Treating rheumatoid arthritis early with disease modifying drugs reduces joint damage: A randomised double blind trial of sulphasalazine vs diclofenac sodium

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Abstract

Background

Current disease management in rheumatoid arthritis (RA) has moved towards "inverting the therapeutic pyramid" by introducing disease-modifying anti-rheumatic drugs (DMARDs) early. Despite the logic of early DMARD therapy, there is a dearth of supportive evidence for this approach. We report a randomised controlled trial comparing sulphasalazine monotherapy with diclofenac monotherapy in early RA. The primary aim was to provide unequivocal evidence that early DMARDs prevent erosive damage. The secondary aim was to evaluate if sulphasalazine used alone has comparable symptomatic benefits to NSAIDs.

Methods

117 patients with RA for under 12 months of diagnosis (mean 2 months) were randomised (62 sulphasalazine; 55 diclofenac). Sulphasalazine patients comprised 76% women, and 58% were rheumatoid factor positive. Diclofenac patients comprised 74% women, and 54% were seropositive. 36% completed 12 months of therapy (16 sulphasalazine; 26 diclofenac); sulphasalazine was given for a mean period of 21 weeks and diclofenac for a mean period of 33 weeks. Results were analysed on an intention to treat basis.

Results

After 12 months the mean number of new erosions in patients randomised to receive sulphasalazine was 2.0 (95%CI 0.9, 3.1) and in patients randomised to receive diclofenac was 7.5 (95%CI 4.1, 10.9; p = 0.002 by Student's unpaired t-test). An analysis of valid compliant completers showed the mean number of new erosions in patients who received 12 months therapy with sulphasalazine was 2.3 (95%CI 0.6, 4.0) and in patients who received 12 months diclofenac was 10.5 (95%CI 5.0, 15.9; p = 0.018 by Student's unpaired t-test). The Ritchie articular index, swollen joint counts and pain scores decreased with both sulphasalazine and diclofenac, with mean falls in both groups of 15-20% at 2 weeks and 30-40% at 4 and 8 weeks. There were no differences between treatments. Disease activity scores showed similar highly significant mean decreases within both treatment groups (P < 0.001 in all cases) of 0.5 at 2 weeks and 1.0 at 4 weeks; at 12 and 26 weeks they were significantly lower with sulphasalazine (p = 0.036 and 0.045). 75% of the patients given sulphasalazine and 65% of those given diclofenac had one or more adverse events with no major differences between treatments.

Conclusions

These results show that an accelerated dosing schedule of sulphasalazine has identical effects to diclofenac in reducing symptoms, indicating it is a rapidly effective DMARD. They also provide unequivocal evidence, analysed on an intention to treat basis, that early treatment with sulphasalazine significantly reduces the extent of radiological progression in active RA.

Key words

Rheumatoid arthritis, treatment, randomised controlled trial, sulphasalazine, early treatment, DMARDs.

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Introduction

Historically non-steroidal anti-inflammatory drugs (NSAIDs) have been the first line treatment for rheumatoid arthritis (RA), while disease modifying anti-rheumatic drugs (DMARDs) have been the second line treatment. One reason for this was the belief that DMARDs had a slow onset of action compared to NSAIDs. This belief was reflected in their alternative categorisation as "slow-acting anti-rheumatic drugs". Another reason was that DMARDs were perceived to be more toxic than NSAIDs.

The current approach to treatment has moved towards "inverting the therapeutic pyramid" by introducing DMARDs at an early stage. One justification is that the onset of joint damage occurs in the early stages of RA (1-4). This can only be prevented if DMARDs are given early. Evidence that DMARDs, when well supervised, have less toxicity that NSAIDs, strengthens the case for their early use (5). Despite the logic of early DMARD therapy, there is a dearth of supportive evidence for this approach from randomised controlled trials.

We report a randomised controlled trial comparing sulphasalazine monotherapy with diclofenac monotherapy in early RA. The primary aim was to provide unequivocal evidence that early DMARDs prevent erosive damage. The secondary aim was to evaluate if sulphasalazine used alone has comparable symptomatic benefits to NSAIDs.

Methods

Study Design

We undertook a 12-month randomised, double blind, placebo-controlled trial that was designed to be analysed on an intention to treat basis. The study was planned between 1989-1992. It was initiated in 1993 and ended in 1997. The analysis was undertaken in 1998 and 1999 and this report was prepared in 2000. Patients were randomised on a centre-by-centre basis. The initial plan was to enrol 130 cases. During the trial it was found that the withdrawal rate was higher than anticipated in the planning phase. For this reason it was considered that the basis for the power calculations had changed; the investigators therefore agreed to end trial entry when between 115-120 cases had been entered. As randomisation was on a centre-by-centre basis this made it likely that the number of cases in each group may be unequal.

Patients

The target population was adults with early RA defined by the American College of Rheumatology criteria (6) attending specialist rheumatology clinics in south east England. The inclusion criteria were: (a) within one year of the diagnosis of RA and (b) evidence of active disease (≥ 6 swollen joints, ≥ 6 tender joints and a disease activity score (DAS) (7) ≥ 3.0). Exclusion criteria were (a) previous DMARD therapy, (b) hypersensitivity to sulphonamides, (c) women at risk of pregnancy and (d) other serious diseases (such as severe cardiac or renal disease). The study protocol was approved by local research ethics committees in all participating hospitals and all patients gave informed written consent.

Treatments

Patients were randomised to receive either sulphasalazine (enteric coated 1 gm daily for two weeks followed by 2 gm daily) or diclofenac sodium tablets 100 mg daily. Patients received matched placebos in a double dummy design taking one active and one placebo treatment. Patients were allowed paracetamol, dextropropoxyphene or dihydrocodeine for analgesia. No other anti-rheumatic drugs or NSAIDs were given. Systemic and intra-articular corticosteroids were not permitted during the study. If a patient withdrew from the study, trial medications were stopped and alternative treatments given according to the supervising rheumatologist's preference, including the use of any DMARD. There were no specific treatment recommendations for withdrawn patients.

Table I. Baseline characteristics of groups. Mean and 95% confidence intervals are shown.

Variable	Sulphasalazine		Diclofenac	
	Mean	95% CI	Mean	95% CI
Age (yrs)	56.5	53.0, 60.0	57.6	56.3, 58.9
Weight (kg)	73.2	69.7, 76.7	70.5	69.7, 71.3
Disease activity score	5.0	4.8, 5.2	5.3	5.2, 5.4
Ritchie index	19.7	17.6, 21.8	23.7	23.7, 23.7
Number of swollen joints	20.9	18.7, 23.1	22.1	21.0, 23.2
Patient's global disease activity (mm)	53.2	48.5, 57.9	55.6	54.8, 56.4
Pain (mm)	63.5	56.6, 70.4	63.5	61.6, 65.4
Morning stiffness (min)	188	119, 257	229	228, 230
HAQ score	1.1	0.9, 1.3	1.3	1.0, 1.6

Assessments

Disease activity was assessed using components of the EULAR core data set 8, initially and after 3, 6 and 12 months. This included the numbers of tender and swollen joints, the Ritchie articular index, pain score (on a 100 mm visual analogue scale), patient global assessment of disease activity (on a 100 mm visual analogue scale), health assessment questionnaire (HAQ), and erythrocyte sedimentation rate (ESR). Plain antero-posterior X-rays of the hands, wrists and feet were taken at 0, 6 and 12 months according to international standards (8) and were scored using Sharps method (9) by a blinded, independent assessor (MJP).

Patients had safety monitoring of their blood counts at monthly intervals in line with current clinical practice. When a patient withdrew from the study due to side effects or active disease, they were followed up as per protocol unless consent was withdrawn.

Analysis

Patients withdrawn from the study were followed up as per protocol. The study was analysed on an intention to treat basis. Mean values and 95% confidence intervals were calculated using SPSS. The primary outcome measure was the number of new erosions on hand and feet x-rays during 12 months. The intention in the protocol was to analyse all X-rays that were available on an intention to treat basis without making any special allowance for those patients in whom X-rays were not available. Treatment groups were compared by unpaired t-tests and Chi-squared tests (for numbers of patients with new erosions grouped as none, 1-5 and over 5).

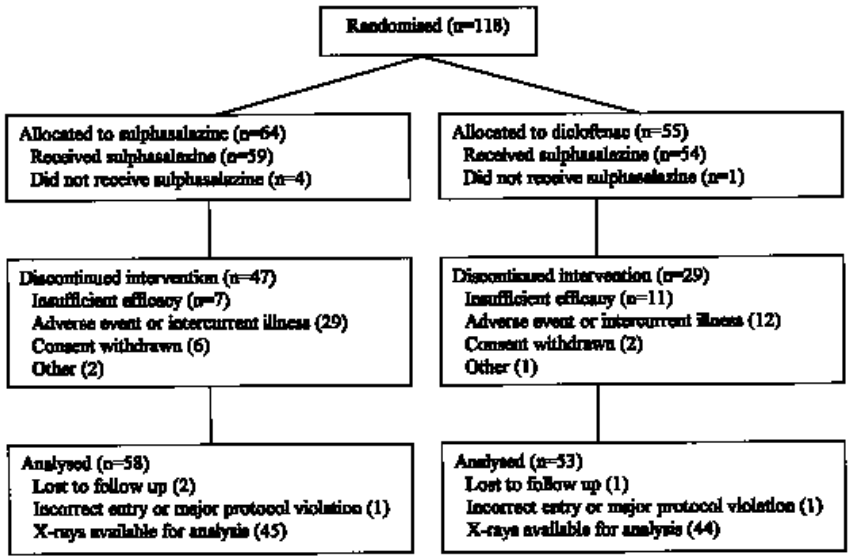


Fig. 1. Flow diagram for patients in the trial.

Results

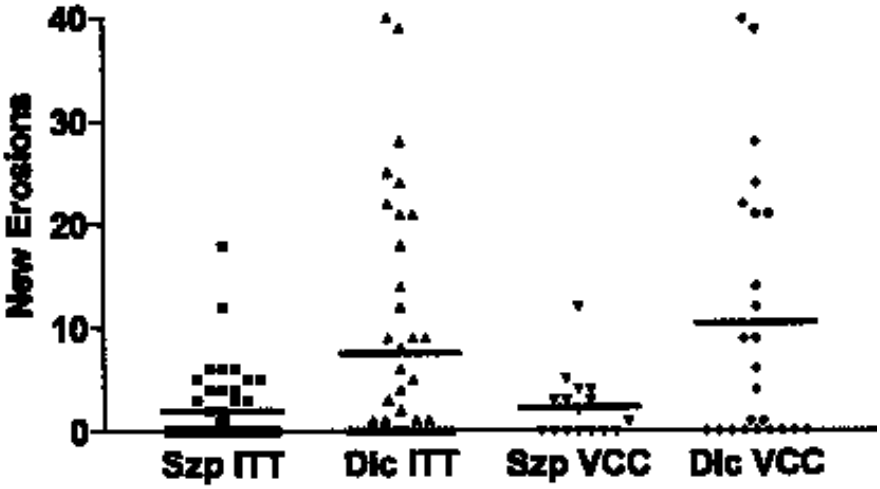
Treatment groups

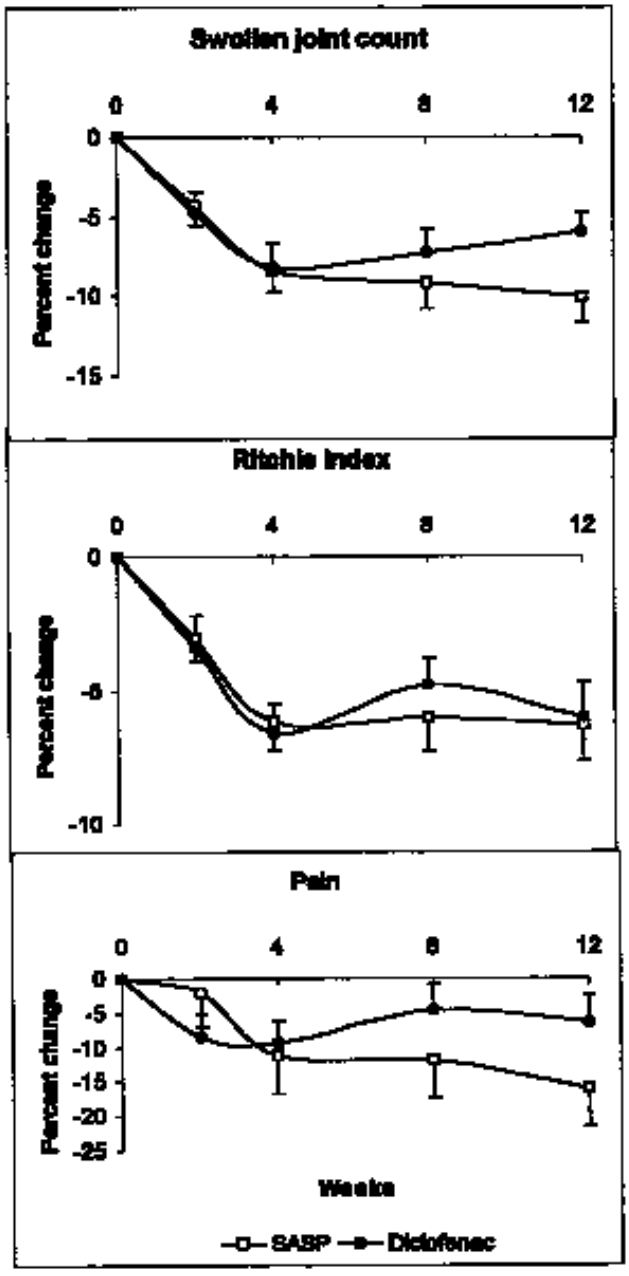
117 patients were randomised, 62 to sulphasalazine and 55 to diclofenac: 59 randomised to sulphasalazine and 54 randomised to diclofenac received at least one dose of therapy. The progress of patients through the study in shown in Figure 1. The sulphasalazine group comprised 45 (76%) women and 14 (24%) males; 34 (58%) were positive for rheumatoid factor. The diclofenac group comprised 40 (74%) women and 14 (26%) males; 29 (54%) were positive for rheumatoid factor. Details of the demographic and clinical variables are summarised in Table I. There were differences between groups. The diclofenac group had marginally higher DAS scores and definitely higher Ritchie indices. Baseline mean total x-ray scores in the sulphasalazine group were 4.1 (SE 0.8) and in the diclofenac group were 3.6 (SE 0.8). Respective mean erosion scores for the sulphasalazine and diclofenac groups were 1.2 (SE 0.4) and 1.2 (SE 0.4) in the hand and were 0.8 (SE 0.3) and 0.5 (SE 0.2) in the feet.

All patients were randomised within 12 months of the diagnosis of RA. The median time from diagnosis was 1.8 months (in both groups) with a range of 0.1 - 11.4 months. The median duration of symptoms related to RA present prior to diagnosis was 5 months in both groups).

Duration of therapy

Therapy was given for a mean of 21 weeks with sulphasalazine and 33 weeks with diclofenac. Forty-two (36%) patients completed 12 months of therapy (16 sulphasalazine and 26 diclofenac) and 75 (64%) were withdrawn (46 sulphasalazine and 29 diclofenac). Forty-eight patients (33 sulphasalazine and 15 diclofenac) received less than 10 weeks of therapy





and 24 patients (10 sulphasalazine and 14 diclofenac) received 10-48 weeks therapy.

The reasons for withdrawal were inefficacy (18 cases), adverse events or intercurrent illness (41), incorrect study entry (2),withdrawn consent (8), lost to follow up (3) and unclassified (3). Withdrawal due to the development of adverse events was 46% in the sulphasalazine and 21% in the diclofenac group. In contrast, withdrawal due to insufficient efficacy was 11% for the sulphasalazine group and 20% for the diclofenac group.

There was no evidence that those patients who completed 12 months of treatment had different initial disease activity from the other cases. The valid compliant completers in whom x-ray scores were available and were randomised to receive sulphasalazine had initial mean Disease Activity Scores of 5.1 (95% confidence intervals 4.5, 5.6) and those randomised to receive diclofenac had mean scores of 5.2 (95% confidence intervals 4.7, 5.6).

Effects on X-ray damage

Complete hand x-rays (at 0, 6 and 12 months) were available in 45 (73%) cases given sulphasalazine and 44 (80%) diclofenac. Complete feet x-rays were available in 42 (67%) of those given sulphasalazine and 43 (78%) of the diclofenac cases. Both hands and feet x-rays were available in 41 (63%) sulphasalazine and 42 (76%) diclofenac treated cases.

After 12 months the mean number of new erosions in patients randomised to receive sulphasalazine was 2.0 (95%CI 0.9, 3.1) and in patients randomised to receive diclofenac it was 7.5 (95%CI

Fig. 2. (a) Numbers of new erosions developing over 12 months in patients randomised to receive sulphasalazine (Szp) or Diclofenac (Dic). An Intention To Treat analysis showed a significant difference between groups (p = 0.002 by Student's unpaired t-test)). A Valid Compliant Completer (VCC) analysis also showed a significant difference between groups (p = 0.018 by Student's unpaired t-test). Bars indicate mean results.
(b) Changes in symptoms of synovitis over 8 weeks.

Table II. Number of patients with new erosions in hands and feet at 12 months.

Group	New erosions	Sulphasalazine	Diclofenac	Significance
Intention to Treat	None	27	19	^{2} = 8.3
	1-5	13	8	DF=2
	> 5	5	16	P ≤ 0.025
Valid Compliant Completer	None	7	9	^{2} = 10.6
	1-5	8	3	DF = 2
	> 5	1	12	P ≤ 0.001

4.1, 10.9). This difference on the intention to treat analysis was significant (p = 0.002 by Student's unpaired t-test; Fig. 2). An additional analysis of valid compliant completers showed that the mean number of new erosions in patients who received 12 months of therapy with sulphasalazine was 2.3 (95%CI 0.6, 4.0) and in patients who received 12 months diclofenac it was 10.5 (95% CI 5.0, 15.9). This difference was also significant (p = 0.018 by Student's unpaired t-test).

An alternative analysis categorised patients into those who developed no new erosions, 1-5 new erosions or over 5 new erosions (Table II). This also showed significant differences between treatment groups. Significantly fewer patients receiving sulphasalazine developed more than 5 new erosions at 12 months in both an intention to treat and valid compliant completer analyses. Interestingly 9 of 24 patients (38%) receiving diclofenac and 7 of 16 (44%) receiving sulphasalazine for 12 months developed no new erosions.

A more detailed analysis of changes in the erosion scores (hands), joint space scores (hands) and total joint scores (hands and feet) is shown in Table III, with patients divided into valid compliant completers, those who stopped therapy for any reason and all cases (intention to treat). There were few differences between groups for joint space scores. Erosion scores (hands) and total joint scores showed broadly similar effects. Patients receiving diclofenac and completing 12 months treatment had high erosion scores and total joint scores compared to those treated with sulphasalazine. In comparison those patients randomised to receive diclofenac who stopped therapy for whatever reason did not have high scores.

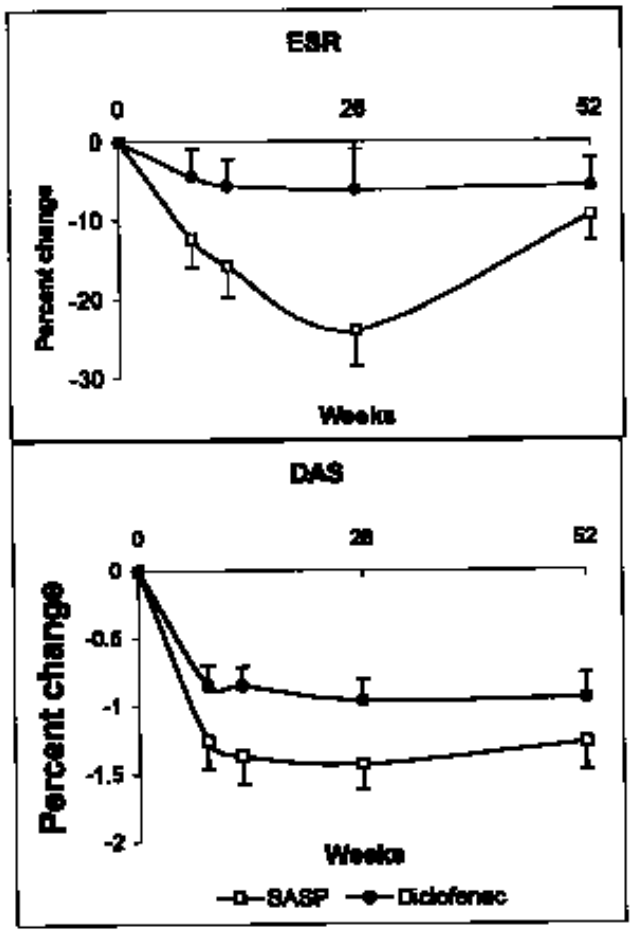


Fig. 3. Changes in the erythrocyte sedimentation rate (ESR) and Disease Activity Score (DAS) over 12 months.

Effect on symptoms

Results for the Ritchie articular index, swollen joint counts and pain scores were available in 43-59 patients randomised to sulphasalazine and 49-54 patients randomised to diclofenac at all time points, whether or not the patients were still receiving therapy. All three assessments decreased with both sulphasalazine and diclofenac (Fig. 3). There were mean falls within groups in the region of 15-20% at 2 weeks and 30-40% at 4 and 8 weeks. These improvements were maintained for 52 weeks. Patient and physician global assessments, morning stiffness and HAQ scores did not clinically relevant changes within or between groups.

Effect on ESR and DAS

Results for DAS and ESR were available in 43-59 patients randomised to sulphasalazine and 49-54 patients randomised to diclofenac at all time points, whether or not the patients were still receiving therapy. The sulphasalazine group showed large mean falls in the ESR from week 8 that continued until week 52. The diclofenac group showed only small falls.

DAS scores showed significant mean falls in both treatment groups (P < 0.001 in all cases) of 0.5 at 2 weeks and 1.0 at 4 weeks. DAS scores subsequently diverged between groups (Fig. 3); at 12 and 26 weeks they were signi-

Table III. Analysis of X-ray scores in valid compliant completers (VCC), patients who stopped therapy (for any reason) before 12 months, and by intention to treat (ITT). Erosion scores and joint space scores are shown in the hands and total joint scores in the hands and feet. Mean values and 95% confidence intervals are shown.

Drug			Erosions Score (Hand)				Joint Space (hands)				Total Joint Score (hands and feet)			
			Initial	6 mth	12 mth	12 mth change	Initial	6 mth	12 mth	12 mth change	Initial	6 mth	12 mth	12 mth change
Sulphasalazine	VCC	Mean	0.69	1.31	1.50	0.81	2.44	3.25	3.88	1.44	4.81	6.88	9.33	4.20
		95% CI	-0.13	0.37	0.44	0.22	0.55	1.01	1.27	0.26	1.61	3.03	4.82	1.96
			1.50	2.26	2.56	1.40	4.32	5.49	6.48	2.61	8.01	10.72	13.85	6.44
	Stopped	Mean	1.52	1.93	2.57	1.24	3.21	3.72	5.25	1.86	6.70	7.14	10.61	3.72
		95% CI	0.19	0.26	0.25	0.19	1.92	2.21	3.05	0.06	3.15	3.41	5.14	1.21
			2.84	3.60	4.89	2.29	4.50	5.23	7.45	3.66	10.26	10.88	16.07	6.24
	ITT	Mean	1.22	1.71	2.18	1.09	2.93	3.56	4.75	1.71	6.00	7.05	10.16	3.89
		95% CI	0.36	0.64	0.73	0.42	1.93	2.38	3.16	0.55	3.61	4.46	6.49	2.17
			2.08	2.78	3.63	1.76	3.93	4.73	6.34	2.88	8.39	9.63	13.83	5.61
Diclofenac	VCC	Mean	1.13	4.88	8.96	7.83	2.00	3.29	3.54	4.46	5.25	7.22	8.00	12.25
		95% CI	0.11	1.58	3.47	3.16	0.50	1.82	1.87	2.68	1.96	3.12	3.36	5.75
			2.14	8.17	14.45	12.50	3.50	4.76	5.21	6.24	8.54	11.31	12.64	18.75
	Stopped	Mean	1.35	2.10	3.40	2.05	2.90	3.50	5.30	2.40	5.78	7.32	12.16	6.68
		95% CI	0.06	0.23	1.02	0.26	0.83	1.23	2.02	0.67	2.41	3.60	5.94	1.90
			2.64	3.97	5.78	3.84	4.97	5.77	8.58	4.13	9.14	11.03	18.38	11.47
	ITT	Mean	1.23	3.61	6.43	5.20	2.41	3.84	6.05	3.64	5.48	10.09	17.07	11.72
		95% CI	0.48	1.71	3.33	2.55	1.24	2.02	3.39	1.62	3.26	5.97	10.49	6.32
			1.98	5.52	9.53	7.86	3.58	5.66	8.70	5.65	7.69	14.21	23.65	17.12

ficantly lower in the sulphasalazine group ($p = 0.036$ and 0.045 respectively). At 52 weeks the mean DAS scores in both groups remained significantly below baseline values ($p < 0.001$ in both groups), but they were not significantly different between groups.

Clinical outcomes at 12 months

Final values and decreases over 12 months in the principal clinical outcome measures analysed by both intention to treat analysis and valid compliant completers are shown in Table IV. Mean final disease activity scores, swollen joint counts, patient global assessments and HAQ scores in patients randomised to receive sulphasalazine were 80-91% of mean values compared with patients randomised to receive diclofenac in the intention to treat analysis. In the valid compliant completer analysis, cases given sulphasalazine had mean values that were 65-82% of those treated with diclofenac. There were broadly similar changes in these clinical outcome measures over 12 months, with the exception of HAQ scores, which did not fall more in patients receiving sulphasalzine. In all cases the 95% confidence intervals overlapped between groups, indicating these differences were not significant.

Adverse events

44 (75%) patients given sulphasalazine and 35 (65%) given diclofenac reported 160 and 120 adverse events, respectively. Gastro-intestinal adverse events predominated; 26 (44%) patients given sulphasalazine and 17 (32%) given diclofenac reporting 70 and 38 adverse gastro-intestinal events respectively. Nausea was particularly common with sulphasalazine (15 cases compared to 4 with diclofenac). Two patients given diclofenac developed anaemia and there was a single case with leucopenia and thrombocytopenia given sulphasalazine. Four patients had serious medical events (myocardial infarction and *herpes zoster* with sulphasalazine; anaemia and prostatic cancer with diclofenac).

Discussion

There is substantial evidence from individual randomised controlled trials (10-23), open clinical studies (24-26) and meta-analyses (27) that sulphasalazine is an effective DMARD in terms of reducing disease activity. There is also evidence that it is effective in combination with other DMARDs (28, 29). Our results extend the evidence-base by showing that, with an accelerated dosing schedule, sulphasalazine has identical swift beneficial effects to an NSAID in reducing symptoms. It is therefore a rapidly effective DMARD. The implication of our results is that DMARDs are not slow-acting drugs, an interpretation that is in keeping with the equally rapid onset of action of leflunomide (22).

There is less evidence about the effects of sulphasalazine on joint damage. Two studies report significant reductions in erosive damage with sulphasalazine compared to placebo (22) and hydroxychloroquine (11) respectively, but another report in early RA showed no significant benefit when compared with placebo (17). Comparative studies against other effective DMARDs are not able to answer this question. Our results provide unequivocal evidence, analysed on an intention to treat basis, that early treatment with sulphasalazine significantly reduces the extent of

radiological progression in patients with active RA.

This trial used the standard dose of sulphasalazine (2 gm daily). There is evidence that some patients show further improvements with higher doses (up to 3 gm daily). It could therefore be argued that our results under-estimate the optimal efficacy of sulphasalazine. We decided not to use a variable dosing schedule with patients able to receive the highest dose of sulphasalazine. Firstly, because such a therapeutic regimen is difficult to implement in a multicentre study using a double-dummy design. Secondly because we rarely if ever use 3 gm daily, and such a dosing schedule would have been irrelevant for our own routine practice.

From one viewpoint this study supports starting DMARD therapy as early as possible, in keeping with the concept of inverting the therapeutic pyramid first proposed by Wilske (30). An alternative interpretation is that the only group to have a substantial risk of developing multiple new erosions were patients remaining on diclofenac for 12 months. Twenty-one of 88 (24%) patients with X-rays available developed over 5 erosions at 12 months; 12 of these (14% of all cases) were valid compliant completers randomised to receive diclofenac. The latter interpretation suggests that the key issue is to avoid extensive delay in starting DMARD therapy rather than initiating it at the first possible opportunity.

Despite such positive findings, DMARD monotherapy is not an optimal approach for achieving long-term control in many patients with early RA. None of our patients entered remission, and 9 of the 16 (56%) valid compliant completers on sulphasalazine developed one or more new erosions. Some of these cases may benefit from combinations of two or more DMARDs. However, 9 of 24 (38%) valid compliant completers who received diclofenac developed no new erosions and giving these cases aggressive therapy risks significant adverse reactions without any obvious therapeutic benefit.

Ideally we need to identify individual risk factors for developing erosions in early RA and use these to optimise therapy. Some groups report apparent success in identifying such risk factors (31), while others have been less convinced (32); at present, the position is undecided. We examined our data to see if there were any predictive factors, such as initial disease activity scores or rheumatoid factor status, which could be used to identify patients most at risk of progressive erosive disease and found none. However our study was neither powered not designed to include such subgroup analysis, and our negative findings are not conclusive (and have therefore not been reported in detail). Large observational studies are needed to provide definitive answers.

Seventy-five (64%) patients withdrew from the treatment they were randomised to receive, including 46 randomised to sulphasalazine and 29 randomised to diclofenac. There are several explanations for this high withdrawal rate. Adverse events accounted for many withdrawals and these may have been exacerbated by the accelerated treatment regimen with sulphasalazine, especially early gastro-intestinal adverse effects. Inefficacy accounted for 18 withdrawals and the absence of NSAIDs in patients randomised to sulphasalazine may have been relevant. Finally we believe that in the south east England patients have hidden concerns about long-term clinical trials research, which may partly explain the 8 patients who withdrew consent during the trial. By contrast the retention of patients on diclofenac was much higher than previously quoted for clinical trials of DMARDs involving placebo therapy, especially the studies of Pullar and Capell from the 1980's (33) in which virtually all cases given placebo therapy withdrew from treatment. Most patients who withdrew from the treatment they were randomised to receive subsequently were given other DMARDs. We have not attempted to analyse the effects of such subsequent DMARD therapy, as it is not possible to do so in a scientifically rigorous manner. However it is noteworthy that patients randomised to receive diclofenac who discontinued therapy had less erosive damage, probably because they received had DMARDs. However, this will tend to underestimate the effect of sulphasalazine and should not affect our main conclusion.

There has been intense debate in recent years about the ethics of placebo-controlled trials in RA, led by Pincus (34), a debate that took place some years after our trial was designed and initiated. Our own view is that the case against placebo therapy is weak. We have independently surveyed our clinic patients and found that a substantial majority approve of placebo therapy. Moreover without placebo-controlled trials it would have been impossible to determine whether or not a new DMARD like leflunomide was effective; with this drug the comparative trial against methotrexate gave inconclusive results (35). Furthermore there is no evidence that any patient in this trial had a long-lasting adverse consequence, though very long-term follow-up would have been needed to fully confirm this. There is no doubt that our trial was ethical given the knowledge and beliefs prevailing when it was set up, though we have no wish to replicate it in the future. The challenge for future trials is to improve the results of treatment so that no patients given DMARDs have progressive erosive disease, without producing excessive toxicity. As many patients given only an NSAID do not have erosive damage, treatment that risks substantial toxicity may not be indicated.

A final important practical question is how to reduce the delay in making the diagnosis of RA, which was fairly common in our cases. Delay may arise from patients seeking medical help late or subsequent delayed referral to a rheumatologist. Clearly, the public needs to be better informed about the symptoms and benefit of early treatment in RA. Since the management of RA is regarded as a specialist issue, developing local guidelines for the early referral of inflammatory arthritis should

be a priority for hospitals, with protocol-defined early RA established where possible to optimise the clinical pathways followed by RA patients.

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