Antimalarials for treating rheumatoid arthritis (Review)

Suarez-Almazor ME, Belseck E, Shea B, Homik J, Wells GA, Tugwell P

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[Intervention Review]

Antimalarials for treating rheumatoid arthritis

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ABSTRACT

Background

Antimalarials have been used for the treatment of rheumatoid arthritis (RA) for several decades. Recently several trials have been published with larger sample sizes, and better design than previous studies. These newer trials have evaluated the efficacy and toxicity of hydroxychloroquine.

Objectives

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

Search methods

We searched the Cochrane Musculoskeletal Group's trials register, the Cochrane Controlled Trials Register, MEDLINE and EMBASE up to and including August 2000. We also carried out a handsearch of the reference lists of the trials retrieved from the electronic search.

Selection criteria

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

Data collection and analysis

Data abstraction was carried out independently by two reviewers. The same two reviewers using a validated checklist (Jadad 1996) assessed the methodological quality of the RCTs and CCTs. Rheumatoid arthritis outcome measures were extracted from the publications for the 6-month endpoint. The pooled analysis was performed using standardized mean differences for joint counts, pain and global assessments. Weighted mean differences were used for erythrocyte sedimentation rate (ESR). Toxicity was evaluated with pooled odds ratios for withdrawals. A chi-square test was used to assess heterogeneity among trials. Fixed effects models were used throughout.

Main results

We found four trials, with 300 patients randomized to hydrochloroquine and 292 to placebo. Only trials evaluating hydroxychloroquine could be pooled in the analysis. A statistically significant benefit was observed when hydroxychloroquine was compared to placebo. The standardized mean differences for the various outcome measures ranged from -0.33 to -0.52, and were statistically significant. Statistically significant differences were also observed for ESR. Overall withdrawals and withdrawals due to lack of efficacy were significantly more frequent in the placebo group. No differences were observed in withdrawals due to toxicity.

Authors' conclusions

Hydroxychloroquine appears to be efficacious for the treatment of RA. Its overall effect appears to be moderate, but its low toxicity profile should be considered when treating patients with RA.

PLAIN LANGUAGE SUMMARY

Antimalarials for treating rheumatoid arthritis

Antimalarials have been used for the treatment of rheumatoid arthritis (RA) for several decades. This review found four trials, with 300 patients receiving hydrochloroquine and 292 receiving placebo. A benefit was observed in the patients taking hydroxychloroquine compared to placebo. There was no difference between the two groups in terms of those who had to withdraw from trials due to side effects.

Hydroxychloroquine appears to be helpful for the treatment of RA.

BACKGROUND

Antimalarials have been used for the treatment of rheumatoid arthritis (RA) for several decades. Although several clinical trials were published in the past, these often had small sample sizes and showed wide discrepancies in their results and sometimes used higher dosages than those accepted today (see table of excluded studies). Several clinical trials have been published this decade with larger sample sizes, and better design. These newer trials have evaluated the efficacy and toxicity of hydroxychloroquine.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and controlled clinical trials (CCTs), 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:
a) Chloroquine >= 250 mg/day or
b) Hydroxychloroquine >= 400 mg/day
Control group: placebo
Duration of treatment in double-blind phase >= 6 months

Types of outcome measures

EFFICACY:
All the outcome measures in OMERACT (OMERACT 1993) were included for potential analysis, although only some were consistently measured.
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
Additionally, the following measures were recorded if included in the publication:
a) Number of patients fulfilling response criteria (American College of Rheumatology, Paulus)
b) Number of patients in remission at the end of the trial
c) Total number of withdrawals and dropouts
d) Number of withdrawals from lack of efficacy
TOXICITY
Toxicity was evaluated with the number of withdrawals and dropouts including:
a) Number of withdrawals due to adverse reactions
b) Number of withdrawals due to system-specific adverse reactions (e.g. gastrointestinal, renal, etc.)

Search methods for identification of studies

1. Electronic searches
We searched MEDLINE using the strategy developed by Dickersin 1994 up to and including August 2000,
EMBASE was searched from 1988 to August 2000, with a strategy similar to the one used for MEDLINE, the Cochrane Musculoskeletal Group's trials register, the Cochrane Controlled Trials Register issue 3, 2000.
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.
1. Efficacy
The results on efficacy were analysed for the 6 month endpoints. Although some trials had longer duration, this endpoint was chosen because it was reported in most trials.
The standard deviations were not reported in one trial (Clark 1993), and we estimated them using the coefficient of variation calculated from the other trials, and weighted by sample size. An additional study reported medians and interquartile ranges. Medians were entered as means, and the interquartile ranges were divided by two to estimate the standard deviation.
End-of-trial results were pooled as standardized mean differences (SMDs) for joint scores, pain, global, and functional 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 with the lower values indicating a better response. Negative values in standardized weighted means indicate a benefit of the active drug over placebo. ESR results were pooled using weighted mean differences.
2. Withdrawals and dropouts
Withdrawals and dropouts at the end of the study were pooled for all trials. Pooled odds ratios (OR) were estimated using Peto's method (Petitti 1994). Toxicity was analysed 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.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Four RCTs and CCTs (Blackburn 1995, Clark 1993, Davis 1991, HERA 1995) met the criteria for inclusion, and reported data suitable for pooling. The patients in these trials were similar as assessed by patient's age, inclusion criteria, duration of disease and activity at entry. In general, patients had relatively early and mild RA, with no prior treatment with DMARDs, and low prevalence of rheumatoid factor (RF). All of the studies evaluated hydroxychloroquine, at 400 mg/day.
Three of the studies reported that the patients had undergone ophthalmologic evaluation, and could be used for the analysis of ocular toxicity.
Eight additional studies had to be excluded because of short duration or inadequate data reported. Some of these studies had evaluated chloroquine (Cohen 1958, Freedman 1960, Popert 1961, Scull 1962).

Risk of bias in included studies

The methodological quality of the studies was assessed using a quality scale validated and published by 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). Two studies had a score of 5, and the other two a score of 4 (see included tables for details)

Effects of interventions

Four trials evaluating hydroxychloroquine against placebo were included in the pooled analysis. In total, 290 patients receiving hydroxychloroquine and 281 receiving placebo were evaluated for efficacy. In the pooled analysis of clinical benefits most efficacy measures considered for the study reached levels of statistical significance of <0.05, favouring hydroxychloroquine over placebo. The standardized mean differences (SMDs) for the various outcome measures were as follows: a) tender joints: -0.33 (95% CI, -0.50,-0.17); b) swollen joints: -0.52 (95% CI, -0.69, -0.36); c) pain: -0.45 (95% CI, -0.63, -0.27); d) physician global assessment; -0.45 (95% CI, -0.66,-0.24); e) patient global assessment: -0.39 (95% CI, -0.59,-0.18). A weighted mean difference (WMD) of 6 mm (95% CI, -8.51, -4.24) favouring hydroxychloroquine was observed for ESR. Only one study measured functional status: no significant differences were observed between hydroxychloroquine and placebo in Health Assessment Questionnaire (HAQ) scores (HERA 1995). Another study reported radiological progression (Davis 1991); no significant differences were observed between groups.

Tests of homogeneity did not show any one study to be statistically different from the others.

The pooled analysis of withdrawals and dropouts included 299 patients receiving hydroxychloroquine and 292 receiving placebo. Patients receiving hydroxychloroquine were less likely to discontinue treatment, overall (OR = 0.59, 95% CI; 0.41, 0.86), or because of insufficient response (OR = 0.55, 95% CI; 0.33, 0.91). Withdrawals due to adverse reactions were rare (4.7% in the antimalarial group and 5.5% in the placebo group). None of the 3 studies which conducted ophthalmologic evaluations reported withdrawals due to ocular toxicity (Blackburn 1995, Clark 1993, HERA 1995). A single patient in the HERA 1995 trial had mild toxicity, not requiring discontinuation.

DISCUSSION

The purpose of this systematic review was to evaluate the efficacy and toxicity of antimalarials for the treatment of patients with RA. Unfortunately, data could only be pooled for trials including hydroxychloroquine, and therefore, our results are limited to this drug. We could not adequately assess the efficacy of chloroquine. Controlled trials including this drug were conducted several decades ago and did not follow standard procedures for reporting the data, such as those proposed by CONSORT (Begg 1996).

We encountered some difficulties in the data extraction of the included trials. One trial reported medians and another did not include standard deviations. We estimated missing data with approximate values derived from the trial per se (e.g. interquartile 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.

Hydroxychloroquine showed a statistically significant difference when compared with placebo for most of the outcome measures included in the trials. The standardized weighted differences for the various outcomes ranged from -0.33 to -0.52, which can be considered as a modest effect (Kazis 1989). A small difference favouring the treatment group was also observed for ESR (6 mm). Total withdrawals and dropouts and withdrawals due to lack of efficacy were also increased in the placebo group, supporting the beneficial effect of hydroxychloroquine. Only one trial examined functional status (Esdaile 1995) and another radiological progression (Davis 1991). No significant differences were observed between placebo and hydroxychloroquine for these outcome measures.

Hydroxychloroquine appeared to be very safe in the short-term with no significant adverse effects, other than one case with involvement of the central nervous system. Withdrawals from ocular toxicity were not reported.

AUTHORS' CONCLUSIONS

Implications for practice

Hydroxychloroquine appears to be efficacious for the treatment of RA. Its overall effect appears to be moderate, but its low toxicity profile should be considered when treating patients with RA.

Implications for research

The use of antimalarials in combination with other therapies is gaining acceptance. Current and future research in this area will determine if the potential of antimalarials can be enhanced through combination with other drugs.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Blackburn 1995

Methods	Randomized allocation Double blind allocation and assessment Duration - 24 wks Sample size at entry Hydroxychloroquine - 124 Placebo - 118
Participants	Patients with active RA Females - 75.5% Mean age - 51.6 yrs Duration of disease - 4.4 yrs Prevalence of RF not reported No previous DMARDS Concomitant use of steroids - 24% No concomitant use of other DMARDS
Interventions	Hydroxychloroquine - 400 mg/day and piroxicam - 20 mg/day Piroxicam - 20 mg/day
Outcomes	Tender joints Swollen joints Pain (0-100 VAS) Physician global (1-5) Patient global (1-5) ESR
Notes	Quality score: 5 Three arm parallel study comparing tenidap, piroxicam, and piroxicam + hydroxychloroquine - only the last 2 arms used in this review Intent to treat analysis - last information carried forward Withdrawals from adverse reactions could only be analyzed for specific systems

Risk of bias

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

Clark 1993

Methods	Randomized allocation Double blind allocation and assessment Duration 24 wks Sample size at entry Hydroxychloroquine - 65 Placebo - 61
Participants	Patients with active RA Mean age - 37.5 yrs Females- 92% Duration of disease - 29 months Prevalence of RF - 48.5% No previous treatment with DMARDS No concomitant use of steroids or other DMARDs
Interventions	Hydroxychloroquine - 400 mg/day
Outcomes	Tender and swollen joints (sum) Pain (0-10 VAS) Physician global assessment Patient global assessment
Notes	Quality score: 4 Intent to treat in 121 patients (5 lost to follow up before first return visit) Joint score pooled with both tender joints and swollen joints. Standard deviations not reported - estimated from the other trials Withdrawals due to lack of effect were not reported

Risk of bias

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

Davis 1991

Methods	Randomized allocation Double blind allocation and assessment Duration 12 months Sample size at entry Hydroxychloroquine - 51 Placebo - 53
Participants	Patients with mild active RA Median age - 46 yrs Females - 64% Median duration of disease: placebo - 12; treatment - 17 Prevalence of RF - 59% No previous use of DMARDS

Davis 1991 (*Continued*)

	No concomitant use of steriods or other DMARDS
Interventions	Hydroxychloroquine - 400mg/day Treatment duration - 12 months
Outcomes	Tender joints Swollen joints ESR
Notes	Quality score: 4 Data pooled for efficacy analysis at 6 months, and withdrawals at 12 months All the outcomes reported as medians and interquartile ranges

Risk of bias

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

HERA 1995

Methods	Randomized allocation Double blind allocation and assessment Duration - 36 wks Sample size at entry Hydroxychloroquine - 60 Placebo - 60
Participants	Patients with active RA Age - 53 yrs Females - 75.5% Duration of disease - < 2 yrs Prevalence of RF - 47% No concomitant use of steriods or other DMARDS No previous use of DMARDS
Interventions	Hydroxychloroquine - 400mg/day
Outcomes	Tender joints Swollen joints Pain (1-10 VAS) Physician global Patient global Functional status (HAQ) ESR
Notes	Quality score: 5 One withdrawal due to protocol violation Intent to treat analysis - last information carried forward

HERA 1995 (*Continued*)

	Only 1 withdrawal in the hydroxychloroquine group due to adverse reactions (central nervous system)

Risk of bias

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

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

Study	Reason for exclusion
Cohen 1958	Duration of trial 10 weeks
Freedman 1960	Data reported not suitable for pooling Short duration of trial (less than 16 weeks)
Hamilton 1962	Cross-over study - 12 weeks duration
Kersley 1959	Complex sequential design - the data could not be adequately extracted to include in the overall analysis
Mainland 1962	Data reported not suitable for pooling
Popert 1961	Data reported inadequate for the analysis Duration 24 months with no reports at 6 months or 1 year comparable to the other trials
Rinehart 1957	2 month cross-over trial. Incomplete data for meta-analysis
Scull 1962	Incomplete data for analysis

DATA AND ANALYSES

Comparison 1. Antimalarials vs. placebo - Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tender joints	4	571	Mean Difference (IV, Fixed, 95% CI)	-2.57 [-3.78, -1.36]
2 Number of swollen joints	4	571	Mean Difference (IV, Fixed, 95% CI)	-3.71 [-4.86, -2.57]
3 Pain	4	484	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.72, -0.18]
4 Physician global assessment	4	365	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.57, -0.21]
5 Patient global assessment	4	365	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.53, -0.15]
6 Functional status	4	125	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.29, 0.17]
7 ESR	4	571	Mean Difference (IV, Fixed, 95% CI)	-6.38 [-8.51, -4.24]
8 Radiological scores	3	95	Mean Difference (IV, Fixed, 95% CI)	0.40 [-1.21, 2.01]
9 Patients with erosions	3	6	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

Comparison 2. Antimalarials vs. placebo - Withdrawals and dropouts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals and dropouts - Total	4	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.41, 0.86]
2 Withdrawals due to lack of efficacy	4	467	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.33, 0.91]
3 Withdrawals due to adverse reactions	4	586	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.40, 1.75]

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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

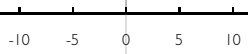
Outcome: 1 Tender joints

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Blackburn 1995	124	16.78 (16.15)	118	19.98 (15.64)		9.1 %	-3.20 [-7.21, 0.81]
Clark 1993	63	7.35 (6.84)	58	11 (8.03)		20.5 %	-3.65 [-6.32, -0.98]
Davis 1991	44	4 (3.75)	45	6 (3.5)		64.2 %	-2.00 [-3.51, -0.49]
HERA 1995	59	15 (13)	60	19 (14)		6.2 %	-4.00 [-8.85, 0.85]
Total (95% CI)	**290**		**281**			**100.0 %**	**-2.57 [-3.78, -1.36]**

Heterogeneity: Chi² = 1.61, df = 3 (P = 0.66); I² =0.0%

Test for overall effect: Z = 4.17 (P = 0.000030)

Test for subgroup differences: Not applicable



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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

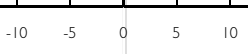
Outcome: 2 Number of swollen joints

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Blackburn 1995	124	13.76 (8.91)	118	18.17 (8.8)		26.4 %	-4.41 [-6.64, -2.18]
Clark 1993	63	7.35 (5.15)	58	11 (5.72)		34.7 %	-3.65 [-5.60, -1.70]
Davis 1991	44	10 (6)	45	13.5 (5.5)		23.0 %	-3.50 [-5.89, -1.11]
HERA 1995	59	9 (8)	60	12 (8)		15.9 %	-3.00 [-5.87, -0.13]
Total (95% CI)	**290**		**281**			**100.0 %**	**-3.71 [-4.86, -2.57]**

Heterogeneity: Chi² = 0.65, df = 3 (P = 0.89); I² =0.0%

Test for overall effect: Z = 6.35 (P < 0.00001)

Test for subgroup differences: Not applicable



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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

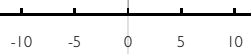
Outcome: 3 Pain

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Blackburn 1995	124	11.06 (9.47)	118	13.97 (9.12)		-2.91 [-5.25, -0.57]
Clark 1993	63	20.5 (17.84)	58	34.1 (22.51)		-13.60 [-20.88, -6.32]
Davis 1991	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
HERA 1995	59	0.8 (0.7)	60	1.2 (0.8)		-0.40 [-0.67, -0.13]
Total (95% CI)	**247**		**237**			**-0.45 [-0.72, -0.18]**

Heterogeneity: Chi^2 = 16.91, df = 2 (P = 0.00021); I^2 =88%

Test for overall effect: Z = 3.30 (P = 0.00098)

Test for subgroup differences: Not applicable



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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

Outcome: 4 Physician global assessment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Blackburn 1995	124	2.42 (0.78)	118	2.78 (0.76)		-0.36 [-0.55, -0.17]
Clark 1993	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Davis 1991	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
HERA 1995	59	-1.67 (1.3)	60	-1.1 (1.47)		-0.57 [-1.07, -0.07]
Total (95% CI)	**185**		**180**			**-0.39 [-0.57, -0.21]**

Heterogeneity: Chi^2 = 0.59, df = 1 (P = 0.44); I^2 =0.0%

Test for overall effect: Z = 4.20 (P = 0.000026)

Test for subgroup differences: Not applicable

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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

Outcome: 5 Patient global assessment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Blackburn 1995	124	2.61 (0.78)	118	2.89 (0.87)		-0.28 [-0.49, -0.07]
Clark 1993	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Davis 1991	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
HERA 1995	59	-2.07 (1.21)	60	-1.4 (1.52)		-0.67 [-1.16, -0.18]
Total (95% CI)	**185**		**180**			**-0.34 [-0.53, -0.15]**

Heterogeneity: Chi² = 2.04, df = 1 (P = 0.15); I² =51%

Test for overall effect: Z = 3.46 (P = 0.00054)

Test for subgroup differences: Not applicable

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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

Outcome: 6 Functional status

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Blackburn 1995	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Clark 1993	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Davis 1991	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
HERA 1995	59	0.69 (0.66)	60	0.75 (0.64)		-0.06 [-0.29, 0.17]
Total (95% CI)	**62**		**63**			**-0.06 [-0.29, 0.17]**

Heterogeneity: Chi² = 0.00, df = 0 (P<0.00001); I² =100%

Test for overall effect: Z = 0.50 (P = 0.61)

Test for subgroup differences: Not applicable

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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

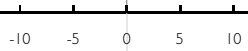
Outcome: 7 ESR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Blackburn 1995	124	31.11 (24.83)	118	35.84 (27.7)		10.3 %	-4.73 [-11.37, 1.91]
Clark 1993	63	30.1 (21.37)	58	33.2 (21.91)		7.6 %	-3.10 [-10.82, 4.62]
Davis 1991	44	10 (5.5)	45	17 (6.5)		72.9 %	-7.00 [-9.50, -4.50]
HERA 1995	59	27 (17)	60	33 (22)		9.1 %	-6.00 [-13.06, 1.06]
Total (95% CI)	**290**		**281**			**100.0 %**	**-6.38 [-8.51, -4.24]**

Heterogeneity: Chi^2 = 1.18, df = 3 (P = 0.76); I^2 =0.0%

Test for overall effect: Z = 5.86 (P < 0.00001)

Test for subgroup differences: Not applicable



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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

Outcome: 8 Radiological scores

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Blackburn 1995	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Davis 1991	44	3.3 (4)	47	2.9 (3.8)		0.40 [-1.21, 2.01]
HERA 1995	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**46**		**49**			**0.40 [-1.21, 2.01]**

Heterogeneity: Chi^2 = 0.00, df = 0 (P<0.00001); I^2 =100%

Test for overall effect: Z = 0.49 (P = 0.63)

Test for subgroup differences: Not applicable

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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 1 Antimalarials vs. placebo - Efficacy

Outcome: 9 Patients with erosions

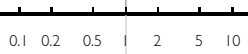
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Blackburn 1995	0/1	0/1		0.0 [0.0, 0.0]
Davis 1991	0/1	0/1		0.0 [0.0, 0.0]
HERA 1995	0/1	0/1		0.0 [0.0, 0.0]
Total (95% CI)	**3**	**3**		**0.0 [0.0, 0.0]**

Total events: 0 (Treatment), 0 (Control)

Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%

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

Test for subgroup differences: Not applicable



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

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 2 Antimalarials vs. placebo - Withdrawals and dropouts

Outcome: 1 Withdrawals and dropouts - Total

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Blackburn 1995	38/124	43/118		48.8 %	0.77 [0.45, 1.32]
Clark 1993	11/65	14/61		18.2 %	0.69 [0.29, 1.64]
Davis 1991	9/51	20/53		19.1 %	0.37 [0.16, 0.87]
HERA 1995	5/59	13/60		13.9 %	0.36 [0.13, 0.98]
Total (95% CI)	**299**	**292**		**100.0 %**	**0.59 [0.41, 0.86]**

Total events: 63 (Treatment), 90 (Control)

Heterogeneity: Chi² = 3.14, df = 3 (P = 0.37); I² =5%

Test for overall effect: Z = 2.76 (P = 0.0057)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Antimalarials vs. placebo - Withdrawals and dropouts, Outcome 2 Withdrawals due to lack of efficacy.

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 2 Antimalarials vs. placebo - Withdrawals and dropouts

Outcome: 2 Withdrawals due to lack of efficacy

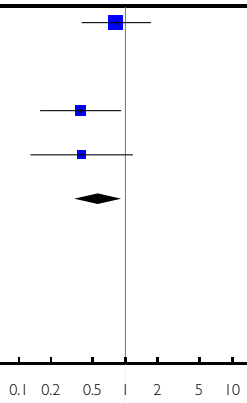
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Blackburn 1995	15/124	17/118		0.82 [0.39, 1.72]
Clark 1993	0/1	0/1		0.0 [0.0, 0.0]
Davis 1991	8/51	18/53		0.38 [0.16, 0.92]
HERA 1995	4/59	10/60		0.39 [0.13, 1.18]
Total (95% CI)	**235**	**232**		**0.55 [0.33, 0.91]**

Total events: 27 (Treatment), 45 (Control)

Heterogeneity: $Chi^2 = 2.14$, df = 2 (P = 0.34); I^2 =6%

Test for overall effect: Z = 2.35 (P = 0.019)

Test for subgroup differences: Not applicable

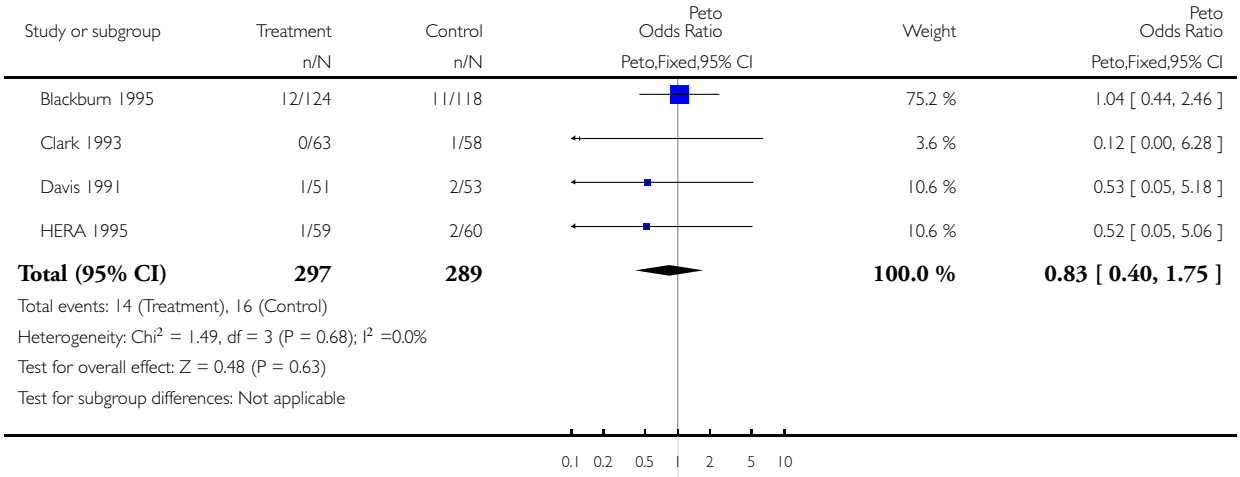


Analysis 2.3. Comparison 2 Antimalarials vs. placebo - Withdrawals and dropouts, Outcome 3 Withdrawals due to adverse reactions.

Review: Antimalarials for treating rheumatoid arthritis

Comparison: 2 Antimalarials vs. placebo - Withdrawals and dropouts

Outcome: 3 Withdrawals due to adverse reactions



WHAT'S NEW

Last assessed as up-to-date: 29 August 2000.

Date	Event	Description
22 September 2008	Amended	Converted to new review format. C005-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)

Antimalarials [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Controlled Clinical Trials as Topic; Randomized Controlled Trials as Topic

MeSH check words

Humans