clinical difference between the groups decreased and was no longer significant after prednisolone was stopped, and there were no further changes after methotrexate was stopped. At 28 weeks, the radiographic damage score had increased by a median of 1 (range 0–28) in the combined-therapy group and 4 (0–44) in the sulphasalazine group (p<0·0001). The increases at week 56 (2 [0–43] *vs* 6 [0–54], p=0·004), and at week 80 (4 [0–80] *vs* 12 [0–72], p=0·01) were also significant. Further analysis suggests that combined therapy immediately suppressed damage progression, whereas sulphasalazine did so less effectively and with a lag of 6 to 12 months. There were fewer withdrawals in the combined therapy than the sulphasalazine group (6 [8%] *vs* 23 [29%]), and they occurred later.

Interpretation This combined-therapy regimen offers additional disease control over and above that of sulphasalazine alone that persists for up to a year after corticosteroids are stopped. Although confirmatory studies and long-term follow-up are needed, this approach may prove useful in the treatment of early rheumatoid arthritis.

Lancet 1997; **350:** 309–18
See Commentary page 304

University Hospital, Maastricht (M Boers MD, A C Verhoeven MD, H J A Schouten, D M F M van der Heijde, A Boonen, S van der Linden); **Zuiderziekenhuis, Rotterdam** (H M Markusse MD); **Medisch Spectrum Twente and Twenteborg Hospital, Enschede and Almelo, Netherlands** (M A F J van der Laar MD); **Pellenberg Hospital, Catholic University, Louvain, Belgium** (R Westhovens MD); **Jan van Breemen Instituut, Amsterdam** (J C van Denderen MD); **Bronovo Hospital, The Hague** (D van Zeben MD); **University Hospital, Leiden** (B A C Dijkmans MD); **Reinier de Graaf Gasthuis, Delft** (A J Peeters MD); **Sint Laurentius Hospital, Roermond** (P Jacobs MD); **Medisch Centrum Alkmaar, Netherlands** (H R van den Brink MD)

Correspondence to: Dr Maarten Boers, Department of Clinical Epidemiology, Free University Hospital, PO Box 7057, 1007 MB Amsterdam, Netherlands

Introduction

The treatment of rheumatoid arthritis is traditionally characterised by escalation. The first step is non-steroidal anti-inflammatory drugs (NSAIDs), and then if necessary a sequence of progressively toxic second-line drugs (disease-modifying antirheumatic drugs) is introduced.[1] There is evidence that some of these disease-modifying drugs provide a degree of disease control[2]—ie, decrease disease activity but also maintain or improve physical function and retard radiographic joint damage.[3] However, both patients and physicians are dissatisfied with the long-term results of traditional therapy. A 1996 study suggested that early introduction of disease-modifying antirheumatic drugs may be more beneficial than delayed introduction for patients with recently diagnosed rheumatoid arthritis.[4] Research is focused towards finding new, more effective drugs, reassessment and earlier use of existing drugs (such as corticosteroids[5]), and treatment with drug combinations.[6]

The COBRA trial (Combinatietherapie Bij Reumatoide Artritis) is an adaptation of the latter two options—step-down bridge therapy with corticosteroids in early rheumatoid arthritis.[1] Our intention was to control disease rapidly at a very early stage, with agents that have overlapping windows of efficacy onset; and then, after 6 months to taper and stop the more toxic components while retaining disease control. We devised a regimen comprising a short period of high-dose oral prednisolone, rapidly tapered to a low maintenance dose. As the other components we chose methotrexate, commonly used as the disease-modifying drug of first choice in the USA, and sulphasalazine as the anchor drug to remain after the other two drugs were withdrawn. In Europe, sulphasalazine is commonly used as the disease-modifying drug of first choice.

We carried out a 56-week multicentre, randomised controlled trial among patients with early, active rheumatoid arthritis to study the degree of disease control afforded by a combination of sulphasalazine, methotrexate, and high/low oral prednisolone given in the first 28 weeks, compared with that achieved with sulphasalazine alone; and to find out whether control could be maintained on sulphasalazine alone, after sequential tapering and withdrawal of prednisolone and methotrexate in the second 28 weeks.

Patient and methods

Patients

We recruited patients between May, 1993, and May, 1995, in ten centres (nine in the Netherlands, one in Belgium). To optimise the benefit/risk ratio in line with the study purpose, we applied strict eligibility criteria to include patients with early rheumatoid arthritis who had very active disease and were most likely to benefit from this intensive treatment, in whom effects could be easily measured, and in whom we believed adverse effects would be least likely. The inclusion criteria were: a diagnosis of rheumatoid arthritis (American College of Rheumatology criteria[7]) with onset of disease at or after 16 years of age; active disease of the joints and inadequate control of arthritis (due to lack of efficacy or toxicity of treatment); and treatment with NSAIDs in adequate doses for at least 3 months. Such treatment could already have been initiated at the start of symptoms, not necessarily at the time of diagnosis. We defined disease activity as the presence of six or more actively inflamed joints, located at three or more different sites (a site is defined as either one large joint or a group of small joints: the joints of the wrist, the metacarpophalangeals, the proximal hand interphalangeals, the distal hand interphalangeals, ankles, the tarsometatarsals, the metatarsophalangeals, and the proximal and distal foot interphalangeals) and presence of at least two of the following: nine or more tender joints (irrespective of site), morning stiffness of 45 min or longer, and a Westergren's erythrocyte sedimentation rate (ESR) of 28 mm or more in the first hour.

We excluded patients who had had rheumatoid arthritis for longer than 2 years, those previously or currently treated with any disease-modifying antirheumatic drug except antimalarials (eg, gold, d-penicillamine, azathioprine, or cyclophosphamide) or corticosteroids (for arthritis or another disease), serious comorbidity or recent (within the 3 months before enrolment) major surgery, or inability to comply with the protocol. Adequate contraception was required. Further exclusion criteria were age below 18 or over 70; hypersensitivity to study medication, sulpha-containing compounds, or aspirin; hypersensitivity to three or more drugs; active infectious disease; a history of tuberculosis, recurrent infections, recent (<3 months) gastritis or gastrointestinal ulceration; any history of gastrointestinal bleeding or neoplasia; diabetes mellitus; hypertension treated with more than one antihypertensive drug; significant cardiovascular disease; liver disease; cataract; glaucoma; haematological disorders; partial or total colectomy; reduced renal function (creatinine clearance <50 mL/h) proteinuria (>0·5 g/day); hypoalbuminaemia; chronic dermatitis; treatment with phenytoin, phenylbutazone, salicylates, barbiturates, cholestyramine, probenecid, oral anticoagulants (dicoumarol derivatives); and a history of alcohol or substance abuse (ie, inability to limit alcohol intake to a maximum of 70 g weekly) or use of any experimental drug less than 2 months before inclusion.

The study protocol was approved by research and medical ethics committees in all participating hospitals. The patients were fully informed about the potential side-effects of all the drugs. To maintain allocation concealment, they were told that response to treatment was variable in onset and efficacy with all three drugs. All patients gave written informed consent.

Intervention

Both groups received sulphasalazine (Salazopyrine enteric-coated tablets of 500 mg, Pharmacia & Upjohn, Uppsala, Sweden) 500 mg/day, increased to 2000 mg/day over a period of 3 weeks. In addition, the combination therapy group received prednisolone and methotrexate; the control group received matching placebo tablets and capsules identical in appearance and taste. The daily prednisolone dose was 60 mg in week 1, 40 mg in week 2, 25 mg in week 3, 20 mg in week 4, 15 mg in week 5, 10 mg in week 6, and 7·5 mg thereafter (week 1–6—one gelatine capsule containing the daily dose, capsule compound by Bufa, Uitgeest, Netherlands; week 7 and later—5 mg tablets by CentraFarm Nederland bv, Etten-Leur, Netherlands; some of these tablets were broken by the pharmacy so that 7·5 mg could be taken daily). The cumulative dose over the first 6 weeks was 1190 mg; over the first 28 weeks it was 2345 mg, corresponding to a mean of 12 mg daily. The methotrexate prescription was 7·5 mg in a single weekly dose (PharmaChemie bv, Haarlem, Netherlands). If an adverse event occurred, the drugs were temporarily withdrawn, and reintroduced at lower doses according to a fixed protocol where possible.

Prednisolone and methotrexate were stopped after 28 weeks and 40 weeks, respectively. Both drugs were gradually withdrawn to decrease the chance of a disease flare. Thus, from week 29 to 35, a day of zero prednisolone dose was introduced each week: first week, no prednisolone on Wednesday; second week, no prednisolone on Tuesday and Saturday; third week, no prednisolone on Monday, Wednesday, and Friday; until after 6 weeks, the prednisolone had been stopped. After 40 weeks of treatment, methotrexate was tapered: the drug was given at 5 mg per week for 3 weeks, then at 2·5 mg per week for 3 weeks, then stopped. If there was a flare in disease activity, the last medication stopped was reintroduced. A flare was defined per protocol as an increase of five in active joint count or an increase from zero to three compared with the situation at week 28 (an active joint is swollen or tender on pressure; counting of joint groups in one hand or foot as above). If the research medication had to be stopped for any reason and a consecutive disease-modifying antirheumatic drug was started, the protocol recommended that a drug not in the combination should be given, preferably intramuscular gold salts. After 56 weeks, the protocol ended, and the treating physician was at liberty to change second-line therapy, or to attempt a second tapering of methotrexate or prednisolone in those patients still on combination therapy. Where possible, blinded protocol treatment was continued. To maintain allocation concealment for other patients still in the protocol, the treatment code was revealed only for those patients still on combination therapy after 80 weeks.

Concurrent therapy

NSAIDs and simple analgesics were allowed; discontinuation was actively pursued. A maximum of two intra-articular steroid injections was allowed in two periods after week 38 of the protocol, but not in the 6-week period preceding independent assessment. Any other intervention with parenteral or oral corticosteroids was not permitted. All patients received folic acid (1 mg/day) during methotrexate or placebo prescription. Vitamin D deficiency apparent at the laboratory screening before inclusion was corrected.

Treatment allocation

Patients who met the eligibility criteria were entered into the study and assigned a unique study identification number by telephone. This number implied random allocation to one of the two treatments with stratification by centre. For each centre, a separate randomisation list was generated by an adaptive biased urn algorithm. In contrast to fixed blocks, this algorithm ensured that the rheumatologists would have no clue to the allocation of each subsequent patient in a setting where unblinding was possible; yet it also guaranteed an approximately equal distribution over the groups even in the centres with smaller numbers of patients.[8] The assignment was known only by the employees of the Maastricht Hospital pharmacy who prepackaged the medication; it was disclosed to the treating physician only in case of an emergency. Primary analysis was done with coded group allocation after entry

of all study data. The full randomisation codes remained concealed until completion of the primary analysis.

Organisation

Each centre was staffed by a rheumatologist, a research nurse, and an independent assessor. The rheumatologist was responsible for the identification and inclusion of the patients, and for all medical policy decisions. The research nurse monitored safety through regular follow-up schedules (first weekly, then every 4 weeks) and also measured disease activity. Independent assessors (mostly physiotherapists) applied the outcome measures at baseline and at weeks 16, 28, 40, and 56; in almost every instance a patient was seen by the same assessor. These health professionals were not involved in care of patients; they were also asked not to discuss disease activity or the treatment with the patients. Independent assessment ensured optimum concealment of primary outcome assessments, especially important in the first 6 weeks of the protocol, when potential effects and side-effects of high-dose prednisolone would be most apparent. These assessments included all primary and core-set outcome measures except pain score, grip strength, and ESR. The follow-up schedule is continuing; all outcomes during the first 56 weeks are reported here. In response to criticism about the follow-up period for the radiographs, we read and analysed the 80-week radiographs at a later stage.

Before the study and then once a year, all study personnel trained together to maintain assessment quality and agreement between observers. A specially designed manual of procedures and assessment techniques was available in each study centre. The trial was coordinated and data managed in the University Hospital Maastricht. Safety and toxicity were monitored by a safety committee of two independent rheumatologists, the Maastricht University pharmacist, and a statistician (HJAS). The pharmacy centre of the University Hospital Maastricht was responsible for drug production, packaging, and distribution.

Assessment of endpoints

The primary endpoint of the therapeutic intervention was a pooled index summarising the change in five measures after 28 weeks of treatment. Pooling is a validated method to increase sensitivity of separate measures.[9] To obtain the pooled index of one of the groups at week 28, we calculated a standardised change score of that group by dividing the mean change in one measure by its pooled SD of change at week 28. This procedure was repeated for each of the five measures; the pooled index is the mean of the standardised scores. To obtain pooled index values for another time point, change scores at that point were standardised through division by the same pooled SD at week 28. Finally, a constant was added to all index values so that the value at baseline was zero. We selected five measures for maximum sensitivity to change:[10] Tender joint count (68 joints[11]); overall assessment by the independent assessor (on a 100 mm visual analogue scale, worst and best imaginable health status at the left and right anchor, respectively); grip strength (by vigorimetry; Martin, Tottlingen, Germany, range 0–150 kPa, mean of medians of three measurements in both hands);[12] ESR (Westergren method); and McMaster Toronto arthritis questionnaire,[13] which follows improvement in five impaired activities elicited and priority-ranked by the patient during a baseline interview, together with change scores for quality of life, psychological, social, and emotional wellbeing. The scores of this questionnaire reflect change, increase as disability improves, and vary from 10 (maximum deterioration) to 40 (maximum improvement). In its original format, the baseline questionnaire score differs from the follow-up scores because the change items are not available. To make these scores directly comparable, we added mock change items at baseline and scored them as "unchanged". Grip strength and ESR were assessed by the research nurses every week at the start of the protocol, then at least every 4 weeks.

We assessed all remaining disease activity measures of the World Health Organisation/International League of Associations for Rheumatology core set as secondary endpoints.[14] As well was tender joint count, assessor's overall assessment, and acute phase reactant (ESR) included in the pooled index, these measures are swollen joint count (48 joints: modified from American College of Rheumatology 66-joint count;[11] small foot joints as one joint site and no midfoot joints), pain (assessed by the patient on a 100 mm visual analogue scale; worst imaginable pain at the right anchor), and patient's overall assessment (on a 100 mm visual analogue scale, worst and best imaginable health status at the left and right anchor, respectively). To facilitate comparisons with other studies, the highly patient-specific McMaster Toronto arthritis questionnaire was complemented with the more generic health assessment questionnaire (Dutch validated version; scores 0–3, 3 indicating a poor functional state).[15]

We expressed improvement in individual patients by the American College of Rheumatology preliminary criteria for remission[16] (occurrence and duration; because no inquiry on fatigue was made we used the concept of a "probable remission' for instances in which a patient would be in remission when absence of fatigue was assumed). Furthermore, we used the American College of Rheumatology preliminary criteria for improvement in rheumatoid arthritis[17] (ie, minimum 20% improvement in tender and swollen joint counts plus a similar improvement in at least three of five remaining core-set measures). Before calculating improvement percentages, we ensured (by recoding if necessary) that all scales decreased on improvement. We also report improvement with application of a 50% threshold instead of the 20% in the American College of Rheumatology criteria.

To facilitate comparison with other European studies, we report the disease activity score, a composite outcome measure containing the Ritchie tender joint index (RI), swollen joint count (JC), ESR, and patient's overall assessment

$$\text{Score}=0{\cdot}54\sqrt{\text{RI}}+0{\cdot}065\text{JC}+0{\cdot}331\text{nESR}+0{\cdot}007\text{OA}$$

The term disease-controlling has been suggested for antirheumatic treatment regimens that improve disease activity, retain or improve physical function, and decrease progression of radiographic damage.[3] A priori, we expected out study to be too small to detect small differences in radiographic progression between the two groups, since both were treated with the disease-controlling drug sulphasalazine. Nevertheless, two trained observers (AB and ACV) assessed radiographic damage, unaware of the identity of the patients. They separately scored radiographs of hands and feet according to van der Heijde's modification of Sharp's method.[2] This method reflects erosions and joint-space narrowing in 44 joints in the hands and feet. The principal measure, the total score, is the sum of erosion and narrowing scores, and ranges from 0 to 448. The method requires radiographs to be presented in ordered fashion (baseline, and weeks 28, 56, and 80). Scores can either be stable or increase; decrease (indicating improvement) is not possible. We report the mean of the two observers' erosion, narrowing, and total scores.

As an exploratory analysis, we also report the cumulative number of joints free of erosions at baseline in which at least one erosion developed during follow-up. For this purpose, joints were grouped into four areas on each side: wrist (six joints), metacarpophalangeal (five joints); proximal interphalangeal (four joints); and foot joints (six joints). The first erosion in each area was counted. Furthermore, we explored the rate of radiographic change in each of the measurement periods by calculating not only the change scores from baseline, but also the change scores between week 28 and 56 and between week 56 and 80.

Toxicity and monitoring

Laboratory monitoring at every control visit comprised complete blood count, measurement of serum total bilirubin, aminotransferases, alkaline phosphatase, creatinine, blood urea nitrogen, and electrolytes, and urinalysis for glucose and albumin. Toxicity was assessed by counting of each adverse event reported and possible subsequent changes to treatment (eg, withdrawal). Each patient underwent pulmonary function tests (expiratory volume and carbon monoxide diffusion capacity) at baseline and twice yearly thereafter. Bone densitometry was done by an operator unaware of treatment assignment, in all centres where a

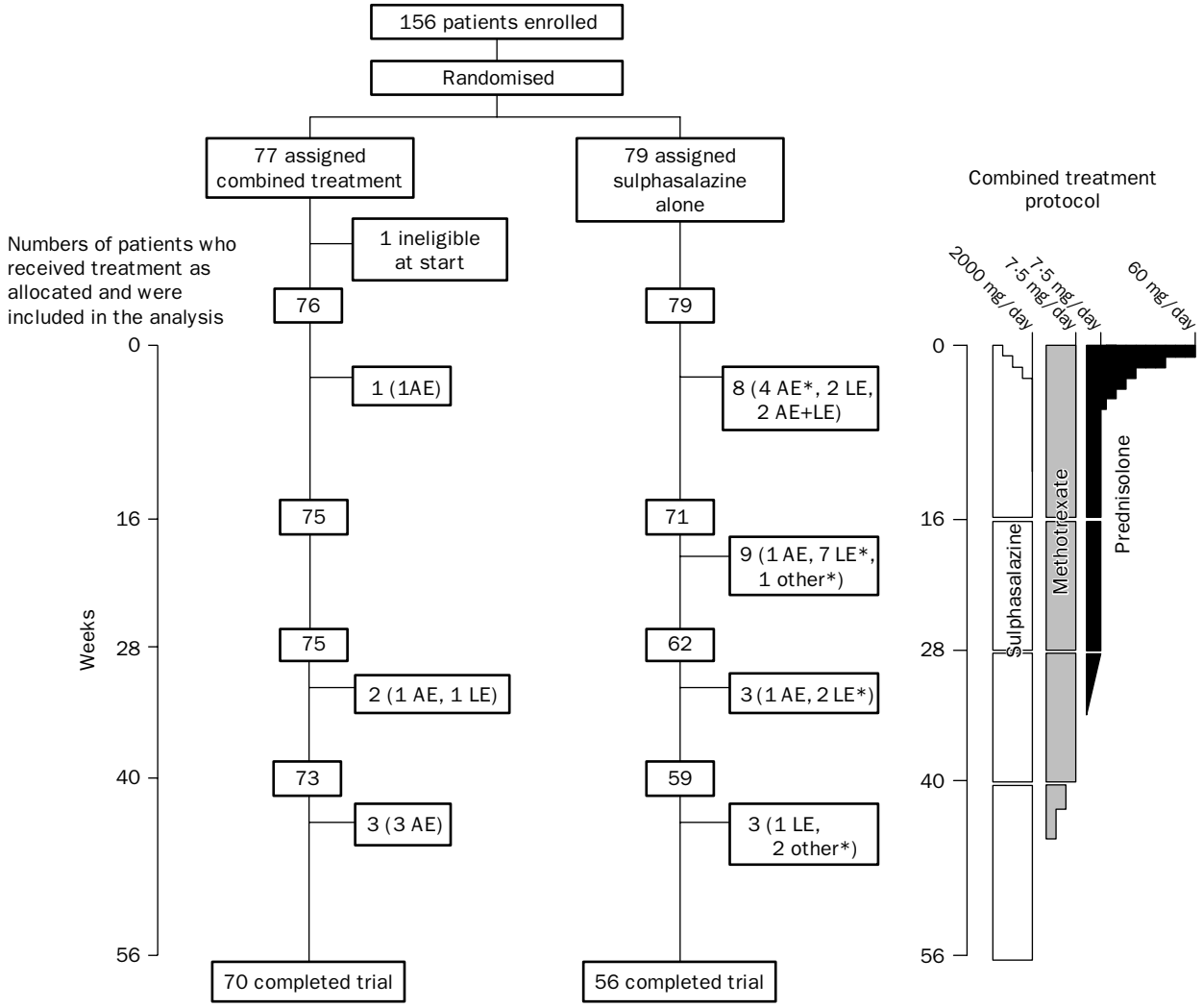

Figure 1: **Trial profile**
*Patient lost to follow-up.
AE=adverse events; LE=loss of efficacy; other includes protocol violations.

dual-energy X-ray absorptiometer was available (Lunar, Hologic, or Norland, in eight centres). We report changes in bone mass for lumbar spine and femoral neck (mean of right and left hip).

We assessed IgM rheumatoid factor serostatus in a time-resolved fluoroimmunoassay (rabbit IgC antigen; Nordic, Tilburg, Netherlands); values over 20 kU/L classified patients as positive for rheumatoid factor.[19] Class II HLA genotype was identified by serological typing (Tissue Typing Laboratory, Maastricht University Hospital).

Compliance

We assessed compliance by tablet counts at every control visit, by questioning (including a quantification of the number of tablets missed), and by measurement of sulphapyridine (a sulphasalazine metabolite) in urine samples taken at weeks 16, 28, and 40. We classified as non-compliant all patients on protocol treatment who were negative for sulphapyridine once or who failed to return tablet boxes at control visits more than once. In the first 28 weeks, we made judgments at every control visit, and classified as "probably non-compliant" patients who in the first 28 weeks on average missed more than one daily dose per week of sulphasalazine or prednisolone, or more than one weekly dose of methotrexate over a period of 6 weeks.

Analysis

The target sample size was 168 patients. This number yields a power of at least 90% to detect a difference of 0·33 or greater in the pooled index (SD 0·45) between the treatment groups at two-sided α=0·05, given a maximum dropout rate of 50%. Enrolment stopped at 156 patients for practical reasons, because the actual dropout rate was 20%. All analyses were based on intention to treat as initially assigned. All available data were used. Data missing due to loss to follow-up were handled by a last observation carried forward approach. For other missing data, values were interpolated if actual assessments were available at least every 28 weeks. No interim analyses were done.

Measures with a Gaussian distribution are expressed at baseline as mean and SD, and as mean change with 95% CI. The main endpoint was initially analysed by two-way ANOVA with treatment, centre, and their interactions as factors. The latter two factors were not significant (centre p=0·07; interaction p=0·79). In view of the large effect of treatment, further analyses ignored centre as a factor, with exception of the multivariate analysis. Measures with a non-Gaussian distribution are expressed as median and median change (range) and analysed with Mann-Whitney tests; measures with a discrete distribution are expressed as counts (%) and analysed by continuity-corrected χ^2 tests or Fisher's exact tests where appropriate. The level of significance was set at p<0·05, two-sided. No adjustment was made for multiple testing.

For the main clinical and radiological outcome, multivariate analyses tested whether imbalance in important prognostic factors between the two groups despite randomisation affected the study results. The dependent variables were the pooled index and the progression in total radiological damage score at 28 weeks. The

latter was log-transformed (new variable=log[total change score +1]) because of a skewed distribution. Full and parsimonious models were constructed: the full models contained the predictive variables: treatment group, centre, sex, age, disease duration, rheumatoid factor status, presence of HLA genotype DR4 or DR2, number of years education, marital status, and baseline scores for disease activity score, the health assessment questionnaire, and radiological damage. The parsimonious models contained only those variables selected in forward stepwise regression analysis (F to enter >4·0). Plots of residuals versus fitted and versus predictor values were inspected for departure of regression analysis assumptions. Because there was still substantial skewness after log transformation on the total radiological damage score, the results of the regression analysis on this variable must be interpreted with caution.

Results

The trial included 156 patients (figure 1). In one patient the protocol medication was stopped within 1 week because his disease was in spontaneous remission at baseline. Data for this patient are not reported. 76 patients received combination treatment, 79 sulphasalazine only. Five patients (3%, all in the sulphasalazine group) were lost to follow-up before week 56. In six patients (all withdrawn) the treatment assignment had to be revealed before week 56 for medical reasons.

The two treatment groups were similar in terms of baseline disease activity, radiographic damage, and demographic and other prognostic variables (table 1). Except for one Asian patient in each group, all patients were white. Our eligibility criteria resulted in a study group with very early, active, and severe rheumatoid arthritis; in 77% the trial medication was the first disease-modifying antirheumatic drug. High rates of rheumatoid-factor positivity, HLA-DR4 genotype, and presence of radiographic damage all indicate a poor a-priori prognosis (table 1). In 21% of all patients (ie, 32% of those with baseline erosive disease) erosions were initially found only in the feet.

	Combined treatment (n=76)	Sulphasalazine (n=79)
Demography		
Mean age (SD) in years	49·5 (11·9)	49·4 (12·3)
Male/female	26 (34%)/50 (66%)	38 (48%)/41 (52%)
Mean (SD) years of education	10·0 (3·0)	9·6 (3·3)
Clinical characteristics		
Median (range) disease duration in months	4 (1–24)	4 (1–23)
Previous treatment with antimalarials	16 (21%)	19 (24%)
Admitted to hospital for rheumatoid arthritis	9 (12%)	11 (14%)
Positive IgM rheumatoid factor	59 (78%)	57 (72%)
HLA-DR4 positive*	44 (60%)	39 (56%)
HLA-DR2 positive*	16 (22%)	12 (16%)
Erosions on hand or foot radiographs†	55 (74%)	59 (79%)

*Homozygotic or heterozygotic DR type, assessed in 143 patients (92%).
†Patients with available baseline radiographs; combined treatment group n=74, sulphasalazine group n=75.

Table 1: **Baseline characteristics of study patients**

Clinical outcome

Within a few weeks, combined therapy greatly improved disease activity in most patients (figure 2, table 2). Sulphasalazine also improved disease activity substantially, although less than combined treatment. There was an almost immediate response to combined treatment in all frequently assessed measures (eg, grip strength, pain, ESR; the latter is shown in figure 2). Despite a daily prednisolone dose of only 7·5 mg from week 7 onwards, further improvement continued up to week 28. At this time, the clinical efficacy of combined treatment was almost double that of sulphasalazine (figure 2, table 2). 55 (72%) of the combined-treatment group compared with 39 (49%) of the sulphasalazine group had improved according to "20%" American College of Rheumatology criteria (p=0·006), and 37 (49%) compared with 21 (27%) had improved under the "50%" criteria (p=0·007).

In the combined-treatment group 16 patients had probable remissions and five definite remissions during the first 28 weeks (total 28%). In the sulphasalazine group, the corresponding numbers were nine and four (total 16%; p=0·14). In the combined-treatment group only, remissions clustered near the beginning and end of the first 28-week period. Almost all of these remissions ended when prednisolone was stopped, and in the second 28 weeks, only a few additional patients had remissions. For the total study period, there were 18 probable and six definite remissions (32%) in the combined-treatment group, compared with 14 and five in the sulphasalazine group (24%; p=0·38). Of these, only one patient in the combined-treatment group and three in the sulphasalazine group had persisting remission at 56 weeks.

The difference in clinical efficacy between the treatment groups decreased and was no longer significant after the withdrawal of prednisolone, and there were no further changes when methotrexate was withdrawn (figure 2). However, differences in two of three measures of physical function (health assessment questionnaire, grip strength) remained near significance (table 2). Prednisolone was restarted (for disease flares) in six patients in the combined-treatment group. Methotrexate was restarted in 13 patients in the combined-treatment group, and methotrexate placebo in three patients in the sulphasalazine group.

Adjustment for prognostic variables did not change the difference in efficacy between treatments (crude coefficient for the additional effect of combined treatment *vs* sulphasalazine on the pooled index at week 28: 0·63 [SE 0·12], p<0·0001; adjusted coefficient 0·59 [0·11], p<0·0001). In stepwise regression analysis, baseline physical disability score and disease duration, as well as study centre, significantly affected the pooled index at week 28; patients with high initial disability and shorter disease duration were more likely to improve. The effect of treatment was not changed in the model incorporating these factors.

Joint destruction on radiography

Radiographs of 147 patients (73 combined treatment, 74 sulphasalazine) were available for assessment (baseline and at least one during follow-up). The between-observer reliability of the assigned total scores was satisfactory (within-class correlation coefficient of absolute scores 0·91, and of change scores 0·88). Because of skewness in the data we also calculated Spearman rank correlations (absolute scores 0·90, change scores 0·89).

The groups were well balanced in terms of damage at baseline (figure 3, table 3). 26% versus 22% of patients had no erosions; 23% versus 19% had a total score of 0. The total score had increased significantly more in the sulphasalazine group than in the combined treatment group at 28 weeks (p<0·0001), 56 weeks (p=0·004), and 80 weeks (p=0·01; table 3, figure 3). The differences

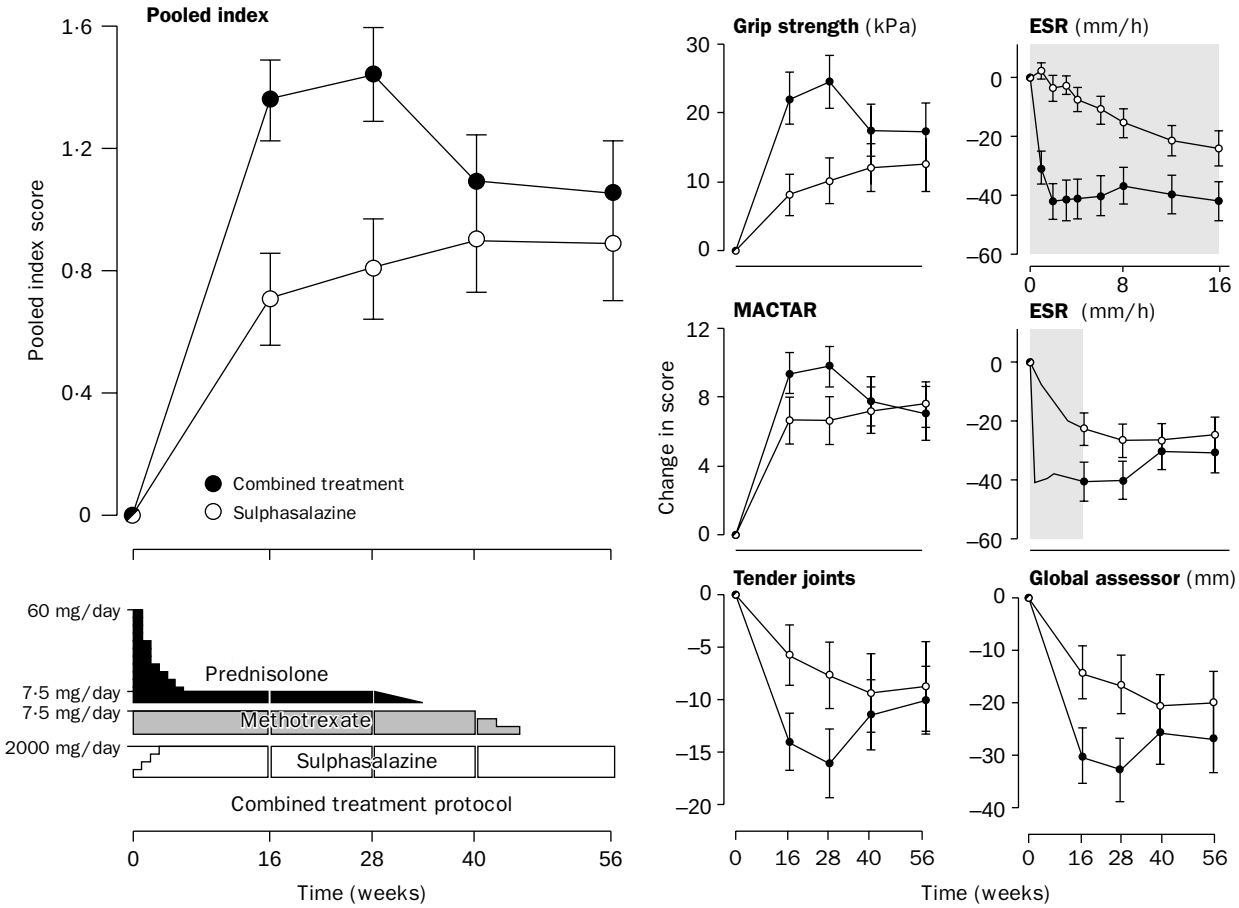

Figure 2: **Clinical outcomes of treatment, expressed as mean (95% CI) pooled index and changes in its component parts**
Positive values indicate improvement in pooled index, grip strength, and MACTAR (McMaster Toronto arthritis) questionnaire. Negative values indicate improvement in the remaining measures. Changes in ESR in first 16 weeks are shown in graph in upper right corner (note different time scale).

between the groups were greatest for increases in the erosion score (table 3). At 28 weeks, 31% of the combined-treatment group versus 13% of the sulphasalazine group had stable scores (p=0·009); at 56 weeks, 19% versus 10% (p=0·23); at 80 weeks, 10% versus 7% (p=0·75). In both groups, patients without erosions at baseline showed little progression over 80 weeks: median increase 2 (0–25).

The findings on new erosive damage appearing in one of eight areas previously free of erosions were similar. After 28 weeks such damage had appeared in median zero areas (0–5) in the combined-treatment group, compared with one (0–6) in the sulphasalazine group (p<0·0001). The corresponding numbers at 56 weeks were zero (0–6) and one (0–7, p<0·0001), and at 80 weeks one (0–7) and two (0–8, p=0·0004).

The damage rates calculated per study period showed slow progression of damage in the combined-treatment group in the first period (baseline to 28 weeks), whereas progression in the sulphasalazine group was more rapid (median increase in total score 0–28 weeks 1 [0–28] in combined-therapy group *vs* 4 [0–44] in sulphasalazine group; p<0·0001). In the second period, in which prednisolone and methotrexate were stopped (28–56 weeks), the rate of progression was again lower in the combined-treatment group than the sulphasalazine group (median increase 1 [0–36] *vs* 2·5 [0–27], p=0·04), but during weeks 56–80 the rate of progression did not differ significantly (1·5 [0–36] vs 2·5 [0–32], p=0·37).

Adjustment for prognostic variables did not change the difference in efficacy between treatments (crude coefficient for the additional effect of combined treatment *vs* sulphasalazine on the log-transformed total score at week 28 −0·302 [SE 0·075], p<0·0001; adjusted coefficient −0·297 [0·062], p<0·0001). In stepwise regression analysis, baseline values for radiological damage, disease activity score, HLA-DR4 genotype, and rheumatoid factor as well as centre significantly affected the progression of radiological damage at week 28. Patients who had higher baseline values for radiological damage and disease activity score and who were positive for HLA DR4 and rheumatoid factor, had higher rates of progression. Again, the effect of treatment was not changed in the model incorporating these factors.

Toxicity

Significantly fewer patients stopped combined treatment than stopped sulphasalazine (table 4, p=0·0008), and combination patients dropped out later. Differences were apparent for both toxic effects and lack of efficacy. For instance, all four withdrawals from the combined-treatment group because of lack of efficacy occurred after week 28, when prednisolone and methotrexate were stopped; by contrast, most of the 19 withdrawals for lack of efficacy in the sulphasalazine group occurred before week 28 (figure 1). The adverse reactions that led to withdrawal of two patients in the combined-treatment group were gastrointestinal-tract complaints and dyspnoea (final diagnosis exacerbation of chronic bronchitis). In the

Clinical outcome measure	Mean (SD) at baseline		28 weeks			p	56 weeks			p
	Combined	SSZ	Mean (SD) change		Mean (95% CI) difference in charge*		Mean SD change		Mean (95% CI) difference in change*	
			Combined	SSZ			Combined	SSZ		
Pooled index†										
Overall value	0	0	1·4 (0·7)	0·8 (0·7)	0·6 (0·4, 0·8)	<0·0001	1·1 (0·8)	0·9 (0·8)	0·2 (−0·1, 0·4)	0·20
Tender joint count	25 (14)	24 (14)	−16 (14)	−8 (14)	8 (4,13)	0·0004	−10 (14)	−9 (19)	1 (−4, 7)	0·62
Grip strength (kPa)†	24 (15)	29 (20)	25 (17)	11 (15)	14 (9,19)	<0·0001	18 (18)	13 (17)	5 (−1,10)	0·09
ESR (mm/h)	57 (34)	53 (32)	−40 (28)	−27 (26)	13 (5,22)	0·002	−31 (28)	−24 (27)	7 (−2, 15)	0·13
Assessor's global assessment (VAS)	53 (24)	51 (22)	−33 (26)	−17 (25)	16 (8,24)	0·0001	−27 (28)	−20 (27)	7 (−15, 20)	0·13
MACTAR questionnaire†	24 (4)	24 (4)	10 (5)	7 (6)	3 (1, 5)	0·0007	7 (7)	8 (6)	−0·5 (−3, 2)	0·62
Other core-set measures										
Pain score (VAS)	55 (21)	54 (22)	−34 (25)	−20 (30)	14 (5,23)	0·002	−23 (29)	−25 (28)	−2 (−11, 7)	0·66
Patient's global assessment (VAS)	47 (20)	52 (19)	−24 (25)	−19 (29)	5 (−4, 14)	0·25	−14 (30)	−21 (31)	−8 (−17, 2)	0·12
Swollen joint count	16 (9)	15 (8)	−10 (8)	−5 (8)	5 (2, 7)	0·001	−7 (7)	−5 (9)	2 (−1, 4)	0·27
Health assessment questionnaire	1·5 (0·7)	1·4 (0·7)	−1·1 (0·8)	−0·6 (0·6)	0·5 (0·3, 0·7)	<0·0001	−0·8 (0·8)	−0·6 (0·7)	0·2 (−0·0, 0·5)	0·06
Disease activity score	4·6 (1·0)	4·5 (1·0)	−2·1 (1·2)	−1·3 (1·2)	0·8 (0·5, 1·2)	<0·0001	−1·4 (1·2)	−1·3 (1·4)	0·1 (−0·4, 0·5)	0·78

SSZ=sulphasalazine alone; VAS=visual analogue scale; MACTAR=McMaster Toronto arthritis questionnaire.
*Combined minus sulphasalazine; positive values indicate better average outcome in combined treatment group.
†Positive values for change indicate improvement,

Table 2: **Main clinical outcomes of treatment after 28 and 56 weeks of combined (n=76) and sulphasalazine (n=79) treatment**

sulphasalazine group the adverse events leading to withdrawal were rashes in four patients, gastrointestinal-tract complaints in two (one with concurrent proteinuria), granulocytopenia with a concurrent increase in aminotransferases in one patient, and thrombocytopenia (diagnosis preleukaemic disease) in one.

The study medication was discontinued and restarted at an adjusted dose according to protocol in five patients. Three of these patients (one in the combined-treatment group) had low granulocyte counts, the other two patients (both combined-treatment group) had high aminotransferase concentrations and gastrointestinal complaints, respectively. The remaining adverse events were not followed by withdrawal of study medication. These included 18 patients (12 combined treatment) with infection, treated as outpatients, 17 patients (nine combined treatment) with gastrointestinal complaints (no ulcer or bleeding); ten (six combined treatment) with cardiovascular disorders, including one myocardial infarction; and eleven (five combined treatment) with skin disorders. Various other complaints and transient laboratory abnormalities were reported in 37 cases (20 combined treatment).

Expected adverse effects such as weight gain and hypertension were monitored at every control visit (ie, at least every 4 weeks); osteoporosis was assessed by twice-yearly bone densitometry where possible (64 combined treatment, 62 sulphasalazine patients assessed). Patients in both the combined-treatment and sulphasalazine groups gained weight (mean gain at 28 weeks 2·5 kg [95% CI 1·8, 3·2] *vs* 0·7 kg [−0·2, 2·2], p=0·002; at 56 weeks 1·7 [0·8, 2·6] *vs* 1·2 [0·2, 2·2] kg, p=0·49). Blood pressure remained stable in both groups. Baseline characteristics and prognosis factors for osteoporosis were balanced and mean initial bone density was normal (1·134 [SD 0·19] g/cm^2 in lumbar spine and 0·920 [0·14] g/cm^2 in femoral neck). Eight women in the combined-treatment group and one in the sulphasalazine group were using hormone replacement therapy. During the first 28 weeks, the mean changes in lumbar bone density change in the combined-treatment and sulphasalazine group (n=64, 62) were −1·2% (−2·0, −0·3) and 0% (−0·9, 0·9) (p=0·06). At 56 weeks, the changes were −1·3% (−2·3, −0·4) and −0·3% (−1·4, 0·8) respectively (p=0·15). In the femoral neck the corresponding bone density changes were −0·6 (−2·1, 0·9) versus −0·7 (−2·1, 0·7) over 28 weeks, and −1·9 (−3·1, −0·7) versus −1·3 (−2·5, −0·1) over 56 weeks (both p>0·2). Eight versus six patients lost more than 5% (mean 8%) of spinal bone; 14 versus nine lost more than 5% (mean 8%) of femoral neck bone. These losses typically occurred in the first 6 months, with stabilisation or improvement thereafter.

Lung function measurements showed no important changes during the first 56 weeks (data not shown).

	Median (range) score[2]		p*
	Combined	SSZ	
Baseline†	n=73	n=74	
Erosion score	2 (0–36)	3 (0–48)	
Narrowing score	1 (0–26)	1 (0–22)	
Total damage score	3 (0–58)	5 (0–48)	
Change at 28 weeks	n=71	n=71	
Erosion score	0 (0–24)	4 (0–26)	<0·0001
Narrowing score	0 (0–11)	1 (0–20)	0·04
Total damage score	1 (0–28)	4 (0–44)	<0·0001
Change at 56 weeks	n=70	n=65	
Erosion score	2 (0–32)	5 (0–32)	0·001
Narrowing score	1 (0–28)	1 (0–30)	0·53
Total damage score	2 (0–43)	6 (0–54)	0·004
Change at 80 weeks	n=65	n=56	
Erosion score	4 (0–46)	7 (0–52)	0·004
Narrowing score	2 (0–35)	2 (0–34)	0·40
Total damage score	4 (0–80)	12 (0–72)	0·01

*Mann-Whitney rank-sum test.
†Patients with baseline and at least one follow-up radiographic assessment.

Table 3: **Radiographic outcome of treatment**

Compliance and protocol violations

Of patients who completed the 56-week treatment protocol, nine (six combined treatment, three

Reason	Combined treatment		Sulphasalazine	
	n	Median (range) time to withdrawal (weeks)	n	Median (range) time to withdrawal (weeks)
Lack of efficacy	4	42 (36–48)	12	17 (16–40)
Adverse reaction	2	16 (3–29)	6	5 (2–31)
Both	. .		2	9·5 (9–10)
Other*	. .		2	28 (16–40)
Protocol violation†	. .		1	50
Total‡	6	38·5 (3–48)	23	16 (2–50)

*One patient emigrated in week 40 of follow-up, one became pregnant.
†Treated with parenteral corticosteroids for pulmonary disease.
‡Difference in total number of withdrawals: p=0·0008.

Table 4: **Reasons for withdrawal of patients from study**

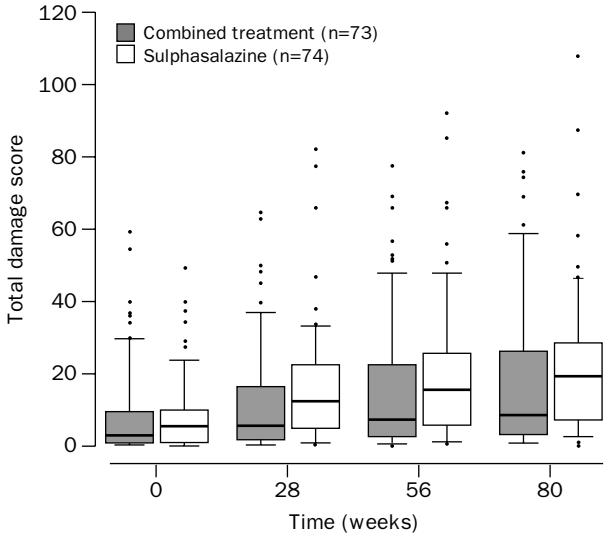

Figure 3: **Effect of treatment on total radiographic damage score**

Box-whisker plots of absolute radiographic damage scores (Sharp van der Heijde method; summed total scores for erosions and joint-space narrowing in hands and feet). Horizontal line in box=median; limits of box=25th and 75th percentiles; whiskers=10th and 90th percentiles; values above and below these plotted separately.

sulphasalazine) were classified as non-compliant—eight were negative for sulphapyridine in at least one of the urine samples taken at weeks 16, 28, and 40; and one did not return medication for pill counts more than once. Fifteen other patients (six combined treatment, nine sulphasalazine) were classified as probably non-compliant. Thus, compliance was deemed satisfactory in 131 patients (85%). Eight patients received intra-articular corticosteroid injections outside the permitted periods (two of them had been withdrawn; three were in combined-treatment group, five in the sulphasalazine group). Eight patients in the sulphasalazine group started treatment with oral corticosteroids after they were withdrawn from the trial. In addition, one patient in the sulphasalazine group was withdrawn because she needed corticosteroids to treat pulmonary disease.

Discussion

The combination of an extended oral pulse or corticosteroids, methotrexate, and sulphasalazine led to an immediate, substantial, and highly significant improvement of disease activity and physical function in most patients with severe, early rheumatoid arthritis. On a low daily maintenance dose of 7·5 mg prednisolone from week 7 onwards, this improvement continued at a slower pace up to week 28, and was almost double that of conventional treatment with sulphasalazine alone in all clinical measures. The study did not have sufficient power to show statistical significance for differences in remission rates. Combined therapy also had beneficial effects on joint damage as shown on hand and foot radiographs. This degree of clinical efficacy could not be maintained by sulphasalazine alone—most of the clinical differences between the groups decreased and were no longer significant after prednisolone was withdrawn, and there were no further changes after methotrexate was stopped. However, from inspection of an area under the curve we suggest that the patients who received combined treatment had major clinical benefit throughout the year. This view is supported by the low withdrawal rate for any reason during the study period. The benefits of combined therapy on radiography persisted up to week 80. We believe, therefore, that this combined therapy can be classified as a disease-controlling antirheumatic therapy.

The differences between combined treatment and sulphasalazine are all the more striking because sulphasalazine alone also performed well as a disease-controlling antirheumatic drug—the onset of action was rapid, the withdrawal rate was low (observed 29%, expected 27–40%), and the radiological progression rate was similar to that in another study in early rheumatoid arthritis.[2] The true clinical relevance of the effects of the combined treatment on radiological progression must be proven by follow-up studies. However, since demonstration of any effect on radiological progression in rheumatoid arthritis is difficult, we believe that the decrease, to a third of that of sulphasalazine—and possibly a sixth of that of "symptom-modifying antirheumatic drugs"[3] such as hydroxychloroquine[2]—will prove clinically relevant.

Withdrawal rates for both toxicity and lack of efficacy were much lower with combined therapy than with sulphasalazine, and expected side-effects (especially of prednisolone such as osteoporosis) were of minor importance. The low withdrawal rate may itself contribute to the differences in efficacy by preventing the loss of antirheumatic effect during the time when treatment is switched from one agent to another. There was a slight increase in infections with combined therapy but none led to (even temporary) protocol interruptions and all could be treated without hospital admission. Such toxicity figures must be interpreted with caution; with its small sample size and short follow-up, a clinical trial is not suited to reliable detection of side-effects that may be important. Given the limited period and dose of the combination, we do not expect important late morbidity. Nevertheless, the study cohort is being followed up so that long-term benefits and risks of the therapy can be assessed. Thus we were able to read, analyse and report the 80-week radiography data ahead of time in response to criticism that 56 weeks of follow-up was too short.

The randomisation procedure of our trial created prognostically similar treatment groups. Protocol violations, contamination, and cointerventions were minor and did not affect the conclusions from intention-to-treat analysis. Compliance was satisfactory, in an admittedly crude assessment. However, concealment of treatment allocation might raise some concerns. The treating rheumatologists responsible for recruitment (but not assessment) could potentially become aware of treatment allocation. However, the randomisation procedure guaranteed that they had no clue to the treatment allocation of subsequent patients. Outcome assessment was fully delegated to independent assessors: they were unaware of the rapid effects of corticosteroids because they were not involved in the care of these patients, and assessed them only at baseline and at weeks 16, 28, 40, and 56. They were asked not to discuss the disease or its treatment with the patients. Since they were health professionals but not physicians, they had less experience of corticosteroid side-effects. The patients were fully informed about the potential side-effects of all the drugs. To protect against unblinding, they were told that response to treatment was variable in onset and efficacy with all three drugs. Although some unblinding due to large differences in efficacy cannot be ruled out, the effects of the subjective clinical measures

were consistent, and reflected those in the objective measures (eg, ESR).

Another concern that might be raised is the method of reading radiographs. To improve precision, these were read without knowledge of the patient's identity or group allocation, but they were ordered in sequence. This approach might be criticised as leading to bias. In general, opinions are divided on the value of having previous information available when a judgment is made. In the case of radiographs in studies of rheumatoid arthritis, and especially in early disease, random-sequence reading introduces a lot of noise, because small changes in positioning can temporarily hide erosions. In any case, both Larsen's original method[20] and the Van der Heijde modification of Sharp's method[2] require sequential reading; these are the methods used in the majority of published studies (although some [eg, Kirwan[5]] did score randomly). In our trial, any bias would work in the same direction in both groups, and would not alter the conclusions based on the differences between the groups.

The eligibility criteria in our trial selected patients with poor a-priori outlooks. For instance, a high proportion of patients had erosive disease at baseline (77%), partly because we included foot radiographs; on the basis of hand radiographs only the proportion of patients with erosive disease would have been 47%. Nevertheless, some patients included might not have needed such an intensive approach as our combined treatment, since predictive variables never provide 100% accuracy.[21] On the other hand, such patients would probably show a good clinical response, and withdrawal of prednisolone and methotrexate would be possible; thus the risks involved in their overtreatment are limited. We arbitrarily excluded patients older than 70, and further study is needed before this therapy can be advised for patients over 70, or for patients with a longer duration of rheumatoid arthritis or concurrent disease. Thus, our results apply to otherwise healthy patients with early and active rheumatoid arthritis treated in a specialist setting. The opportunity to intervene early with second-line antirheumatic drugs relies heavily on the early diagnosis of rheumatoid arthritis and rapid referral of patients; health-care systems should be specifically organised to facilitate this process.

Combination therapy can be applied in many different ways. We chose a step-down strategy with rapidly acting drugs. This approach optimised the chance of efficacy in a potentially limited window of opportunity. Our results support the view that corticosteroids are among the most effective and rapidly working disease-controlling antirheumatic drugs. A meta-analysis has confirmed that low-dose corticosteroids can be beneficial.[22] The toxic effects of corticosteroids may be comparable to those of some other disease-modifying antirheumatic drugs[23] and even NSAIDs, and their use in established rheumatoid arthritis is widespread. However, doubts about the longevity of the effects, and fears of cumulative morbidity have limited their use in early rheumatoid arthritis. The optimum dosing schedule is also unclear.

In 1959 a trial of prednisolone at daily doses of 10–20 mg indicated antirheumatic properties (both clinical and radiological), but with substantial side-effects.[25] Kirwan and colleagues[5] showed an effect of 7·5 mg prednisone daily on the development of radiological damage together with only temporary effect on disease activity measures, and no side-effects. These investigators have since reported that joint destruction recommences after corticosteroids are withdrawn.[26] By contrast, the effect of our combined treatment on the progression of joint destruction persisted for up to 1 year after corticosteroids were stopped. The initially more rapid progression in the sulphasalazine group slowed and approached that of the combined-treatment group with a lag of 1 year. These differences between our study and that of Kirwan might be the result of more effective treatment not only in our experimental group but also in our control group.

Van Schaardenburg and colleagues[27] found only temporary clinical effects of a prednisone regimen starting with 15 mg daily. Other studies with step-down strategies and oral or parental steroid pulses showing limited benefit and troubling rebound effects.[28–30] The limited clinical efficacy of corticosteroids in other trials may be due to the use of doses inadequate to bring the disease under control from the outset. Our results support the concept of step-down bridge therapy, and suggest that immediate and intensive suppression of high damage progression rates by a rapidly acting regimen may be sustained by another regimen with a slower mode of onset (eg, sulphasalazine).

60 mg prednisolone is a high daily dose for rheumatoid arthritis. However, the rapid tapering schedule resulted in a mean daily dose of 12 mg overall, and 7·5 mg daily from week 7 onwards. Also, the initial dose is not high compared with standard (but not always proven) therapy for most other severe autoimmune diseases (eg, myositis, vasculitis, lupus nephritis) and is much lower than the intravenous methylprednisolone pulses that have been tried with limited success for many indications, including rheumatoid arthritis. The tapering schedule after week 28 proved to be too rapid, resulting in partial loss of benefit and some disease flares. This factor may have contributed to the low numbers of lasting remissions. We look forward to further studies with slower tapering schedules.

We chose methotrexate as the second drug in the combination because the onset of effect is rapid. However, in this and another trial, the response to sulphasalazine was as rapid as that to methotrexate.[31] In the design phase, we set a fixed, low dose of methotrexate because little was known about the toxicity of our combination. We would, with the data available, now probably try dose intensification of methotrexate or sulphasalazine in case of suboptimum response (with the risk of additional toxic effects). The value of the combination of methotrexate and sulphasalazine is uncertain.[31–33]. In our study, tapering of methotrexate had little impact on the mean results, although some patients had disease flares, which might be attributable to the withdrawal of prednisolone in the preceding period. The contribution of 7·5 mg methotrexate weekly to efficacy and toxicity was probably small in the second 6 months of treatment. However, whether the efficacy of the full combination in the first 6 months can be equalled by prednisolone/sulphasalazine or prednisolone/methotrexate combinations remains to be seen. In view of the high benefit-risk ratio of our combined treatment in the first 6 months, we believe maintenance of this ratio in the subsequent period is more desirable than reduction of the already low risk in the first 6 months.

To date, most drug combination trials have not shown addition or synergy (ie, benefits equal or better than the sum of benefits attributed to the single drugs). At best, investigators showed some enhanced efficacy at the expense of some extra toxic effects. However, Tugwell and colleagues[23] found that patients with long-standing rheumatoid arthritis who had only a partial response to

methotrexate showed clinically important improvement when cyclosporin was added to their regimen. O'Dell and colleagues achieved 50% improvement in composite symptoms of arthritis with methotrexate, sulphasalazine, and hydroxychloroquine.[34] 80% and 50%, respectively, of patients in these two studies were on low-dose corticosteroid maintenance therapy. Both studies show that substantial improvement is possible in established disease, and that more study on the merits of combination therapy is necessary.

Our study supports the view that corticosteroids in the proper regimen are among the most powerful disease-controlling antirheumatic drugs available. Early and intensive intervention in rheumatoid arthritis with this combination step-down schedule offers additional disease control over an above that of sulphasalazine alone. Damage control persists for up to 1 year after corticosteroids are stopped, but to maintain optimum clinical efficacy after 28 weeks, another tapering schedule is probably necessary.

Contributors

All the authors contributed to design, analysis, and writing the report. Maarten Boers was the principal investigator and study centre coordinator, Maastricht. Arco Verhoeven was trial coordinator, read radiographs, and coordinated laboratory samples. Mart van de Laar was study centre coordinator Enschede/Almelo, and coordinated rheumatoid factor and ANA measurements. Harry Markusse, René Westhovens, Christiaan van Denderen, Derkjen van Zeben, Ben Dijkmans, André Peeters, Piet Jacobs, and Hans van den Brink were study centre coordinators at their respective centres. Hubert Schouten coordinated statistical design and analysis and was a member of the safety committee. Désirée van der Heijde did radiographic training and was quality supervisor. Annelies Boonen read radiographs. Sjef van der Linden was division chief.

Acknowledgments

The COBRA trial was funded by Ontwikkelingsgeneeskunde, Ziekenfondsraad, The Netherlands (grant number 92-045). We thank Pharmacia & Upjohn, Uppsala, Sweden, for providing sulphasalazine; the members of the safety committee A Beysens (clinical pharmacist) A Cats, and H Rasker (rheumatologists); M van der Westerlaken and F de Stoppelaar (clinical pharmacists) for preparation and distribution of the trial medication; M Braeken, L Heusschen-Houben, and all other research personnel; and all participating patients.

References

1 Harris ED Jr. Management of rheumatoid arthritis. In: Kelley WN, Harris ED, Ruddy S, Sledge CB, eds. Textbook of rheumatology. Philadelphia: WB Saunders, 1993; 912–23.

2 van der Heijde DMFM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LBA. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989; i: 1036–38.

3 Edmonds JP, Scott DL, Furst DE, Brooks P, Paulus HE. Antirheumatic drugs: a proposed new classification. *Arthritis Rheum* 1993; **36:** 336–39.

4 Van der Heide A, Jacobs JWG, Bijlsma JWJ, et al. The effectiveness of early treatment with 'second-line' antirheumatic drugs, a randomised, controlled trial. *Ann Intern Med* 1996; **124:** 699–707.

5 Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-dose Glucocorticoid Study Group. *N Engl J Med* 1995; **333:** 142–46.

6 Tugwell P, Boers M. Long acting drug combinations in rheumatoid arthritis: updated overview. In: Wolfe F, Pincus T, eds. Rheumatoid arthritis: pathogenesis, assessment, outcome, and treatment. New York: Marcel Dekker, 1994: 357–71.

7 Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; **31:** 315–24.

8 Schouten HJA. Adaptive biased urn randomisation in small strata when blinding is impossible. *Biometrics* 1995; **51:** 1529–35.

9 Smythe HA, Helewa A, Goldsmith CH. "Independent assessor" and "pooled index" as techniques for measuring treatment effects in rheumatoid arthritis. *J Rheumatol* 1977; **4:** 144–52.

10 Anderson JJ, Felson DT, Meenan RF, Williams HJ. Which traditional measures should be used in rheumatoid arthritis clinical trials: *Arthritis Rheum* 1989; **32:** 1093–99.

11 The cooperating clinics committee of the American Rheumatism Association: a seven-day variability study of 499 patients with peripheral rheumatoid arthritis. *Arthritis Rheum* 1965; **8:** 302–34.

12 Jones E, Hanly JG, Mooney R, et al. Strength and function in the normal and rheumatoid hand. *J Rheumatol* 1991; **18:** 1313–18.

13 Tugwell P, Bombardier C, Buchanan WW, Goldsmith CH, Grace E, Hanna B. The MACTAR patient preference disability questionnaire: an individualized functional priority approach for assessing improvement in physical disability in clinical trials in rheumatoid arthritis. *J Rheumatol* 1987; **14:** 446–51.

14 Boers M, Tugwell P, Felson DT, et al. World Health Organisation and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. *J Rheumatol* 1994; **41** (suppl): 86–89.

15 Siegert CEH, Vleming LJ, Vanderbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. *Clin Rheumatol* 1984; **3:** 305–09.

16 Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; **24:** 1308–15.

17 Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; **38:** 727–35.

18 Van der Heijde DMFM, van 't Hof MA, Van riel PLCM, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990; **49:** 916–20.

19 Van der Sluys Veer G, Soons JWPH. A time-resolved fluoroimmuno assay of the IgM-rheumatoid factor. *Eur J Clin Chem Clin Biochem* 1992; **30:** 301–05.

20 Larsen A, Dale K, Eck M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol* 1997; **18:** 481–91.

21 van Zeben D, Hazes JMW, Zwinderman AH, Vandenbroucke JP, Breedveld FC. Factors predicting outcome of rheumatoid arthritis: results of a follow-up study. *J Rheumatol* 1993; **20:** 1288–96.

22 Saag KG, Criswell LA, Sems KM, Nettleman MD, Kolluri S. Low-dose corticosteroids in rheumatoid arthritis. *Arthritis Rheum* 1996; **39:** 1818–25.

23 Fries JF, Williams CA, Ramey D, Bloch DA. The relative toxicity of disease-modifying antirheumatic drugs. *Arthritis Rheum* 1993; **36:** 297–306.

24 Morrison E, Capell H. Corticosteroids in the management of rheumatoid arthritis. *Br J Rheumatol* 1996; **35:** 1–4.

25 Joint Committee of the Medical Research Council and Nuffield Foundation. A comparison of prednisolone with aspirin or other analgesics in the treatment of rheumatoid arthritis. *Ann Rheum Dis* 1959; **18:** 173–87.

26 Kirwan JR, Hickling P, Jacoby R. Joint destruction recommences after glucocorticoids are withdrawn in early rheumatoid arthritis. *Arthritis Rheum* 1996; **39** (suppl): S218.

27 van Schaardenburg D, Valkema R, Dijkmans BAC, et al. Prednisone treatment of elderly-onset rheumatoid arthritis; disease activity and bone mass in comparison with chloroquine treatment. *Arthritis Rheum* 1995; **38:** 334–42.

28 Ciconelli RM, Ferraz MB, Visioni RA, Oliviera, Atra E. A randomized double-blind controlled trial of sulphasalazine combined with pulses of methylprednisolone or placebo in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1996; **35:** 150–54.

29 van Gestel AM, Laan RFJM, Haagsma CJ, et al. Oral steroids as bridge therapy in RA patients starting with parental gold: a randomised double blind placebo controlled trial. *Br J Rheumatol* 1995; **34:** 347–51.

30 Weusten BLAM, Jacobs JWG, Bijlsma JWJ. Corticosteroid pulse therapy in active rheumatoid arthritis. *Semin Arthritis Rheum* 1993; **23:** 183–92.

31 Haagsma C, van de Putte L, van Riel P. Sulfasalazine, methotrexate and combination in early rheumatoid arthritis, a double blind randomised study. *Arthritis Rheum* 1995; **38** (suppl): S368.

32 Haagsma CJ, van Riel PLCM, de Rooji DJRAM, et al. Combination of methotrexate and sulphasalazine versus methotrexate alone. A randomised open clinical trial in rheumatoid arthritis patients resistant to sulphasalazine therapy. *Br J Rheumatol* 1994; **33:** 1049–55.

33 Dougados M, Cantagrel A, Goupille P, et al. Sulfasalazine, methotrexate, and the combination in early rheumatoid arthritis: a double blind randomized study. *Arthritis Rheum* 1996; **39** (suppl): S103.

34 Tugwell P, Pincus T, Yocum D, et al. Combination with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995; **333:** 137–41.

35 O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; **334:** 1287–91.