Sulfasalazine for treating rheumatoid arthritis (Review)

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[Intervention Review]

Sulfasalazine for treating rheumatoid arthritis

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ABSTRACT

Background

Sulfasalazine has become a common second line drug (DMARD) for the treatment of rheumatoid arthritis (RA).

Objectives

To estimate the short-term efficacy and toxicity of sulfasalazine for the treatment of rheumatoid arthritis (RA).

Search methods

We searched the Cochrane Musculoskeletal Group trials register, and Medline, up to July 1997, using the search strategy developed by the Cochrane Collaboration (Dickersin 1994). The search was complemented with bibliography searching of the reference list of the trials retrieved from the electronic search. Key experts in the area were contacted for further published and unpublished articles.

Selection criteria

All randomized controlled trials (RCTs) and controlled clinical trials (CCTs) comparing sulfasalazine against placebo in patients with RA.

Data collection and analysis

Two reviewers determined the studies to be included based on inclusion and exclusion criteria (GW, MSA). Data were independently abstracted by two reviewers (EB, MSA), and checked by a third reviewer (BS) using a pre-developed form for the rheumatoid arthritis sub-group of the Cochrane Musculoskeletal Group.

The same two reviewers, using a validated scale (Jadad 1996) assessed the methodological quality of the RCTs and CCTs independently. Rheumatoid arthritis outcome measures were extracted from the publications. The pooled analysis was performed using standardized mean differences (SMDs) for joint counts, pain, and global and functional assessments. Weighted mean differences (WMDs) were used for erythrocyte sedimentation rate (ESR). Toxicity was evaluated with pooled odds ratios (OR) for withdrawals. A chi-square test was used to assess heterogeneity among trials. Fixed effects models were used throughout and random effects for outcomes showing heterogeneity.

Main results

Six trials, including 468 patients were included. A statistically significant benefit was observed for sulfasalazine when compared to placebo for tender and swollen joint scores, pain and ESR. The standardized weighted mean difference between treatment and placebo was -0.49 for tender and swollen joint scores, and -0.42 for pain. The difference for ESR was -17.6mm. Withdrawals from adverse reactions were significantly higher in the sulfasalazine group (OR=3.0). Patients receiving placebo were four times more likely to discontinue treatment because of lack of efficacy than patients receiving sulfasalazine.

Authors' conclusions

Sulfasalazine appears to have a clinically and statistically significant benefit on the disease activity of patients with RA. Its effects on overall health status and radiological progression are not clear at this time, but would appear to be modest.

PLAIN LANGUAGE SUMMARY

Sulfasalazine for treating rheumatoid arthritis

Sulfasalazine has become a common second line drug (DMARD) for the treatment of rheumatoid arthritis (RA).

Six trials, including 468 patients were included. A statistically significant benefit was observed for sulfasalazine when compared to placebo for tender and swollen joint scores, pain and ESR. The standardized weighted mean difference between treatment and placebo was -0.49 for tender and swollen joint scores, and -0.42 for pain. The difference for ESR was -17.6mm. Withdrawals from adverse reactions were significantly higher in the sulfasalazine group (OR=3.0). Patients receiving placebo were four times more likely to discontinue treatment because of lack of efficacy than patients receiving sulfasalazine.

Sulfasalazine appears to have a clinically and statistically significant benefit on the disease activity of patients with RA. Its effects on overall health status and radiological progression are not clear at this time, but would appear to be modest.

BACKGROUND

Sulfasalazine has become a common second line drug (DMARD) for the treatment of rheumatoid arthritis (RA), but is more frequently used in some areas of the world such as the United Kingdom as compared to Canada or the United States. Some of the variation in use may relate to the differences in the reported magnitude of clinical benefits across trials.

OBJECTIVES

To evaluate the short-term efficacy and toxicity of sulfasalazine for the treatment of RA, by conducting a systematic review of randomized controlled trials (RCTs) and controlled clinical trials (CCT) comparing sulfasalazine and placebo.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and controlled clinical trials (CCT) , with a minimum duration of the study of 6 months.

Types of participants

Patients with a diagnosis of RA (as stated in the publication)

Types of interventions

Intervention group: sulfasalazine - minimum dosage 1.5 g/day, oral administration
Control group: placebo

Types of outcome measures

1. Efficacy
All the outcome measures in OMERACT 1993 were included for potential analysis, although only some were consistently reported across trials.
OMERACT measures for efficacy include:
a) Number of tender joints per patient
b) Number of swollen joints per patient
c) Pain
d) Physician global assessment
e) Patient global assessment
f) Functional status
g) Acute phase reactants
h) Radiological damage
2. Withdrawals and dropouts - these were analyzed as:
a) Total number of withdrawals and dropouts
b) Number of withdrawals from lack of efficacy
c) Number of withdrawals due to adverse reactions
d) Number of withdrawals due to system-specific adverse reactions (e.g. gastrointestinal, renal, etc.)

Search methods for identification of studies

1. Electronic searches
A comprehensive MEDLINE search was performed using the strategy developed by Dickersin 1994 from 1966 to July 1997.
EMBASE was searched from 1988 to July 1997, with a strategy similar to the one used for MEDLINE
2. Hand searches
Reference lists of all the trials selected through the electronic search were manually searched to identify additional trials.
3. The Cochrane Controlled Trials Register (CCTR) was also searched.

Data collection and analysis

Data extracted from the publications included study characteristics and outcome measures of efficacy and toxicity. Data was extracted by one reviewer and cross checked by a second. (EB, MS)
1. Efficacy
The results on efficacy were analyzed for the 6-month endpoint. Although some trials had longer duration, this endpoint was chosen because it was reported in most of the trials, and was thought to be the minimum required time to adequately assess the efficacy of sulfasalazine.
Six trials were included in the review. Only 4 trials could be evaluated for efficacy by meta-analysis of OMERACT outcome measures (Ebringer 1992, Farr 1995, Hannonen 1993, Williams 1988). The most consistently reported measures were joint scores. The other two trials (Pullar 1983, Skosey 1988) were only pooled to compare withdrawals and dropouts.
When the standard deviation was not reported, we used either the baseline standard deviation or estimated it from the coefficient of variation calculated from the other trials. One trial reported medians and ranges: the medians were entered as means, and the range was divided by 3 to estimate the standard deviation. We thought these procedures would introduce less bias than excluding the trial altogether.
End-of-trial results were pooled as standardized weighted mean differences for joint scores, pain, and global assessments. This was necessary because of the variation in the outcome measures included in each study (e.g. different number of swollen joints). Trial results were entered in RevMan 3.0 using the same direction to enable the pooling of results where the lowest value was improvement and the highest value was worsening. Negative values in standardized weighted means indicate a benefit of the active drug over placebo. ESR results were pooled using a weighted mean difference.
2. Withdrawals and dropouts
Adverse reactions were generally reported as overall results at the end of the trial. We therefore pooled withdrawals and dropouts at the end of the study, although in some cases follow-ups exceeded 6 months. Toxicity was analyzed using a pooled odds ratio for total withdrawals from adverse reactions, and withdrawals for system-specific side-effects.
The heterogeneity of the trials for each pooled analysis was estimated using a chi-square test.
Fixed effects models were used throughout. Random effects models were only used for outcomes showing statistically significant heterogeneity.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Six RCTs and CCTs (Ebringer 1992, Farr 1995, Hannonen 1993, Pullar 1983, Skosey 1988, Williams 1988) met the criteria for inclusion.
Sulfasalazine was administered orally at a dose of 3g/day for one trial (Pullar 1983) and 2g/day for the remaining 5 trials.
One trial had a duration of 48 weeks (Hannonen 1993). Disease activity was reported for the 6-month endpoint. Withdrawals were reported for the duration of the trial and were pooled with the 6-month trials. Another study (Williams 1988) had a duration of 37 weeks and the results reported at this point were pooled with results of the other trials.
Half of the trials were conducted in patients with a disease duration of 5 years or less [Ebringer 1992, Farr 1995, Williams 1988). In these 3 studies and in the study by Hannonen 1993 patients had

not received previous DMARDS. One trial was conducted in seronegative patients (Farr 1995).

Risk of bias in included studies

The methodological quality of the studies was assessed by two of the investigators (EB, MS) using a quality scale validated and published by Jadad (Jadad 1996). This scale includes an assessment of randomization, double-blinding procedures and description of withdrawals. The possible range of scores is 0 (worst) to 5 (best). Three studies had a score of 5, and the remaining had scores of 4, 3 and 2 respectively (see included tables).

Effects of interventions

In the pooled analysis sulfasalazine was statistically significantly superior than placebo for the following OMERACT outcome measures: tender joints, swollen joints, pain and ESR. The standardized weighted mean difference for the tender joint score was -0.49 (95%CI: -0.75; -0.36), for swollen joints -0.49 (95%CI: -0.79; -0.12), and for pain -0.42 (95%CI -0.72;-0.12). The weighted mean difference for ESR between treatment and placebo groups was -17.6mm (95% CI -21.93, -13.23).

Fewer patients could be pooled to evaluate global assessments. Differences between placebo and sulfasalazine did not reach statistical significance. The effect size for the physician's global assessment was -0.22 (95% CI -0.55, 0.10) and for the patient's -0.32 (95% CI -0.64, 0.00).

Analysis of withdrawals and dropouts was available for all trials. Overall, patients on sulfasalazine were less likely to withdraw than those receiving placebo, but the difference only reached borderline significance: OR=0.70 95%CI: 0.48,1.01). Patients on sulfasalazine were significantly less likely to withdraw from lack of efficacy (OR=0.23 95%CI: 0.14,0.37). Adverse reactions requiring withdrawal were 3 times more frequent in the treatment group (22% vs 8%). The most frequent side effects responsible for sulfasalazine discontinuation were gastrointestinal symptoms in 10% of the patients and mucocutaneous reactions in 7%. Four of 205 (2%) evaluable patients receiving sulfasalazine developed hematological abnormalities requiring discontinuation.

Statistically significant heterogeneity was only observed for ESR. A random effects model for this measure produced a similar point estimate with wider confidence intervals: -16.8 (95%CI: -25.7; -7.9).

DISCUSSION

Sulfasalazine was initially used for the treatment of RA several decades ago (Svartz 1948, Kuzell 1950). A few open trials had suggested a beneficial effect, but these results were not confirmed in a subsequent report (Sinclair 1949), and sulfasalazine did not become an accepted drug for the treatment of RA until much later. In 1980, McConkey et al (McConkey 1980) published an open uncontrolled trial suggesting potential benefits. In the past 15 years, several studies have evaluated the efficacy of the drug in patients with RA.

The purpose of this systematic review was to evaluate the efficacy and toxicity of sulfasalazine for the treatment of patients with RA, when compared to placebo. We only included in this review placebo-controlled RCTs and CCTs, reporting results at approximately 6 months. The minimum dosage of sulfasalazine in these trials was the usually accepted, 2g/day. One trial used 3 g/day (Pullar 1983), but no consistent differences in efficacy or toxicity were observed when compared to other studies.

Although some of the major outcome measures in the trials were sufficiently homogeneous to allow pooling, there was some lack of standardization of the outcome measurements and even complete omission of some outcomes in some studies. Many of these studies were all published before the publication of OMERACT and the American College of Rheumatology (ACR) core set of measures for RA (OMERACT 1993, Felson 1993).

We encountered some difficulties in the data extraction given the lack of standardization in the data reported. One trial reported medians and others did not include the end-of-trial standard deviations. We estimated missing data with approximate values derived from the trial per se (e.g. range as a measure of dispersion), or from results from the other trials (e.g. coefficient of variation to estimate standard deviations relative to the mean). Although these procedures may have created some bias, because they were similarly applied to both groups (treatment and control), their overall impact on the estimation of differences between groups is probably small. Our preference was to estimate some of these parameters as opposed to completely excluding some trials.

Statistically significant differences between placebo and sulfasalazine were observed for various measures of disease activity, including tender and swollen joint scores, pain and ESR. The differences in global assessments did not reach statistical significance, but fewer trials evaluated these outcomes. The effect size for joint counts was -0.49, and for pain -0.42 which can be considered as clinically significant effects (Kazis 1989). None of the studies examined functional outcomes with comprehensive functional scales and therefore, this outcome could not be adequately assessed in our meta-analysis. Two studies examined radiological progression. Although no statistically significant differences were observed, the total sample size was small and lacked adequate power.

Overall, patients receiving sulfasalazine were less likely to withdraw from the study, and patients receiving placebo were almost 4 times more likely to withdraw because of lack of effect. Adverse reactions were more frequent in the sulfasalazine group, with most

withdrawals due to gastrointestinal symptoms and skin reactions. Two percent of the patients in the sulfasalazine group discontinued treatment because of hematological side effects. The use of sulfasalazine may be somewhat limited by the high prevalence of adverse reactions; most of these however, appear to be non threatening and self-limited.

The studies pooled generally used similar inclusion criteria, but only one included patients with sero negative RA (Farr 1995), and their results were not substantially different from the other trials. Of interest, half of the trials included patients with relatively short duration of disease, who had not received second line drugs previously. Since patients with early disease may respond better to treatment, it may be difficult to generalize these findings to patients with more advanced disease.

AUTHORS' CONCLUSIONS

Implications for practice

Sulfasalazine appears to be efficacious in the short-term treatment of patients with RA (6 months), and has a clinically and statistically significant benefit on the disease activity of these patients. Its effects on overall health status and radiological progression are not clear at this time, but would appear to be more modest.

Implications for research

Systematic reviews of long-term studies are necessary to better evaluate the effectiveness of sulfasalazine in the long-term. Although its efficacy appears to be clinically significant its effects on global assessments and structural damage are unclear, but appear to be modest. The role of sulfasalazine in combination with other DMARDS appears promising and deserves further study.

The difficulties in obtaining consistent data across trials emphasize the need for guidelines in relation to the reporting of clinical trial results for DMARDS, following an approach as that proposed by CONSORT (Begg 1996).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Danis 1992

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Ebringer 1992

Methods	Randomized allocation Double blind allocation and assessment Sample size at entry: sulfasalazine - 53; placebo - 52
Participants	Patients with active RA Mean age - 53.9 +/- 13.2 Females - not reported Duration of disease - < 12 months Prevalence of RF not reported No concomittant use of steroids or other DMARDS No previous use of DMARDS
Interventions	Sulfasalazine - 2 g /day Treatment duration - 6 months
Outcomes	Tender joints Swollen joints Pain ESR Radiological erosions
Notes	Quality score: 5 Standard deviations estimated from baseline

Risk of bias

Ebringer 1992 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Farr 1995

Methods	Randomized allocation Double blind allocation and assessment Sample size at entry: sulfasalazine - 16; placebo - 16
Participants	Patients with probable active RA Median age: Tx - 53; Con - 42 Median duration of disease - 3yrs Prevalence of RF - 0% (all patients seronegative) No concomittant use of steroids or other DMARDS Previous use of DMARDS - 25%
Interventions	Sulfasalazine - 2 g/day Treatment duration - 6 months
Outcomes	Tender joints ESR
Notes	Quality score: 4 Intent to treat analysis Means & standard deviations estimated from medians and ranges

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hannonen 1993

Methods	Randomized allocation Double blind allocation and assessment Sample size at entry: Sulfasalazine - 38; placebo - 40
Participants	Patients with active RA Mean age - 51.3 Females - 64% Duration of disease - 66.7 months Prevalence of RF - 67% Concomitant use of steriods - 27.6% No concomitant use of other DMARDS No previous use of DMARDS

Hannonen 1993 (*Continued*)

Interventions	Sulfasalazine - 2 g/day Treatment duration - 48wks
Outcomes	Tender joints Swollen joints Pain Physician global Patient global ESR Radiological scores
Notes	Quality score: 5 Intent to treat Standard deviation estimated from baseline and range (for radiological scores) Disease activity measures estimated at 6 months; radiological scores at 48 weeks

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Pullar 1983

Methods	Randomized allocation Double blind allocation and assessment Sample size on entry: sulfasalazine - 30; placebo - 30
Participants	Patients with active RA Mean age - 57 Females - not reported Mean duration of disease - 7.7 yrs Prevalence of RF - 67% No concomittant use of steroids Use of concomitant DMARDS unknown Previous use of DMARDS unknown
Interventions	Sulfasalazine - 3g/day Treatment duration - 24wks
Outcomes	Actual values of outcome measures not reported - only statistical significance of differences between groups reported favouring sulfasalazine (articular index p<0.001; ESR p<0.005) Results pooled only for withdrawals and dropouts
Notes	Quality score: 3

Risk of bias

Pullar 1983 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Skosey 1988

Methods	Double blind allocation and assessment Sample size on entry: Sulfasalazine - 37; placebo - 36
Participants	Patients with active RA Mean age - 52.3 Females - 73.3% Mean duration of disease - 95.2 months Prevalence of RF not reported Use of concomitant steroid or other DMARD not reported Previous use of DMARDS not reported
Interventions	Sulfasalazine - 2 g/day Study included 2 groups with lower dosages not included in our analysis Treatment duration - 28wks
Outcomes	Values of outcome measures not adequately reported for pooling Results pooled only for withdrawals and dropouts
Notes	Quality score: 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Williams 1988

Methods	Randomized allocation Double blind allocation and assessment Sample size on entry: Sulfasalazine - 69; placebo - 51
Participants	Patients with active RA Mean age - 50.5 Females - 59.5% Mean duration of disease - 60 months Prevalence of RF not reported No concomitant use of other DMARDS Concomitant use of steroids not reported No previous use of DMARDS

Williams 1988 (*Continued*)

Interventions	Sulfasalazine - 2gm/day Treatment duration - 37wks
Outcomes	Tender joints Swollen joints Pain Physician global Patient global ESR
Notes	Quality score: 5 37-week endpoint used for 6 months Standard deviation for ESR estimated from other trials

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Jajic 1988	Paper from Yugoslavia - Unable to translate
Neumann 1985	All patients received IV pulses of methylprednisolone throughout the study. Patients in the control group (methylprednisolone alone) only completed 8 wks of treatment
Nishioka 1991	Paper from Japan - unable to translate
Pinals 1986	Inadequate trial duration

DATA AND ANALYSES

Comparison 1. Sulfasalazine vs. placebo - Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tender joints	6	256	Mean Difference (IV, Fixed, 95% CI)	-2.45 [-4.15, -0.74]
2 Number of swollen joints	6	226	Mean Difference (IV, Fixed, 95% CI)	-2.38 [-3.73, -1.03]
3 Pain	6	179	Mean Difference (IV, Fixed, 95% CI)	-8.71 [-14.80, -2.62]
4 Physician global assessment	6	163	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.37, 0.06]
5 Patient global assessment	6	163	Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Functional status	6	12	Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 ESR	6	178	Mean Difference (IV, Fixed, 95% CI)	-17.58 [-21.93, -13.23]
8 Radiological scores	1	73	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-11.13, 3.93]
9 Patients with erosions	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.11, 3.21]

Comparison 2. Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals and dropouts - Total	6	468	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.48, 1.01]
2 Withdrawals due to inefficacy	6	468	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.14, 0.37]
3 Withdrawals due to adverse reactions	6	468	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.01 [1.82, 4.99]
4 Withdrawals due to gastrointestinal adverse reactions	6	392	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.44 [1.12, 5.32]
5 Withdrawals due to skin and mucosal adverse reactions	6	392	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.43 [1.30, 9.09]
6 Withdrawals due to renal adverse reactions	6	392	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.10 [0.00, 5.01]
7 Withdrawals due to liver abnormalities	6	392	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.63 [0.72, 18.23]
8 Withdrawals due to hemaetological adverse reactions	6	392	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.84 [0.48, 16.75]

Analysis 1.1. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 1 Tender joints.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

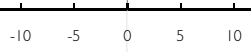
Outcome: 1 Tender joints

Study or subgroup	Sulfasalazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Ebringer 1992	29	5.5 (8)	36	9.2 (9)		-3.70 [-7.84, 0.44]
Farr 1995	16	4 (7)	16	6 (5.3)		-2.00 [-6.30, 2.30]
Hannonen 1993	36	7 (5.2)	40	8.5 (4.2)		-1.50 [-3.64, 0.64]
Pullar 1983	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Skosey 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1988	47	9 (13.2)	32	24 (23.3)		-15.00 [-23.91, -6.09]
Total (95% CI)	**130**		**126**			**-2.45 [-4.15, -0.74]**

Heterogeneity: Chi^2 = 8.77, df = 3 (P = 0.03); I^2 =66%

Test for overall effect: Z = 2.81 (P = 0.0049)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 2 Number of swollen joints.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

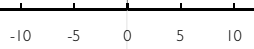
Outcome: 2 Number of swollen joints

Study or subgroup	Sulfasalazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Ebringer 1992	29	9.9 (10)	36	16.4 (13)		-6.50 [-12.09, -0.91]
Farr 1995	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Hannonen 1993	36	4 (3.3)	40	6 (3.3)		-2.00 [-3.49, -0.51]
Pullar 1983	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Skosey 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1988	47	10 (8.8)	32	13 (8.8)		-3.00 [-6.95, 0.95]
Total (95% CI)	**115**		**111**			**-2.38 [-3.73, -1.03]**

Heterogeneity: Chi^2 = 2.43, df = 2 (P = 0.30); I^2 =18%

Test for overall effect: Z = 3.45 (P = 0.00055)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 3 Pain.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

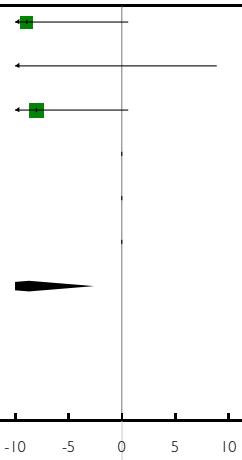
Outcome: 3 Pain

Study or subgroup	Sulfasalazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Ebringer 1992	29	19.9 (17)	36	28.8 (22)		-8.90 [-18.38, 0.58]
Farr 1995	16	21 (27)	16	33 (33)		-12.00 [-32.89, 8.89]
Hannonen 1993	36	22 (20)	40	30 (18)		-8.00 [-16.59, 0.59]
Pullar 1983	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Skosey 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**84**		**95**			**-8.71 [-14.80, -2.62]**

Heterogeneity: $Chi^2 = 0.12$, df = 2 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 2.80 (P = 0.00511)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 4 Physician global assessment.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

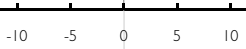
Outcome: 4 Physician global assessment

Study or subgroup	Sulfasalazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Ebringer 1992	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Farr 1995	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Hannonen 1993	36	2.5 (0.7)	40	2.8 (0.6)		-0.30 [-0.59, -0.01]
Pullar 1983	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Skosey 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1988	47	2 (0.7)	32	2 (0.7)		0.0 [-0.31, 0.31]
Total (95% CI)	**87**		**76**			**-0.16 [-0.37, 0.06]**

Heterogeneity: Chi^2 = 1.86, df = 1 (P = 0.17); I^2 =46%

Test for overall effect: Z = 1.46 (P = 0.15)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 5 Patient global assessment.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

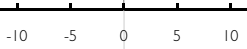
Outcome: 5 Patient global assessment

Study or subgroup	Sulfasalazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Ebringer 1992	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Farr 1995	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Hannonen 1993	36	2.3 (0.8)	40	2.8 (0.7)		-0.50 [-0.84, -0.16]
Pullar 1983	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Skosey 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1988	47	2 (0.7)	32	2 (0.7)		0.0 [-0.31, 0.31]
Total (95% CI)	**87**		**76**			**-0.23 [-0.46, 0.00]**

Heterogeneity: Chi^2 = 4.48, df = 1 (P = 0.03); I^2 =78%

Test for overall effect: Z = 1.96 (P = 0.050)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 6 Functional status.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

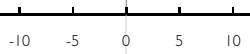
Outcome: 6 Functional status

Study or subgroup	Sulfasalazine		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Ebringer 1992	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Farr 1995	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Hannonen 1993	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Pullar 1983	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Skosey 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**6**		**6**			**0.0 [0.0, 0.0]**

Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 7 ESR.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

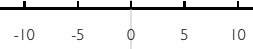
Outcome: 7 ESR

Study or subgroup	Sulfasalazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Ebringer 1992	28	11 (5.5)	33	27.6 (14)		-16.60 [-21.79, -11.41]
Farr 1995	16	28 (26)	16	28.5 (29)		-0.50 [-19.58, 18.58]
Hannonen 1993	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Pullar 1983	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Skosey 1988	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1988	47	23 (11.5)	32	47 (23.5)		-24.00 [-32.78, -15.22]
Total (95% CI)	**94**		**84**			**-17.58 [-21.93, -13.23]**

Heterogeneity: Chi² = 5.27, df = 2 (P = 0.07); I² =62%

Test for overall effect: Z = 7.92 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 8 Radiological scores.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

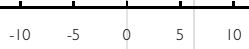
Outcome: 8 Radiological scores

Study or subgroup	Sulfasalazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hannonen 1993	36	3.5 (10.7)	37	7.1 (20.7)		100.0 %	-3.60 [-11.13, 3.93]
Total (95% CI)	**36**		**37**			**100.0 %**	**-3.60 [-11.13, 3.93]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.94 (P = 0.35)

Test for subgroup differences: Not applicable

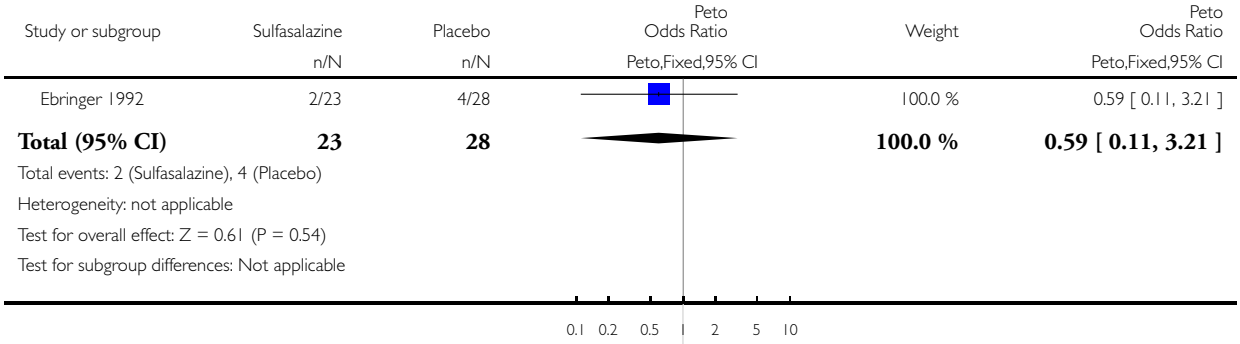


Analysis 1.9. Comparison 1 Sulfasalazine vs. placebo - Efficacy, Outcome 9 Patients with erosions.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 1 Sulfasalazine vs. placebo - Efficacy

Outcome: 9 Patients with erosions

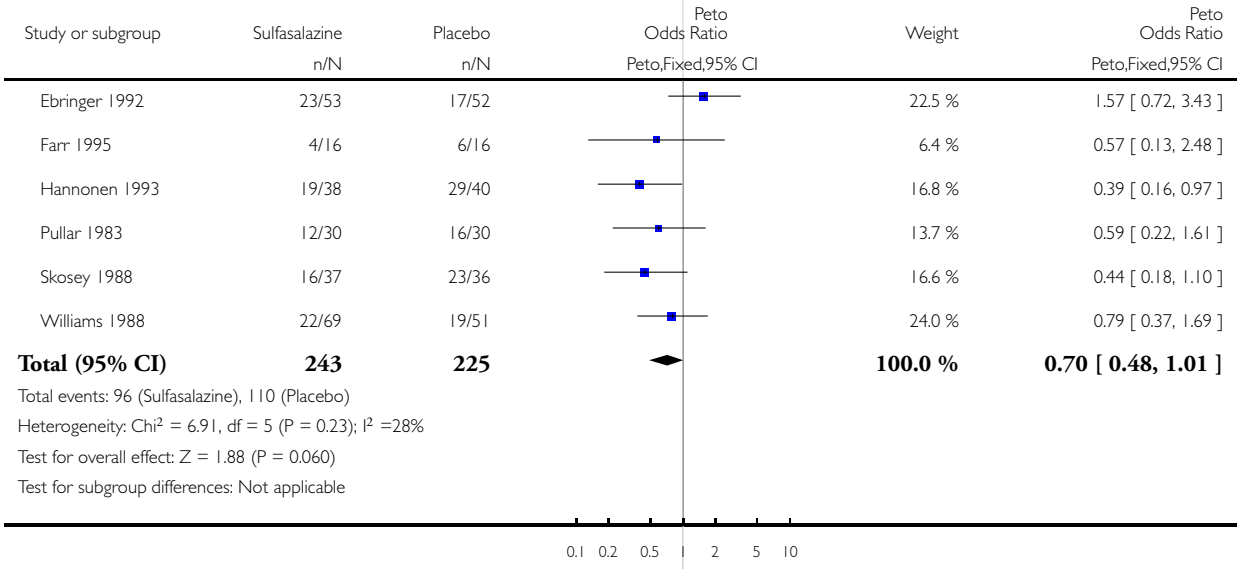


Analysis 2.1. Comparison 2 Sulfasalazine vs. placebo - Withdrawals and dropouts, Outcome 1 Withdrawals and dropouts - Total.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 2 Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome: 1 Withdrawals and dropouts - Total



Analysis 2.2. Comparison 2 Sulfasalazine vs. placebo - Withdrawals and dropouts, Outcome 2 Withdrawals due to inefficacy.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 2 Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome: 2 Withdrawals due to inefficacy

Study or subgroup	Sulfasalazine n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ebringer 1992	2/53	5/52		10.0 %	0.39 [0.09, 1.82]
Farr 1995	0/16	5/16		6.6 %	0.10 [0.02, 0.66]
Hannonen 1993	14/38	28/40		29.8 %	0.27 [0.11, 0.65]
Pullar 1983	2/30	13/30		17.4 %	0.15 [0.05, 0.47]
Skosey 1988	1/37	11/36		15.4 %	0.14 [0.04, 0.46]
Williams 1988	6/69	10/51		20.8 %	0.39 [0.14, 1.13]
Total (95% CI)	**243**	**225**		**100.0 %**	**0.23 [0.14, 0.37]**

Total events: 25 (Sulfasalazine), 72 (Placebo)

Heterogeneity: $Chi^2 = 3.61$, df = 5 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 5.98 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Sulfasalazine vs. placebo - Withdrawals and dropouts, Outcome 3 Withdrawals due to adverse reactions.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 2 Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome: 3 Withdrawals due to adverse reactions

Study or subgroup	Sulfasalazine n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ebringer 1992	14/53	4/52		24.9 %	3.69 [1.34, 10.13]
Farr 1995	4/16	1/16		7.2 %	3.97 [0.61, 25.95]
Hannonen 1993	5/38	1/40		9.3 %	4.40 [0.84, 23.04]
Pullar 1983	9/30	2/30		15.1 %	4.63 [1.27, 16.93]
Skosey 1988	11/37	5/36		20.9 %	2.49 [0.83, 7.50]
Williams 1988	11/69	5/51		22.6 %	1.69 [0.59, 4.89]
Total (95% CI)	**243**	**225**		**100.0 %**	**3.01 [1.82, 4.99]**

Total events: 54 (Sulfasalazine), 18 (Placebo)

Heterogeneity: $Chi^2 = 2.11$, df = 5 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 4.29 (P = 0.000018)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Sulfasalazine vs. placebo - Withdrawals and dropouts, Outcome 4 Withdrawals due to gastrointestinal adverse reactions.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 2 Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome: 4 Withdrawals due to gastrointestinal adverse reactions

Study or subgroup	Sulfasalazine n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ebringer 1992	3/53	2/52		1.49 [0.25, 8.88]
Farr 1995	2/16	0/16		7.90 [0.47, 132.20]
Hannonen 1993	0/1	0/1		0.0 [0.0, 0.0]
Pullar 1983	6/30	2/30		3.11 [0.71, 13.61]
Skosey 1988	7/37	3/36		2.42 [0.64, 9.10]
Williams 1988	2/69	1/51		1.46 [0.15, 14.73]
Total (95% CI)	**206**	**186**		**2.44 [1.12, 5.32]**

Total events: 20 (Sulfasalazine), 8 (Placebo)

Heterogeneity: Chi^2 = 1.25, df = 4 (P = 0.87); I^2 =0.0%

Test for overall effect: Z = 2.25 (P = 0.024)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Sulfasalazine vs. placebo - Withdrawals and dropouts, Outcome 5 Withdrawals due to skin and mucosal adverse reactions.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 2 Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome: 5 Withdrawals due to skin and mucosal adverse reactions

Study or subgroup	Sulfasalazine n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ebringer 1992	5/53	1/52		3.98 [0.77, 20.51]
Farr 1995	0/16	0/16		0.0 [0.0, 0.0]
Hannonen 1993	0/1	0/1		0.0 [0.0, 0.0]
Pullar 1983	2/30	0/30		7.65 [0.47, 125.22]
Skosey 1988	2/37	1/36		1.93 [0.19, 19.17]
Williams 1988	5/69	1/51		3.01 [0.58, 15.76]
Total (95% CI)	**206**	**186**		**3.43 [1.30, 9.09]**

Total events: 14 (Sulfasalazine), 3 (Placebo)

Heterogeneity: $Chi^2 = 0.61$, df = 3 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 2.48 (P = 0.013)

Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Sulfasalazine vs. placebo - Withdrawals and dropouts, Outcome 6 Withdrawals due to renal adverse reactions.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 2 Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome: 6 Withdrawals due to renal adverse reactions

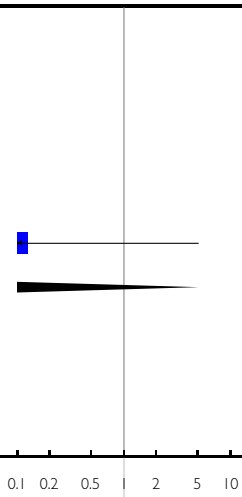
Study or subgroup	Sulfasalazine n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ebringer 1992	0/53	0/52		0.0 [0.0, 0.0]
Farr 1995	0/16	0/16		0.0 [0.0, 0.0]
Hannonen 1993	0/1	0/1		0.0 [0.0, 0.0]
Pullar 1983	0/30	0/30		0.0 [0.0, 0.0]
Skosey 1988	0/37	0/36		0.0 [0.0, 0.0]
Williams 1988	0/69	1/51		0.10 [0.00, 5.01]
Total (95% CI)	**206**	**186**		**0.10 [0.00, 5.01]**

Total events: 0 (Sulfasalazine), 1 (Placebo)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.16 (P = 0.24)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 Sulfasalazine vs. placebo - Withdrawals and dropouts, Outcome 7 Withdrawals due to liver abnormalities.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 2 Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome: 7 Withdrawals due to liver abnormalities

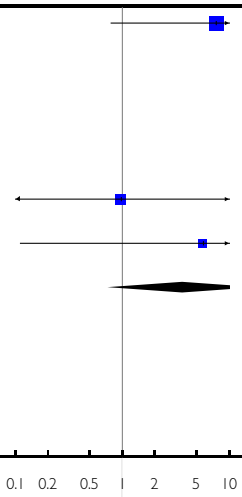
Study or subgroup	Sulfasalazine n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ebringer 1992	3/53	0/52		7.54 [0.77, 74.09]
Farr 1995	0/16	0/16		0.0 [0.0, 0.0]
Hannonen 1993	0/1	0/1		0.0 [0.0, 0.0]
Pullar 1983	0/30	0/30		0.0 [0.0, 0.0]
Skosey 1988	1/37	1/36		0.97 [0.06, 15.86]
Williams 1988	1/69	0/51		5.69 [0.11, 300.04]
Total (95% CI)	**206**	**186**		**3.63 [0.72, 18.23]**

Total events: 5 (Sulfasalazine), 1 (Placebo)

Heterogeneity: Chi^2 = 1.30, df = 2 (P = 0.52); I^2 =0.0%

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2 Sulfasalazine vs. placebo - Withdrawals and dropouts, Outcome 8 Withdrawals due to hemaetological adverse reactions.

Review: Sulfasalazine for treating rheumatoid arthritis

Comparison: 2 Sulfasalazine vs. placebo - Withdrawals and dropouts

Outcome: 8 Withdrawals due to hemaetological adverse reactions

Study or subgroup	Sulfasalazine n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ebringer 1992	0/53	0/52		0.0 [0.0, 0.0]
Farr 1995	1/16	0/16		7.39 [0.15, 372.38]
Hannonen 1993	0/1	0/1		0.0 [0.0, 0.0]
Pullar 1983	1/30	0/30		7.39 [0.15, 372.38]
Skosey 1988	0/37	0/36		0.0 [0.0, 0.0]
Williams 1988	2/69	1/51		1.46 [0.15, 14.73]
Total (95% CI)	**206**	**186**		**2.84 [0.48, 16.75]**

Total events: 4 (Sulfasalazine), 1 (Placebo)

Heterogeneity: Chi^2 = 0.77, df = 2 (P = 0.68); I^2 =0.0%

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: Not applicable

WHAT'S NEW

Last assessed as up-to-date: 29 November 1997.

Date	Event	Description
9 November 2008	Amended	Converted to new review format. CMSG ID: C080-R

HISTORY

Review first published: Issue 1, 1998

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Alberta Hospitals Foundation, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Sulfasalazine [*therapeutic use]

MeSH check words

Humans