Methotrexate for treating rheumatoid arthritis (Review)

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[Intervention Review]

Methotrexate for treating rheumatoid arthritis

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ABSTRACT

Background

Methotrexate (MTX) is a folic acid antagonist widely used for the treatment of neoplastic disorders. MTX inhibits the synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins by binding to dihydrofolate reductase. Currently, MTX is among the most commonly used drugs for the treatment of rheumatoid arthritis (RA).

Objectives

To evaluate the short term efficacy and toxicity of methotrexate (MTX) for the treatment of rheumatoid arthritis (RA).

Search methods

We searched the Cochrane Musculoskeletal Group register, Cochrane Controlled Trials Register (CCTR), MEDLINE (1966 to July 1997) and EMBASE (1988 to July 1997) using the strategy developed by Dickersin 1994. The search was complemented with a bibliography search of the reference lists of the trials retrieved from the electronic search. Key experts in the area were contacted for further published and unpublished articles.

Selection criteria

Randomized controlled trials and controlled clinical trials comparing MTX against placebo in people with RA.

Data collection and analysis

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

The same two reviewers independently assessed the methodological quality of the trials using a validated scale (Jadad 1996). 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, although random effects models were used for outcomes showing heterogeneity.

Main results

Five trials and 300 participants were included. A statistically significant benefit was observed for MTX when compared to placebo. Statistically significant differences were observed for all measures except ESR. The standardized weighted difference (effect size) between MTX and placebo for the various outcome measures varied between -0.43 and -1.5. No differences were observed in the total number of withdrawals and dropouts (OR 0.95) although participants on MTX were three times more likely to discontinue treatment because of adverse reactions (OR 3.47) and four times less likely to withdraw due to lack of response (OR 0.22). Twenty-two percent of people on MTX withdrew due to adverse effects compared to seven percent of the placebo group.

Authors' conclusions

MTX has a substantial clinical and statistically significant benefit compared to placebo in the short term treatment of people with RA although its use is associated with a high withdrawal rate due to adverse events.

PLAIN LANGUAGE SUMMARY

Methotrexate has substantial clinical benefit in the short term treatment of people with rheumatoid arthritis

Methotrexate (MTX) is a dihydrofolate reductase inhibitor used in the treatment of rheumatoid arthritis (RA). Five trials and 300 participants were included in this review. Participants had severe RA of long duration and had previously failed other therapy. They received MTX treatment, or placebo, over 12 to 18 weeks. Statistically significant benefits were observed with MTX on joint counts, pain, and global and functional assessments. People on MTX were three times more likely to discontinue treatment because of adverse reactions.

BACKGROUND

Methotrexate (MTX) is a folic acid antagonist widely used for the treatment of neoplastic disorders. MTX inhibits the synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins by binding to dihydrofolate reductase.

MTX has been extensively used for the treatment of psoriasis and psoriatic arthritis. Its potential benefits for rheumatoid arthritis (RA) were originally suggested by Gubner 1951 in a case series study of six patients with RA. Subsequent open trials supported the efficacy of the drug (Willkens 1980, Steinsson 1982, Groff 1983). The first controlled trials of MTX against placebo in RA were reported in the 1980's. Currently, MTX is among the most commonly used drugs for the treatment of RA.

OBJECTIVES

To evaluate the short term efficacy and toxicity of MTX for the treatment of RA.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and clinical controlled trials (CCTs) comparing MTX with placebo and with a minimum duration of 12 weeks.

Types of participants

People with a diagnosis of RA that is severe and of long duration who had a high prevalence of positive rheumatoid factor (RF) and had previously failed other second line agent (DMARD) therapy.

Types of interventions

Intervention group: methotrexate (oral or parenteral) at a dose level of at least 7.5 mg per week
Control group: placebo
Duration of treatment in double-blind phase: at least 12 weeks

Types of outcome measures

1. Efficacy
All the outcome measures in OMERACT 1993 were included for potential analysis.
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 - including erythrocyte sedimentation rate (ESR) (ESR is a measurement of how fast red blodd cells (erthrocytes) fall to the bottom of a test tube filled with whole blood; those with RA have high levels of sedimentation).
h) Radiological damage (Joint damage shown on X-ray).
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
The Cochrane Musculoskeletal Group register, Cochrane Controlled Trials Register (CCTR), MEDLINE (1966 to July 1997) and EMBASE (1988 to July 1997) were searched using the strategy developed by Dickersin 1994.
2. Handsearches
Reference lists of all the trials selected through the electronic search were manually searched to identify additional trials. Key experts in the area were contacted for further published and unpublished articles.

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 analyzed for the study endpoints ranging from 12 to 18 weeks. Twelve weeks was thought to be the minimum treatment duration required to adequately assess the efficacy of MTX.
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 counted). Trial results were entered in RevMan using the same direction in order to enable the pooling of results, with the lower values indicating better responses. Negative values in SMDs indicated a benefit of the active drug over placebo. ESR results were pooled using weighted mean differences.
When the end-of-trial standard deviation was not reported we used the baseline standard deviation for the pooled analysis. In our experience, the baseline standard deviation of RA outcome measures is often very close to the end-of-trial standard deviation, perhaps slightly higher. This resultant bias would therefore result in decreased weighting of the studies, and is preferable to completely excluding them.
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. Random effects models were used for outcomes showing statistically significant heterogeneity.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Five RCTs met the inclusion criteria (Andersen 1985, Furst 1990, Pinheiro 1993, Weinblatt 1985, Williams 1985).
MTX was administered orally in four studies and Intramuscularly (IM) in one study (Andersen 1985). Doses ranged between 7.5 and 25 mg per week.
The duration of the trials ranged between 12 and 18 weeks.
The population in all the RCTs included in the review had severe RA of long duration and a high prevalence of positive rheumatoid factor (RF). All participants had previously failed other second line agents (DMARD) therapy. Most were allowed concurrent use of steroids.
Generally, the trials included most of the OMERACT outcome measures. Functional status was only reported in three (Furst 1990, Pinheiro 1993, Williams 1985), but walking time was reported in all trials.
Four of the trials were conducted in North America and one in Brazil.

Risk of bias in included studies

The methodological quality of the studies was assessed by two reviewers 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). Three studies had a score of 5 and the other two a score of 4.

Effects of interventions

Five trials were included in the pooled analysis. In total, 161 participants received MTX and 160 received placebo. The analysis of efficacy for the most frequently reported outcome measure (tender joint score) was conducted in 113 participants receiving MTX and 106 receiving placebo. In the pooled analysis of clinical benefits, most efficacy measures considered for the study reached levels of statistical significance with probability that the observed results could have occurred by chance (p-value) less than 0.05, favouring MTX over placebo. The standardized weighted differences for the various outcome measures were as follows: a) tender joints [SMD -0.86 (95% CI: -1.14 to -0.58)]; b) swollen joints [SMD -0.65 (95% CI: -0.95 to -0.36)]; c) pain [SMD -1.02 (95% CI: -1.33 to -0.72)]; d) physician global assessment [SMD -1.15 (95% CI: -1.47 to -0.84)]; e) patient global assessment [SMD -1.09 (95% CI: -1.40, -0.78)]; f) walking time [SMD -0.43 (95% CI: -0.72 to -0.15)]; g) functional status [SMD -1.48 (95% CI: -1.82 to -1.14)].

Statistically significant heterogeneity among trials was observed for all outcome measures other than the joint counts. The beneficial effect of MTX continued to be statistically significant when using random effects but showed larger confidence intervals.

A weighted mean difference of 9 mm, favouring MTX, was observed for ESR. This difference did not reach statistical significance (95% CI: -18.2 to 0.27) but fewer patients were analyzed for this outcome since the largest trial (Williams 1985) did not report values for ESR that could be used in the pooled analysis. The differences in ESR in the Williams trial were reported to be statistically significant in favour of MTX (p less than 0.0001).

The pooled analysis of withdrawals and dropouts were from 157 participants receiving MTX and 156 receiving placebo. Eight participants in the Pinheiro trial were lost to follow up before completion of the first month, for unknown reasons, and were not included in any of the analyses. No differences were observed in the total number of withdrawals and dropouts [OR 0.95 (95% CI: 0.58 to 1.58)]. Participants on MTX were more likely to discontinue treatment because of adverse reactions [OR 3.47 (95% CI: 1.82 to 6.64)] but less likely to withdraw because of poor response [OR 0.22 (95% CI: 0.09 to 0.52)]. The most common cause for discontinuation in MTX participants was the presence of liver enzyme abnormalities, however, all the withdrawals for this adverse reaction occurred in a single study (Williams 1985).

DISCUSSION

Methotrexate (MTX) was initially used for the treatment of rheumatoid arthritis (RA) in 1951(Gubner 1951). Since then, several open studies, RCTs and CCTs have suggested beneficial effects. The purpose of this systematic review was to evaluate the efficacy and toxicity of MTX for the treatment of people with RA when compared to placebo. We only included in this review placebo controlled CCTs and RCTs reporting results after a minimum of 12 weeks of treatment. The dosage of MTX in these trials ranged from 7.5 to 25 mg per week.

The trials included in the review were all conducted in the 1980's or later. Most outcome measures of interest (OMERACT 1993, Felson 1993) were reported. The methodological quality of the trials was high (four or greater). Two trials used a cross-over design. Because of how the data were reported, we used the final results for one (Andersen 1985) and the first arm for the other (Weinblatt 1985). In two trials (Pinheiro 1993, Weinblatt 1985) we used the baseline standard deviation to pool the results. This procedure may have created some bias. It was similarly applied to both groups (treatment and control) and the overall impact on the estimation of differences between groups is probably small. Moreover, this bias is expected to result in decreased weighting of these studies which was preferable, in our view, to excluding the trials.

Substantial differences between placebo and MTX were observed for all measures of disease activity, in favour of MTX. These differences were statistically significant for all measures other than ESR. For ESR, fewer patients were pooled in the analysis since data from the largest trial (Williams 1985) could not be included. This study had nevertheless reported a statistically significant difference in ESR with greater improvement in the MTX group. The standardized weighted differences between MTX and placebo for the various outcome measures varied between -0.43 and -1.5. These effects can be considered to be substantial. The minimum effect size considered to be clinically meaningful in RA has been estimated at 0.30 (Kazis 1989).

Statistically significant heterogeneity among trials was observed for all outcome measures other than the joint counts. The heterogeneity remained significant with random effects models. As expected, random effects pooling resulted in larger confidence intervals than those obtained from fixed effects. Nevertheless, all outcome measures remained statistically significant. The reasons for heterogeneity are not apparent but are not likely to relate to the RA populations in the trial since participants were quite similar, having longstanding, severe RA. More likely, differences may have resulted from the various methods used to estimate these outcomes, which required standardization. For instance, global assessments were measured in different trials with Likert scales or visual analogue scales (VAS).

No significant differences were observed in the overall number of withdrawals and dropouts, but MTX participants were signifi-

cantly more likely to discontinue treatment because of adverse reactions and placebo participants because of lack of response. The most frequent side effects with MTX were raised liver enzymes but were only observed in a single trial (Williams 1985).

The trials included in this review used similar inclusion criteria and the participant populations had longstanding severe RA, often seropositive, and had failed previous DMARDs. Despite the severity of the disease, the improvement was substantial. Both crossover trials reported a failure in the disease state after discontinuation of MTX, which suggests that the drug has to be continued to maintain the benefit. The long term effectiveness or safety profile of MTX cannot be established with this review.

AUTHORS' CONCLUSIONS

Implications for practice

Methotrexate has a substantial clinical and statistically significant benefitcompared to placebo in the short term treatment of people with rheumatoid arthritis (RA).

Implications for research

The long term effectiveness or safety profile of MTX cannot be established with this review. A review of long term studies is required to evaluate the longer term effects of the drug.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Andersen 1985

Methods	Randomized allocation Double blind allocation and assessment Cross-over design Duration - 14 wks Sample size at entry - 15 Completed crossover - 12
Participants	Patients with active RA Mean age - 60.4 yrs Females - 75% Mean duration of disease - 14 yrs Prevalence of RF - 91.5% Concomitant use of steroids - 90% No concomitant use of other DMARDs Previous DMARD use - 100%
Interventions	IM MTX - 1 patient 20mg /wk 11 patients 25 mg /wk
Outcomes	Tender joints Swollen joints Pain (joint discomfort) Patient global (0-10 VAS) Physician global (0-4) Walking time ESR
Notes	Quality score - 5 Pain and global scores were entered with a negative sign, to reflect worsening with higher scores Results pooled for both arms 12 completed crossover, included in efficacy analysis 14 included in toxicity analysis (1 moved away)

Risk of bias

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

Furst 1990

Methods	Randomized allocation Double blind allocation and assessment Parallel group design Sample size at entry: MTX - 17 Placebo - 16 Duration - 18wks
Participants	Patients with active RA Mean age - 55.6 Females - 63% Duration of disease - unknown Positive rheumatoid factor - 87% Concomitant steriod use - 54% No concomitant DMARD use Previous DMARD use - 100%
Interventions	Oral MTX 10 mg/m2/wk Study comparing 2 dosages (5 and 10mg/m2/wk) - only higher dose included
Outcomes	Tender joints Swollen joints Pain (0-100 VAS) Physician global (0-100 VAS) Patient global (0-100 VAS) Walking time Function (ADL score) ESR
Notes	Quality score: 4 Intent to treat

Risk of bias

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

Pinheiro 1993

Methods	Randomized allocation Double blind allocation and assessment Sample size at entry - 28 Duration - 12 wks
Participants	Patients with active RA Mean age - 47.4 yrs Females - 89%% Mean duration of disease - 8 yrs

Pinheiro 1993 (*Continued*)

	Prevalence of RF - 90% Concomitant use of steroids - 57%% No concomitant use of other DMARDs Previous DMARD use - 100%
Interventions	Oral MTX 15mg/wk
Outcomes	Tender joints Pain (0-10 VAS) Walking time Function (modified HAQ) ESR
Notes	Quality score: 4

Risk of bias

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

Weinblatt 1985

Methods	Randomized allocation Double blind allocation and assessment Cross-over design Duration 12 wks Sample size at entry - 35 First arm MTX - 17 Placebo - 18
Participants	Patients with active RA Mean age - 60 Females - 71.4% Mean duration of disease - 119 months Positive rheumatoid factor - 97% Concomitant use of steriods - 54.2% Concomitant use of other DMARDS - unknown Previous DMARD use - 100%
Interventions	Oral MTX - 15mg/wk
Outcomes	Tender joints Swollen joints Physician global (0-4) Patient global (0-4) Walking time ESR

Weinblatt 1985 (*Continued*)

Notes	Quality score: 5 Results pooled for first arm

Risk of bias

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

Williams 1985

Methods	Randomize allocation Double blind allocation and assessment Parallel group design Duration 18 wks Sample size at entry MTX - 95 Placebo - 94
Participants	Patients with active RA Mean age - 54 Females - 71.9% Mean duration of disease - 13.5 yrs Prevalence of RF - not reported Concomitant steroid use - 54% Previous use of DMARDS - 100% No concomitant use of other DMARDS
Interventions	Oral MTX - 7.5mg (33%) - 15mg (66%) /wk
Outcomes	Tender joints Swollen joints Pain (0-100 VAS) Physician global (1-5) Patient global (1-5) Function (MACTAR) ESR (measured but reported in format not suitable for pooling)
Notes	Quality score: 5 MACTAR scores from publication by Tugwell 1990 ESR differences favoured MTX (p<0.0001)

Risk of bias

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

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

Study	Reason for exclusion
Cannon 1990	Inadequate data for inclusion in the analysis
Szanto 1986	Inadequate data for inclusion in the analysis
Thompson 1984	Short duration of trial: 6 weeks

DATA AND ANALYSES

Comparison 1. MTX vs. placebo - Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of tender joints	5	219	Mean Difference (IV, Fixed, 95% CI)	-17.85 [-23.97, -11.73]
2 Number of swollen joints	5	194	Mean Difference (IV, Fixed, 95% CI)	-7.31 [-10.44, -4.18]
3 Pain	5	194	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-4.07, -1.93]
4 Physician global assessment	5	194	Mean Difference (IV, Fixed, 95% CI)	-1.05 [-1.31, -0.80]
5 Patient global assessment	5	200	Mean Difference (IV, Fixed, 95% CI)	-0.91 [-1.20, -0.63]
6 Walking time	5	203	Mean Difference (IV, Fixed, 95% CI)	-3.19 [-4.78, -1.59]
7 Functional status	5	183	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.58, -0.38]
8 ESR	5	113	Mean Difference (IV, Fixed, 95% CI)	-8.95 [-18.17, 0.27]

Comparison 2. MTX - Withdrawals and dropouts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals and dropouts - Total	5	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.58, 1.58]
2 Withdrawals due to lack of efficacy	5	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.09, 0.52]
3 Withdrawals due to adverse reactions	5	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.47 [1.82, 6.64]
4 Withdrawals due to gastrointestinal adverse reactions	5	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.32 [0.57, 19.30]
5 Withdrawals due to mucocutaneous adverse reactions	5	314	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.33, 4.79]
6 Withdrawals due to liver enzyme abnormalities	5	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.14 [1.71, 10.05]
7 Withdrawals due to hemaetological adverse reactions	5	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.20 [0.94, 18.68]
8 Withdrawals due to infection	2	61	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.97 [0.14, 351.74]

Analysis 1.1. Comparison 1 MTX vs. placebo - Efficacy, Outcome 1 Number of tender joints.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 1 MTX vs. placebo - Efficacy

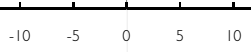
Outcome: 1 Number of tender joints

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Andersen 1985	12	13.5 (18.01)	12	33.8 (24.25)		12.8 %	-20.30 [-37.39, -3.21]
Furst 1990	17	34 (25)	16	70 (41)		6.9 %	-36.00 [-59.34, -12.66]
Pinheiro 1993	13	16.6 (12.62)	14	22.1 (13.1)		39.8 %	-5.50 [-15.20, 4.20]
Weinblatt 1985	15	12 (27.11)	16	46 (24)		11.5 %	-34.00 [-52.07, -15.93]
Williams 1985	56	26 (24.9)	48	49 (32.8)		29.1 %	-23.00 [-34.34, -11.66]
Total (95% CI)	**113**		**106**			**100.0 %**	**-17.85 [-23.97, -11.73]**

Heterogeneity: Chi^2 = 12.49, df = 4 (P = 0.01); I^2 =68%

Test for overall effect: Z = 5.72 (P < 0.00001)

Test for subgroup differences: Not applicable



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

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 1 MTX vs. placebo - Efficacy

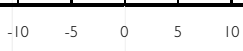
Outcome: 2 Number of swollen joints

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Weinblatt 1985	15	20 (7.75)	16	23 (8)		-3.00 [-8.55, 2.55]
Andersen 1985	12	6.9 (5.2)	12	19.4 (12.2)		-12.50 [-20.00, -5.00]
Furst 1990	17	18 (11)	16	27 (15)		-9.00 [-18.02, 0.02]
Pinheiro 1993	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1985	56	17 (12.6)	48	25 (13.4)		-8.00 [-13.03, -2.97]
Total (95% CI)	**101**		**93**			**-7.31 [-10.44, -4.18]**

Heterogeneity: Chi^2 = 4.37, df = 3 (P = 0.22); I^2 =31%

Test for overall effect: Z = 4.58 (P < 0.00001)

Test for subgroup differences: Not applicable



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

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 1 MTX vs. placebo - Efficacy

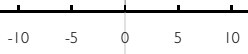
Outcome: 3 Pain

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Andersen 1985	11	-4.8 (2.98)	11	-1.1 (1.99)		-3.70 [-5.82, -1.58]
Furst 1990	17	38 (18)	16	69 (19)		-31.00 [-43.64, -18.36]
Pinheiro 1993	13	2.9 (1.44)	14	5.1 (1.87)		-2.20 [-3.45, -0.95]
Weinblatt 1985	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1985	57	30 (24.1)	53	50 (28.2)		-20.00 [-29.84, -10.16]
Total (95% CI)	**99**		**95**			**-3.00 [-4.07, -1.93]**

Heterogeneity: Chi^2 = 32.29, df = 3 (P<0.00001); I^2 =91%

Test for overall effect: Z = 5.50 (P < 0.00001)

Test for subgroup differences: Not applicable



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

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 1 MTX vs. placebo - Efficacy

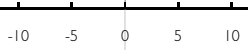
Outcome: 4 Physician global assessment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Andersen 1985	12	-2.4 (1.04)	12	-0.2 (0.35)		-2.20 [-2.82, -1.58]
Furst 1990	17	33 (18)	16	64 (19)		-31.00 [-43.64, -18.36]
Pinheiro 1993	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Weinblatt 1985	15	1.2 (0.77)	16	2.6 (0.8)		-1.40 [-1.95, -0.85]
Williams 1985	56	2.5 (0.74)	48	3.1 (0.92)		-0.60 [-0.92, -0.28]
Total (95% CI)	**101**		**93**			**-1.05 [-1.31, -0.80]**

Heterogeneity: Chi^2 = 43.66, df = 3 (P<0.00001); I^2 =93%

Test for overall effect: Z = 8.09 (P < 0.00001)

Test for subgroup differences: Not applicable



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

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 1 MTX vs. placebo - Efficacy

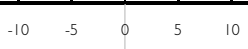
Outcome: 5 Patient global assessment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Andersen 1985	12	-5.8 (2.65)	12	-1.6 (1.99)		-4.20 [-6.08, -2.32]
Furst 1990	17	36 (17)	16	69 (16)		-33.00 [-44.26, -21.74]
Pinheiro 1993	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Weinblatt 1985	15	1.2 (0.77)	16	2.6 (0.8)		-1.40 [-1.95, -0.85]
Williams 1985	57	2.3 (0.71)	53	2.9 (1.04)		-0.60 [-0.94, -0.26]
Total (95% CI)	**102**		**98**			**-0.91 [-1.20, -0.63]**

Heterogeneity: Chi^2 = 49.34, df = 3 (P<0.00001); I^2 =94%

Test for overall effect: Z = 6.32 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 MTX vs. placebo - Efficacy, Outcome 6 Walking time.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 1 MTX vs. placebo - Efficacy

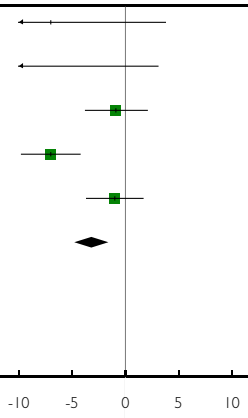
Outcome: 6 Walking time

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Andersen 1985	11	16.1 (9.62)	11	23.1 (15.59)		2.2 %	-7.00 [-17.83, 3.83]
Furst 1990	17	16.3 (9)	16	31.2 (35.7)		0.8 %	-14.90 [-32.91, 3.11]
Pinheiro 1993	13	14.43 (3.61)	14	15.3 (4.12)		29.8 %	-0.87 [-3.79, 2.05]
Weinblatt 1985	15	12 (3.87)	13	19 (3.6)		33.1 %	-7.00 [-9.77, -4.23]
Williams 1985	49	14 (7.5)	44	15 (5.9)		34.1 %	-1.00 [-3.73, 1.73]
Total (95% CI)	**105**		**98**			**100.0 %**	**-3.19 [-4.78, -1.59]**

Heterogeneity: Chi^2 = 14.28, df = 4 (P = 0.01); I^2 =72%

Test for overall effect: Z = 3.92 (P = 0.000088)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 MTX vs. placebo - Efficacy, Outcome 7 Functional status.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 1 MTX vs. placebo - Efficacy

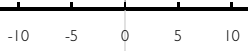
Outcome: 7 Functional status

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Andersen 1985	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Furst 1990	17	72 (29)	16	122 (23)		-50.00 [-67.81, -32.19]
Pinheiro 1993	14	0.39 (0.37)	14	0.53 (0.37)		-0.14 [-0.41, 0.13]
Weinblatt 1985	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Williams 1985	63	-0.41 (0.36)	55	0.12 (0.22)		-0.53 [-0.64, -0.42]
Total (95% CI)	**96**		**87**			**-0.48 [-0.58, -0.38]**

Heterogeneity: Chi^2 = 36.47, df = 2 (P<0.00001); I^2 =95%

Test for overall effect: Z = 9.51 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 MTX vs. placebo - Efficacy, Outcome 8 ESR.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 1 MTX vs. placebo - Efficacy

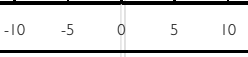
Outcome: 8 ESR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Andersen 1985	12	33 (25.98)	12	61.1 (25.63)		-28.10 [-48.75, -7.45]
Furst 1990	17	47 (36)	16	51 (33)		-4.00 [-27.54, 19.54]
Pinheiro 1993	14	34.7 (18.33)	11	47.7 (20.83)		-13.00 [-28.61, 2.61]
Weinblatt 1985	15	60 (27.11)	14	54 (18.71)		6.00 [-10.86, 22.86]
Williams 1985	1	0 (0)	1	0 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**59**		**54**			**-8.95 [-18.17, 0.27]**

Heterogeneity: Chi^2 = 6.75, df = 3 (P = 0.08); I^2 =56%

Test for overall effect: Z = 1.90 (P = 0.057)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 MTX - Withdrawals and dropouts, Outcome 1 Withdrawals and dropouts - Total.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 2 MTX - Withdrawals and dropouts

Outcome: 1 Withdrawals and dropouts - Total

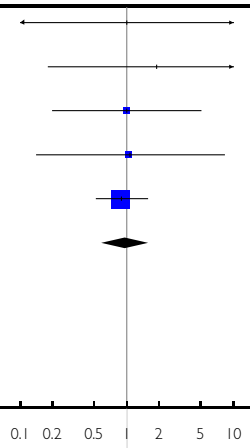
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Andersen 1985	1/14	1/14		3.2 %	1.00 [0.06, 16.85]
Furst 1990	2/17	1/16		4.6 %	1.91 [0.18, 19.80]
Pinheiro 1993	4/14	4/14		9.8 %	1.00 [0.20, 5.00]
Weinblatt 1985	2/17	2/18		6.0 %	1.06 [0.14, 8.30]
Williams 1985	39/95	41/94		76.4 %	0.90 [0.51, 1.60]
Total (95% CI)	**157**	**156**		**100.0 %**	**0.95 [0.58, 1.58]**

Total events: 48 (Treatment), 49 (Control)

Heterogeneity: $Chi^2 = 0.39$, df = 4 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable



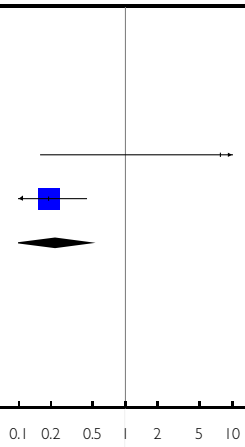
Analysis 2.2. Comparison 2 MTX - Withdrawals and dropouts, Outcome 2 Withdrawals due to lack of efficacy.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 2 MTX - 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
Andersen 1985	0/14	0/14		0.0 [0.0, 0.0]
Furst 1990	0/17	0/16		0.0 [0.0, 0.0]
Pinheiro 1993	0/14	0/14		0.0 [0.0, 0.0]
Weinblatt 1985	1/17	0/18		7.84 [0.16, 395.58]
Williams 1985	3/95	20/94		0.19 [0.08, 0.44]
Total (95% CI)	**157**	**156**		**0.22 [0.09, 0.52]**
Total events: 4 (Treatment), 20 (Control)				
Heterogeneity: Chi^2 = 3.34, df = 1 (P = 0.07); I^2 =70%				
Test for overall effect: Z = 3.49 (P = 0.00049)				
Test for subgroup differences: Not applicable				



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

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 2 MTX - Withdrawals and dropouts

Outcome: 3 Withdrawals due to adverse reactions

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Andersen 1985	1/14	0/14		7.39 [0.15, 372.38]
Furst 1990	2/17	1/16		1.91 [0.18, 19.80]
Pinheiro 1993	0/14	0/14		0.0 [0.0, 0.0]
Weinblatt 1985	1/17	0/18		7.84 [0.16, 395.58]
Williams 1985	30/95	10/94		3.48 [1.74, 6.99]
Total (95% CI)	**157**	**156**		**3.47 [1.82, 6.64]**

Total events: 34 (Treatment), 11 (Control)

Heterogeneity: Chi^2 = 0.56, df = 3 (P = 0.91); I^2 =0.0%

Test for overall effect: Z = 3.76 (P = 0.00017)

Test for subgroup differences: Not applicable

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

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 2 MTX - Withdrawals and dropouts

Outcome: 4 Withdrawals due to gastrointestinal adverse reactions

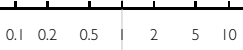
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Andersen 1985	0/14	0/14		0.0 [0.0, 0.0]
Furst 1990	0/17	1/16		0.13 [0.00, 6.42]
Pinheiro 1993	0/14	0/14		0.0 [0.0, 0.0]
Weinblatt 1985	1/17	0/18		7.84 [0.16, 395.58]
Williams 1985	3/95	0/94		7.47 [0.77, 72.69]
Total (95% CI)	**157**	**156**		**3.32 [0.57, 19.30]**

Total events: 4 (Treatment), 1 (Control)

Heterogeneity: $Chi^2 = 3.33$, df = 2 (P = 0.19); $I^2 = 40\%$

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2 MTX - Withdrawals and dropouts, Outcome 5 Withdrawals due to mucocutaneous adverse reactions.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 2 MTX - Withdrawals and dropouts

Outcome: 5 Withdrawals due to mucocutaneous adverse reactions

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Andersen 1985	0/14	0/14		0.0 [0.0, 0.0]
Furst 1990	0/17	0/16		0.0 [0.0, 0.0]
Pinheiro 1993	0/14	0/14		0.0 [0.0, 0.0]
Weinblatt 1985	0/17	0/18		0.0 [0.0, 0.0]
Williams 1985	5/95	4/95		1.26 [0.33, 4.79]
Total (95% CI)	**157**	**157**		**1.26 [0.33, 4.79]**

Total events: 5 (Treatment), 4 (Control)

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

Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 MTX - Withdrawals and dropouts, Outcome 6 Withdrawals due to liver enzyme abnormalities.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 2 MTX - Withdrawals and dropouts

Outcome: 6 Withdrawals due to liver enzyme abnormalities

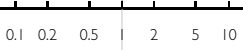
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Andersen 1985	0/14	0/14		0.0 [0.0, 0.0]
Furst 1990	0/17	0/16		0.0 [0.0, 0.0]
Pinheiro 1993	0/14	0/14		0.0 [0.0, 0.0]
Weinblatt 1985	0/17	0/18		0.0 [0.0, 0.0]
Williams 1985	18/95	4/94		4.14 [1.71, 10.05]
Total (95% CI)	**157**	**156**		**4.14 [1.71, 10.05]**

Total events: 18 (Treatment), 4 (Control)

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

Test for overall effect: Z = 3.14 (P = 0.0017)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 MTX - Withdrawals and dropouts, Outcome 7 Withdrawals due to hemaetological adverse reactions.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 2 MTX - Withdrawals and dropouts

Outcome: 7 Withdrawals due to hemaetological adverse reactions

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Andersen 1985	1/14	0/14		7.39 [0.15, 372.38]
Furst 1990	1/17	0/16		6.97 [0.14, 351.74]
Pinheiro 1993	0/14	0/14		0.0 [0.0, 0.0]
Weinblatt 1985	0/17	0/18		0.0 [0.0, 0.0]
Williams 1985	4/95	1/94		3.37 [0.57, 19.83]
Total (95% CI)	**157**	**156**		**4.20 [0.94, 18.68]**

Total events: 6 (Treatment), 1 (Control)

Heterogeneity: Chi^2 = 0.20, df = 2 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 1.88 (P = 0.060)

Test for subgroup differences: Not applicable

Analysis 2.8. Comparison 2 MTX - Withdrawals and dropouts, Outcome 8 Withdrawals due to infection.

Review: Methotrexate for treating rheumatoid arthritis

Comparison: 2 MTX - Withdrawals and dropouts

Outcome: 8 Withdrawals due to infection

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Andersen 1985	0/14	0/14		0.0 [0.0, 0.0]
Furst 1990	1/17	0/16		6.97 [0.14, 351.74]
Total (95% CI)	**31**	**30**		**6.97 [0.14, 351.74]**

Total events: 1 (Treatment), 0 (Control)

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

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable

WHAT'S NEW

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

Date	Event	Description
5 November 2008	Amended	Converted to new review format. CMSG ID: C052-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)

Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Folic Acid Antagonists [*therapeutic use]; Methotrexate [*therapeutic use]

MeSH check words

Humans