

Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy and toxicity of methotrexate (MTX) monotherapy compared with MTX combination with non-biological disease-modifying antirheumatic drugs (DMARDs) in adults with rheumatoid arthritis.

Method: A systematic review of randomised trials comparing MTX alone and in combination with other non-biological DMARDs was carried out. Trials were identified in Medline, EMBASE, the Cochrane Library and ACR/EULAR meeting abstracts. Primary outcomes were withdrawals for adverse events or lack of efficacy.

Results: A total of 19 trials (2025 patients) from 6938 citations were grouped by the type of patients randomised. Trials in DMARD naive patients showed no significant advantage of the MTX combination versus monotherapy; withdrawals for lack of efficacy or toxicity were similar in both groups (relative risk (RR) = 1.16; 95% CI 0.70 to 1.93). Trials in MTX or non-MTX DMARD inadequate responder patients also showed no difference in withdrawal rates between the MTX combo versus mono groups (RR = 0.86; 95% CI 0.49 to 1.51 and RR = 0.75; 95% CI 0.41 to 1.35), but in one study the specific combination of MTX with sulfasalazine and hydroxychloroquine showed a better efficacy/toxicity ratio than MTX alone with RR = 0.3 (95% CI 0.14 to 0.65). Adding leflunomide to MTX non-responders improved efficacy but increased the risk of gastrointestinal side effects and liver toxicity. Withdrawals for toxicity were most significant with ciclosporin and azathioprine combinations.

Conclusion: In DMARD naive patients the balance of efficacy/toxicity favours MTX monotherapy. In DMARD inadequate responders the evidence is inconclusive. Trials are needed that compare currently used MTX doses and combination therapies.

Methotrexate (MTX) is among the most effective disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) with less toxicity and better tolerability. Unfortunately, MTX alone may not fully control disease activity. Increasingly, MTX is used in combination with other non-biological DMARDs.^{1–3}

Many MTX and traditional DMARDs combination regimens have been studied, but several important questions remain.^{4–6} What is the relative benefit and toxicity of MTX mono versus MTX combination with DMARDs? When should the

combination DMARD therapy be used: initially or only after a trial of MTX monotherapy? Finally, which is the preferred combination DMARD strategy? These questions are particularly salient as formularies in many countries require the use of MTX mono and MTX combo therapies before reimbursing for the more expensive biological drugs. The objective of this paper was to systematically review randomised trials that compared MTX monotherapy with MTX in combination with other non-biological DMARDs. This manuscript is part of the 3E (Evidence, Expertise and Exchange) Initiative described in more details in the same issue of this journal.⁷

MATERIALS AND METHODS

Literature search

We performed a search of electronic bibliographic databases including Medline (1950 to June week 3 2007), EMBASE (1980 to 2007 week 25) and the Cochrane Central Register of Controlled Trials (2nd quarter 2007) using a search strategy that combined terms for “rheumatoid arthritis”, “methotrexate” and “randomised controlled trials” (full search strategy available online at <http://www.annrheumdis.com/supplemental>). We also searched the abstracts of the Annual scientific meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) from 2005 to 2007, the references lists of all relevant studies, letters and review articles, and all languages were included.

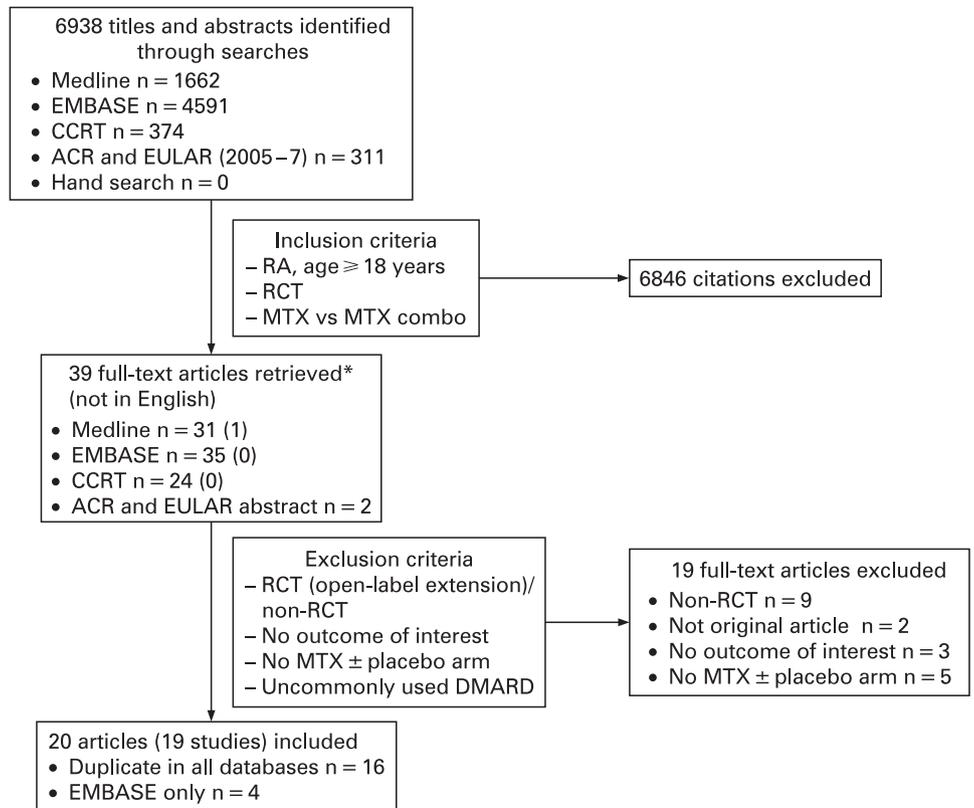
Study selection

Two reviewers (WK, JT) independently screened the titles and abstracts of the citations and retrieved relevant articles. The following selection criteria were used: (a) randomised controlled trials of MTX monotherapy versus MTX combined with other DMARDs of at least 12 weeks of trial duration (open-label extensions were excluded as well as studies comparing DMARDs not currently used—for example, oral gold); (b) patients with RA ≥ 18 years old; (c) data available on one or more of following prespecified outcomes: ACR core set⁸; ACR 20, 50 or 70 responses⁹; ACR remission¹⁰; Disease Activity Score (DAS)^{11 12}; EULAR response¹³; withdrawal due to lack of efficacy or adverse events (AEs);



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Figure 1 Results of the literature search and disposition of the potentially relevant studies. *Number is not equal to the sum of the number from each database owing to duplication among databases. ACR, American College of rheumatology; CCRT, Cochrane Central Register of Controlled Trials; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomised controlled trial.



number of total or individual AEs (only commonly reported individual AEs are presented).

Data abstraction and quality assessment

Two reviewers (WK, VP) independently extracted the data and assessed the quality of relevant studies. Study quality was assessed using van Tulder ‘s scale.¹⁴ This scale comprises 11

questions, including randomisation, blinding procedure (patients, provider and outcome assessor), concealed treatment allocation, similarity of the important baseline characteristics, co-intervention, timing of the outcome assessment, compliance and withdrawals and intention-to-treat analysis. Each item is rated as “yes” = 1 and “no or do not know” = 0. The score ranges from 0 to 11.

Table 1 Excluded studies and reason for exclusion

Study	Reason for exclusion
Calguneri, 1999	No methotrexate monotherapy arm (data combined with sulfasalazine and hydroxychloroquine monotherapy)
Clegg, 1997	No outcome of interest
Haagsma, 1995	Summary of Haagsma <i>et al.</i> (included in this review) ²⁷
Kremer, 2004	Open-label extension of randomised controlled trial
Maillefert, 2003	Open-label extension of randomised controlled trial
Matucci-Cerinic, 2003	Summary of Kremer <i>et al.</i> (included in this review) ²⁰
Mottaghi, 2005	Non-randomised controlled trial
Mroczkowski, 1999	Open-label extension of randomised controlled trial
Nagashima, 2006	Non-randomised controlled trial
Nisar, 1994	Non-randomised controlled trial
O’Dell, 1996	Open-label extension of randomised controlled trial
Rau, 1998	Non-randomised controlled trial
Stein, 1997	Open-label extension of randomised controlled trial
Trnavsky, 1993	No methotrexate monotherapy arm
Willkens, 1996	Published in the journal supplements and the key data have been reported in Willkens <i>et al.</i> (included in this review) ²⁵
Krause D <i>et al.</i> (German), 1998	Non-randomised controlled trial
Gekoop-Ruiterman YPM, 2005	No MTX monotherapy arm
Gekoop-Ruiterman YPM, 2007	No MTX monotherapy arm
Mottonen T <i>et al.</i> , 1999	No MTX monotherapy arm

Data synthesis

We used RevMan 4.2.10 for analysis. The efficacy analysis was stratified into three groups based on previous DMARD use. The “DMARD naïve, parallel strategy” refers to trials in which patients who never received DMARDs (including MTX) were randomised to start MTX alone or MTX plus another DMARD; The “MTX inadequate response, step-up strategy” refers to trials in which patients with inadequate response to MTX were randomised to continue the use of MTX alone or to add a second DMARD. The “non-MTX DMARDs inadequate response, step-up strategy” refers to trials where patients with inadequate response to DMARDs (other than MTX) were randomly switched to MTX alone or MTX plus another DMARD. The toxicity analysis was stratified by DMARD combination and pooled across trials for each combination.

For continuous measures of efficacy, we used either end of trial data or change from baseline and pooled them as weighted mean differences using a random effect model.¹⁵ For the categorical measures of efficacy, the end of trial results were pooled and estimated using the relative risk (RR) with random effect model. An RR >1 favours MTX combination therapy. For the analysis of patient withdrawals, an RR >1 favours MTX monotherapy (MTX monotherapy results in less withdrawal than MTX combination). Our prespecified primary analysis was based on total withdrawal rates for efficacy or toxicity.

Table 2 Characteristic of included studies

Study	Sample size	Study duration (months)	Strategy*	MTX (mg/week)			Quality rating† (0–11)
				Mono	Combo	DMARD	
Haagsma, 1997 ¹⁶	105	12	DMARD-N	15	7.5	SSZ 3 g/day	10
Dougados, 1999 ⁶	209	12	DMARD-N	Up to 15	Up to 15	SSZ 3 g/day	7
Marchesoni, 2003 ⁴	61	12	DMARD-N	11.2	9.5	CSA 2.5 mg/kg/day	8
Tascioglu, 2003 ⁵	70	12	DMARD-N	7.5	7.5	SSZ 2 g/day	5
Hetland, 2006 ¹⁷	160	12	DMARD-N	15	12.5	CSA 2.5 mg/kg/day	9
O'Dell, 2006 ¹⁸	66	24	DMARD-N	7.5–17.5	7.5–17.5	DOXY 20 or 100 mg twice/day	7
Tugwell, 1995 ¹⁹	148	6	MTX-IR	15	15	CSA 2.5–5 mg/kg/day	7
Kremer, 2002 ²⁰	263	6	MTX-IR	16.1	16.8	LEF 20 mg/day	10
Lehman, 2005 ²¹	65	12	MTX-IR	18	18	IM gold 50 mg/week	8
Jarrett, 2005 ²²	39	6	MTX-IR	11.9	14	Zoledronic acid 5 mg IV twice	7
Ogrendik, 2007 ²³	76	6	MTX-IR	17.5	15	LEV 500 mg/day	8
Willkens, 1992, ²⁴ 1995 ²⁵	212	6	Non-MTX-IR	5–15	5–15	AZA 50–150 mg/day	8
Ferraz, 1994 ²⁶	82	6	Non-MTX-IR	7.5	7.5	CQ 250 mg/day	9
Haagsma, 1994 ²⁷	40	6	Non-MTX-IR	8.3	7.9	SSZ 2 g/day	7
O'Dell, 1996 ²⁸	102	6	Non-MTX-IR	Up to 17.5	Up to 17.5	SSZ 1 g/day HCQ 400 mg/day	9
Hanyu, 1999 ²⁹	37	60	Non-MTX-IR	7.5	5	Previous DMARD (penicillamine, BUC, IM gold)	3
Ichikawa, 2005 ³⁰	71	24	Non-MTX-IR	8	8	BUC 200 mg/day	7
Capell, 2007 ³¹	165	12	Non-MTX-IR	15	12.5	SSZ 2 g/day	8
Islam, 2000 ³²	54	6	Not clear	7.5–15		SSZ 2 g/day	3

Our analysis included data only from patients in the MTX ± placebo and MTX+other DMARDs arms (n = 158).

*DMARD-N, disease-modifying antirheumatic drug naïve patients; MTX-IR, methotrexate inadequate response patients; non-MTX-IR, non-MTX DMARDs inadequate response patients; †Van Tulder's scale.

AZA, azathioprine; BUC, bucillamine; CQ, chloroquine; CSA, ciclosporin; DOXY, doxycycline; HCQ, hydroxychloroquine; IM gold, intramuscular gold; LEF, leflunomide; LEV, levofloxacin; SSZ, sulfasalazine.

The heterogeneity of the trials for each pooled analysis was estimated using the χ^2 test and I^2 test.

RESULTS

Our search retrieved 6938 citations. After review of titles and abstracts and removal of duplicates across databases, 39 full-text articles were retrieved for further evaluation and 20 articles (from 19 studies) were retained for our analysis (fig 1). Table 1 summarises the excluded studies and reason for exclusion.

Characteristics of the included studies

Table 2 gives the characteristics of the included studies. The total number of patients in the trials was 2025. Most of the trials were 6 or 12 months in duration. The doses of MTX ranged between 5 and 18 mg/week but most were between 7 and 15 mg/week. MTX was administered orally in all trials.

Methodological quality of studies

Ten studies^{16–18 20 21 24–26 28 31} demonstrated appropriate randomisation, adequate blinding of intervention in both patients and care providers as well as clearly reported number and reason for withdrawal and drop out. Seven of these^{16 17 20 24–26 28} were high-quality (comparison groups had similar baseline characteristics and co-interventions and acceptable withdrawals and drop outs) but one study¹⁸ had a high drop-out rate (~59%). In two studies,^{21 31} there were unequal co-interventions including steroid or non-steroidal anti-inflammatory drugs (NSAIDs) between the treatment groups. One of these²¹ also had a high drop-out rate in the MTX + placebo group due to lack of efficacy (52% vs 24% in MTX vs MTX+gold, respectively).

In five studies,^{6 19 22 23 30} the method of randomisation was not explicitly described; additionally co-intervention was either unclear^{6 19} or higher^{22 30} (NSAIDs or steroid) in the MTX treatment group

Owing to their open-label nature, five studies^{4 5 27 29 32} were rated lower and in three the method of randomisation was also unclear.^{5 29 32}

Efficacy

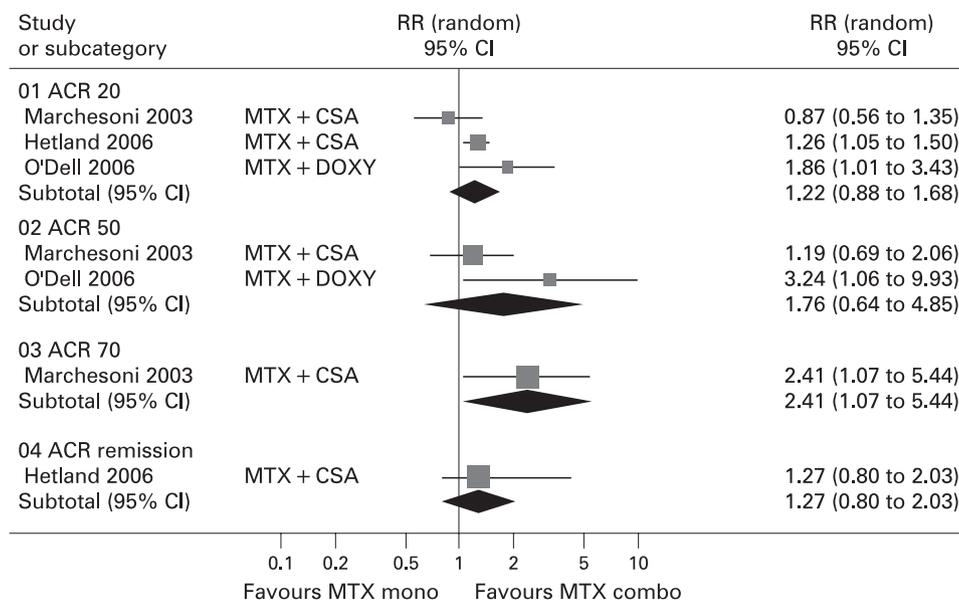
DMARD naïve, parallel design

The ACR responses were available in three of the six trials that compared MTX mono with MTX combo therapies in MTX naïve patients (fig 2). These trials included a total of 287 patients. Combinations arms were MTX+ciclosporin (CSA)^{4 17} and MTX+doxycycline.¹⁸ The only significant result was for the ACR 70 response in one CSA trial with RR = 2.41 (95% CI 1.07 to 5.44) favouring the MTX combination arm.

The EULAR response was available in an additional two trials (368 patients) with combination of MTX+ sulfasalazine (SSZ)^{6 16} or MTX+CSA¹⁷ (fig A, online only). There was no significant difference between the two groups for a “good” or “moderate” EULAR response or remission.

The number of patients who withdrew owing to lack of efficacy was available in five of the six trials (405 patients) with combination of MTX+SSZ,^{5 6 16} MTX+CSA⁴ and MTX+doxycycline¹⁸ (fig B, online only). MTX combination therapy resulted in less patient withdrawal than monotherapy but it was not significant (RR = 0.63, 95% CI 0.34 to 1.17) furthermore, the number of patients who withdrew because of

Figure 2 American College of Rheumatology (ACR) response: MTX combination vs MTX monotherapy in DMARD naïve group. CSA, ciclosporin; DMARD, disease-modifying antirheumatic drug; DOXY, doxycycline; MTX, methotrexate.



toxicity was significantly increased 1.72 (95% CI 1.04 to 2.83) (fig C, online only).

MTX inadequate response, step-up design

The ACR responses were available in four of five trials (552 patients) that compared MTX mono with MTX combo therapies in MTX inadequate response patients (fig 3). Combination arms included MTX+leflunomide (LEF),²⁰ MTX+CSA,¹⁹ MTX+ intramuscular gold (IM gold)²¹ and MTX+ levofloxacin.²³ In this group of trials combination therapy was significantly more effective than MTX monotherapy with RR = 2.51 (95% CI 1.92 to 3.28), RR = 4.54 (95% CI 2.51 to 8.20) and RR = 5.59 (95% CI 2.08 to 15.01) for ACR 20, 50 and 70 response, respectively. There were no data on ACR remission and EULAR response.

The number of patients who withdrew owing to lack of efficacy was available in three of the five trials (476 patients) with combination of MTX+LEF,²⁰ MTX+CSA¹⁹ and MTX+ IM

gold²¹ (fig B, online only), showing significantly fewer patient withdrawals than in the MTX monotherapy group with RR = 0.42 (95% CI 0.21 to 0.84). However, the number of patients who withdrew because of toxicity was significantly increased 1.89 (95% CI 1.05 to 3.41) (fig C, online only).

Non-MTX DMARD inadequate response, step-up design

The ACR responses were available in two of eight trials (158 patients) that compared MTX mono with MTX combo therapies in non-MTX inadequate responders (fig 4). Only the pooled ACR 20 showed a significant benefits for the combination of MTX+SSZ³¹ and MTX+bucillamine (BUC)³⁰ over monotherapy with RR = 1.85 (95% CI 1.21 to 2.83). There were no data on ACR remission.

The EULAR response criteria were available for one of these two studies³¹ (fig D, online only) and showed no statistically significant different between two groups.

Figure 3 American College of Rheumatology (ACR) response: MTX combination vs MTX monotherapy in MTX inadequate response group. CSA, ciclosporin; IM gold, intramuscular gold; LEF, leflunomide; LEV, levofloxacin; MTX, methotrexate.

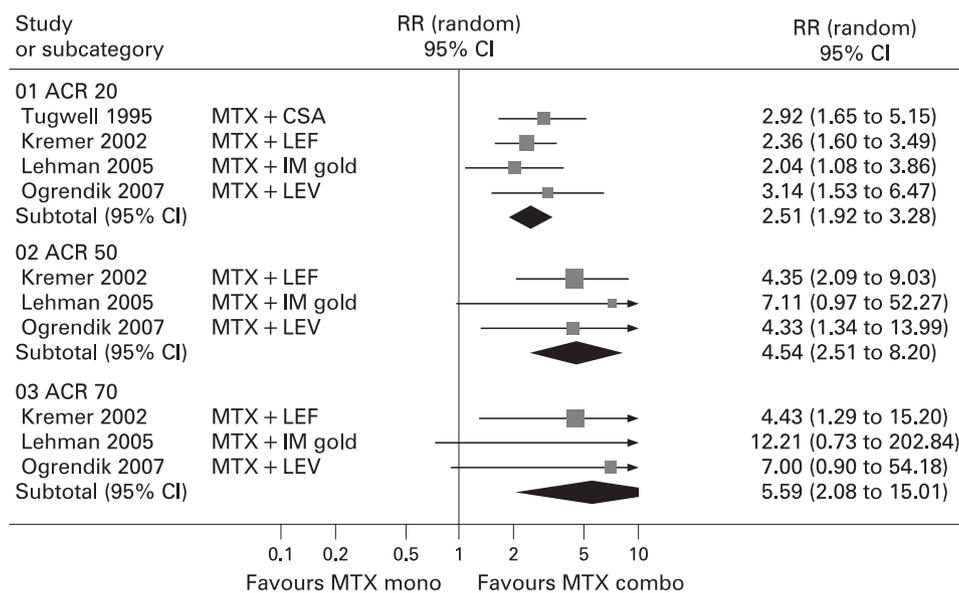
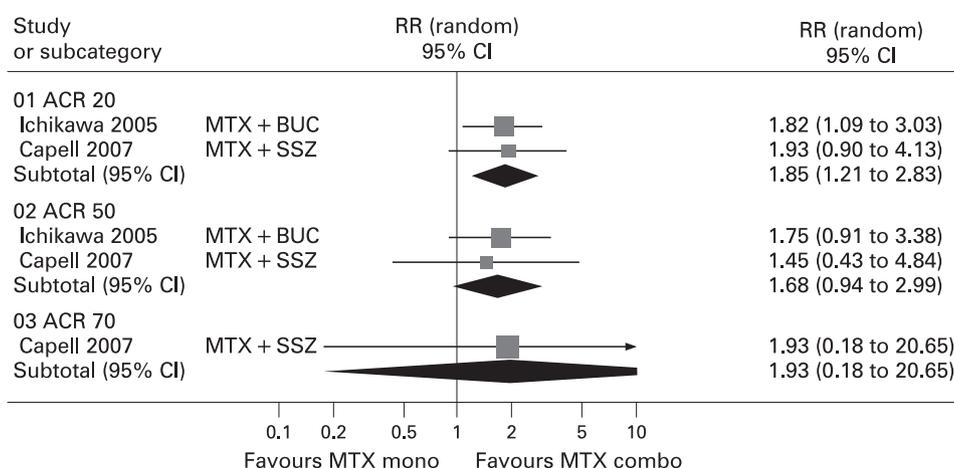


Figure 4 American College of Rheumatology (ACR) response: MTX combination vs MTX monotherapy in non-MTX inadequate response group. BUC, bucillamine; MTX, methotrexate; SSZ, sulfasalazine.



The number of patients who withdrew owing to lack of efficacy was available in five of eight trials (329 patients) with combination of MTX+chloroquine (CQ),²⁶ MTX+SSZ+hydroxychloroquine (HCQ),³³ MTX+SSZ,³¹ MTX+BUC³⁰ and MTX+ previous DMARDs (BUC, D-penicillamine and IM gold).²⁹ MTX combination therapy yielded significantly fewer patient withdrawals than monotherapy with RR = 0.37 and 95% CI 0.16 to 0.87 (fig B, online only).

Toxicity

Number of total or individual reported adverse events

The azathioprine²⁵ and IM gold²¹ MTX combinations increased the risk of the number of total side effects RR = 1.67 (95% CI 1.21 to 2.3) and RR = 2.61 (95% CI 1.22 to 5.55), respectively. The sulfasalazine^{5, 6, 16, 27} and leflunomide²⁰ MTX combinations increased the risk of gastrointestinal (GI) side effects (RR = 1.75, 95% CI 1.14 to 2.67 and RR = 1.67, 95% CI 1.17 to 2.4, respectively). The leflunomide MTX combination²⁰ also increased the risk of an abnormal liver function test with RR = 4.3 (95% CI 2.58 to 7.15).

Withdrawal due to adverse reaction

In 17 of the 19 trials (1624 patients: 824 in combination group vs 800 monotherapy group) combination therapy resulted in more withdrawal due to adverse reactions than monotherapy but the differences were significant only for the CSA^{4, 17, 19} and azathioprine²⁴ combinations with RR = 1.88, 95% CI 1.02 to 3.50 and RR = 5.18 (95% CI 1.58 to 16.96), respectively (fig 5).

Combined withdrawal due to lack of efficacy and toxicity (fig 6)

Our primary analysis was based on withdrawals for both efficacy and safety; data were available for 13 of the 19 trials. In DMARD naïve patients as well as in MTX inadequate responders pooled results showed no advantage of combination therapy over MTX monotherapy (RR = 1.16, 95% CI 0.70 to 1.93 and RR = 0.86, 95% CI 0.49 to 1.51, respectively). The non-MTX DMARD inadequate responders also showed no advantage of combination therapy (RR = 0.75, 95% CI 0.41 to 1.35). However, there was significant heterogeneity in this group ($I^2 = 57.4\%$) with one important outlier: the combination of MTX+SSZ+HCQ showed a better efficacy/toxicity ratio than MTX alone with RR = 0.3 (95% CI 0.14 to 0.65).

DISCUSSION

Despite the introduction of new biological treatments, MTX alone or in combination with other traditional DMARDs

remain the recommended first-line treatments for most patients with RA. Our systematic review examined their respective risks and benefits. The simplest criterion of benefit/risk ratio for drug evaluation is whether a drug is stopped owing to inefficacy or AEs. These data were available for 13/19 trials and therefore represent the most powerful results from our meta-analysis. Overall, there were no benefits of MTX combo over monotherapy either within the three design strategies or across all trials (RR = 0.89, 95% CI 0.66 to 1.21) (fig 6). However, one study of the combination MTX, SSZ and HCQ showed better efficacy/toxicity ratio than MTX alone with RR = 0.3 (95% CI 0.14 to 0.65).

Outcome measures other than withdrawals were not reported consistently across trials. In the “DMARD naïve, parallel strategy” ACR responses showed a significant improvement for the combination therapies only for the ACR 70 but with increasing risk of withdrawals due to toxicity. Additionally, none of the trials that reported other composite or single outcome measures could demonstrate a benefit of an initial course of combination therapy over MTX monotherapy in DMARD naïve patients.

In the “MTX inadequate response, step-up strategy” four trials that reported ACR responses showed that combination therapy was significantly more effective than MTX monotherapy (with an equally significant increase in risk of withdrawal for toxicity). These trials, however, do not reflect current practice. The dose of MTX (7–15 mg/week) is lower than current use and patients randomised to the MTX monotherapy arm continued to receive the same inadequate low dose of MTX. In actual practice doctors would increase the dose of MTX or change to parenteral administration before adding another DMARD. Therefore, the current evidence in patients with inadequate response to MTX is inconclusive pending results from new trials that compare maximum doses of MTX monotherapy with combination therapies.

In the “non-MTX DMARDs inadequate response, step-up strategy” only two studies^{30, 31} were available for the ACR response analysis. Unfortunately, no conclusions can be reached. In Capell’s study, patients for whom SSZ 2 g/day had already failed were randomised to receive MTX alone or MTX + the “same dose” of SSZ; so in reality this was a study comparing MTX in both arms. The second is a trial of bucillamine which is not commonly used in North America or Europe.

For toxicity analyses, GI and liver adverse events were higher in the sulfasalazine and leflunomide MTX combinations but did

Figure 5 Withdrawal due to adverse reaction stratified by combination of disease-modifying antirheumatic drugs (DMARDs). AZA, azathioprine; BUC, bucillamine; CSA, ciclosporin; CQ, chloroquine; HCQ, hydroxychloroquine; IM gold, intramuscular gold; LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine.

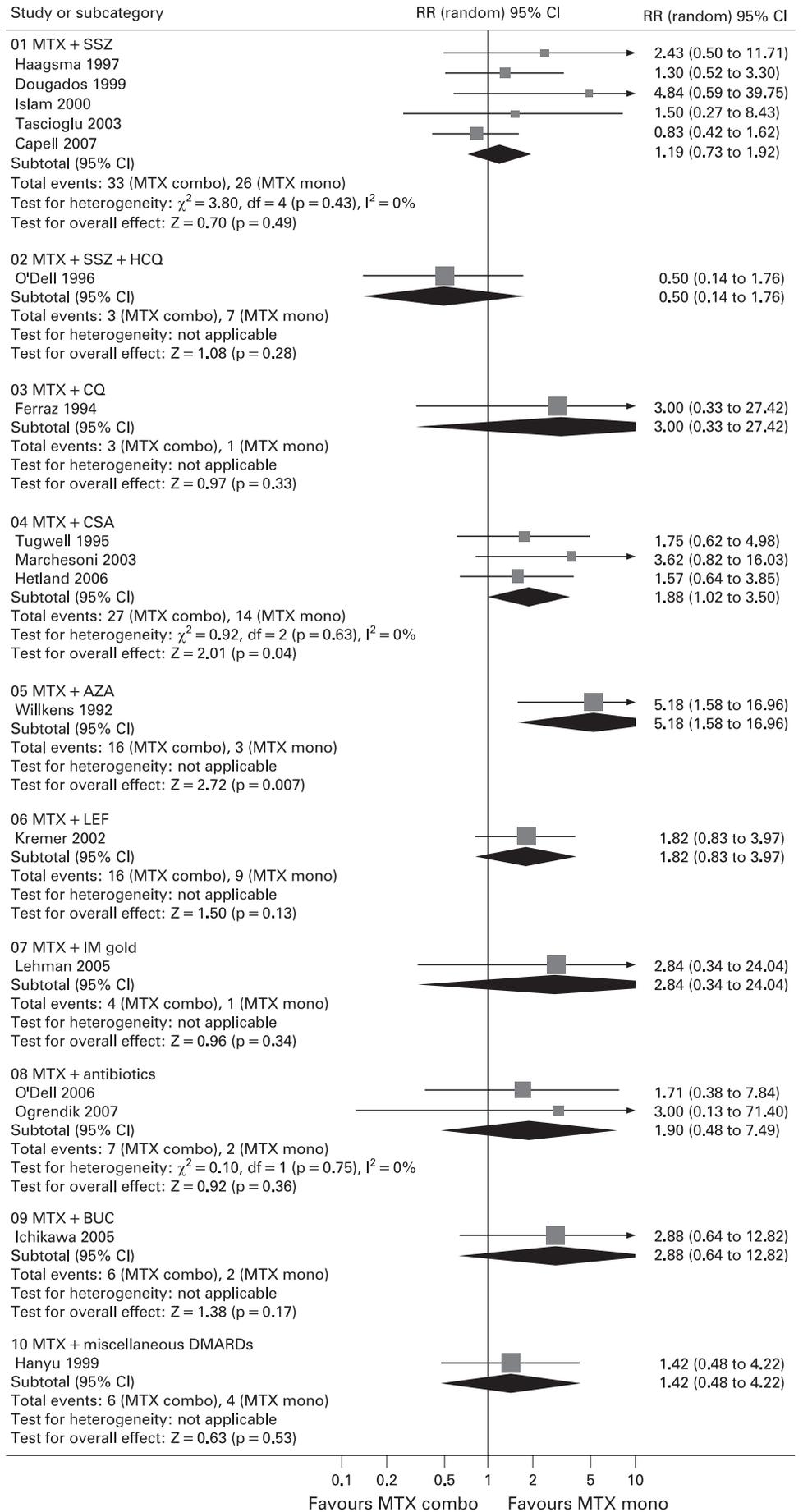
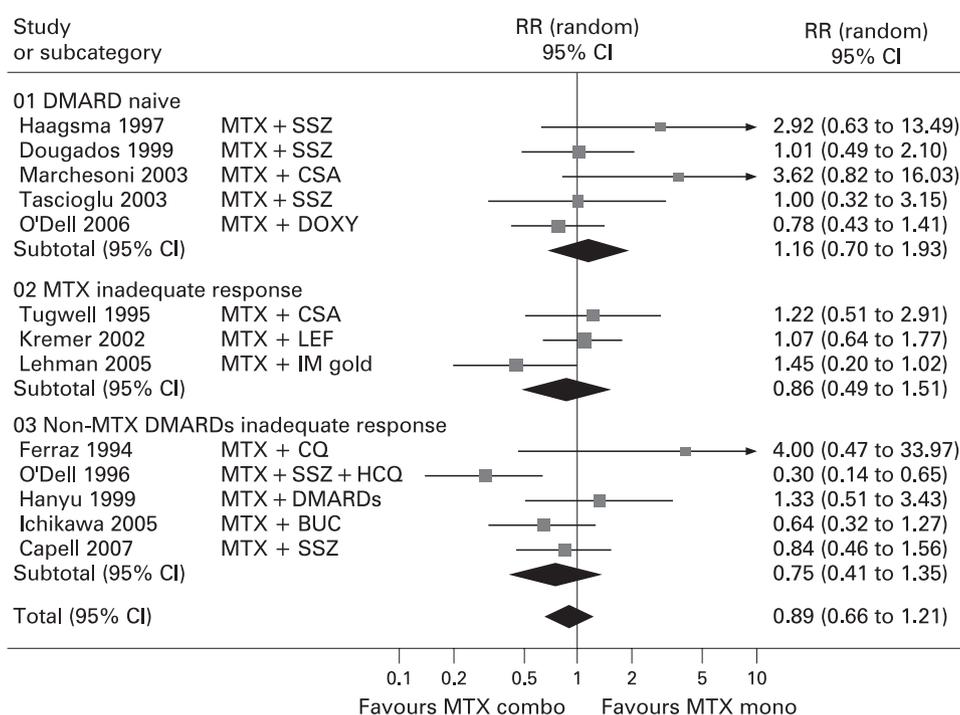


Figure 6 Withdrawal due to either lack of efficacy or toxicity: MTX combination vs MTX monotherapy in disease-modifying antirheumatic drug (DMARD) naïve, MTX inadequate response and non-MTX inadequate response groups. BUC, bucillamine; CQ, chloroquine; CSA, ciclosporin; DOXY, doxycycline; HCQ, hydroxychloroquine; IM gold, intramuscular gold; LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine.



not lead to significant differences in withdrawal rates. The total number of side effects was higher with gold and azathioprine MTX combinations. Withdrawal rates due to adverse reactions were higher in all the combination therapies, but the differences were significant only for the combinations of MTX+ciclosporin and MTX+azathioprine.

There are important limitations to our analyses; many of the studies included a small number of patients; most used lower doses of MTX than in current practice and had different length of follow-up and several studies were done with drugs that are not commonly used (bucillamine, doxycycline, levofloxacin, chloroquine, IM gold and ciclosporin). Furthermore, most of the combinations were studied in only one or two trials, except the combination MTX+SSZ, which included five trials. Also, outcome measures were inconsistently reported; European trials used DAS or DAS28 while others reported ACR responses, some (studies before 2000) reported only individual clinical and laboratory outcomes. All these limitations complicate the pooling of results across studies. Nonetheless, this meta-analysis presents useful information, particularly when looking at total withdrawal rates where combination across a number of studies is possible.

Three previous systematic reviews^{34–36} and two meta-analyses^{37,38} compared DMARD monotherapy with combination therapy. Felson *et al* (1994)³⁷ and Verhoeven *et al* (1998)³⁵ concluded that combination DMARD therapy does not substantially improve efficacy and toxicity is increased; this is consistent with our overall results that included more recent trials. Hochberg *et al* (2001)³⁶ included only MTX inadequate responder studies and found that ACR responses improved significantly when a second DMARD was added. Choy *et al* (2005)³⁸ reached the same conclusion in this subgroup of patients based on analysis of withdrawals but added that improved efficacy is associated with an increased risk of adverse events. Donahue *et al* (2008)³⁴ reported only on a small subset of our included trials (mostly of sulfasalazine combinations) and the remainder of his and Choy's data cannot be compared with

our study because they included biologic agents as well as monotherapies with non-biological DMARDs other than MTX.

In summary, when the balance of efficacy and toxicity is taken into account, the evidence from our systematic review showed no significant advantage of the MTX combination versus monotherapy; only one study with the specific combination of MTX+SSZ+HCQ showed a better efficacy/toxicity ratio than MTX alone. Adding leflunomide to MTX non-responders improved efficacy but increased the risk of GI side effects and liver toxicity. Withdrawals because of toxicity varied but were most significant with ciclosporin and azathioprine combinations. Trials are needed that compare currently used MTX doses and combination therapies.

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APPENDIX

The results and figures of the search strategy (appendix 1), efficacy (EULAR response, withdrawal due to lack of efficacy, significant results of continuous data) and toxicity (appendix 2) are available on the website.