Cochrane Library

Cochrane Database of Systematic Reviews

Leflunomide for the treatment of rheumatoid arthritis (Review)

Osiri M, Shea B, Welch V, Suarez-Almazor ME, Strand V, Tugwell P, Wells GA

Osiri M, Shea B, Welch V, Suarez-Almazor ME, Strand V, Tugwell P, Wells GA.
Leflunomide for the treatment of rheumatoid arthritis.
Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD002047.
DOI: 10.1002/14651858.CD002047.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Leflunomide for the treatment of rheumatoid arthritis

Manathip Osiri[1], Beverley Shea[2], Vivian Welch[3], Maria E Suarez-Almazor[4], Vibeke Strand[5], Peter Tugwell[6], George A Wells[7]

[1]Department of Medicine, Faculty of Medicine, Bangkok, Thailand. [2]Institute of Population Health, University of Ottawa, Ottawa, Canada. [3]Centre for Global Health, Institute of Population Health, University of Ottawa, Ottawa, Canada. [4]General Internal Medicine, Ambulatory Treatment and Emergency Care, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA. [5]Division of Immunology, Stanford University, Portola Valley, California, USA. [6]Centre for Global Health, Institute of Population Health, Department of Medicine, Ottawa Hospital, Ottawa, Canada. [7]Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, Canada

Contact address: Manathip Osiri, Department of Medicine, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok, 10330, Thailand. Manathip.O@chula.ac.th.

Editorial group: Cochrane Musculoskeletal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 7, 2010.

Citation: Osiri M, Shea B, Welch V, Suarez-Almazor ME, Strand V, Tugwell P, Wells GA. Leflunomide for the treatment of rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2002, Issue 3. Art. No.: CD002047. DOI: 10.1002/14651858.CD002047.

ABSTRACT

Background

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease. Leflunomide is one of the more recent oral agents, classified as a disease-modifying antirheumatic drug (DMARD). It has a different mechanism of action than other existing DMARDs.

Objectives

To determine the efficacy and toxicity of leflunomide (monotherapy or combined with another DMARD) compared to placebo or other DMARDs in the treatment of RA.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, EMBASE, and Current Contents for trials (to June 2008). We also handsearched reference lists and consulted content experts.

Selection criteria

Two independent authors selected the trials that met predetermined inclusion criteria.

Data collection and analysis

Two authors independently extracted data and assessed methodologic quality using standardized forms.

Main results

Thirty-three trials were included, compared with six trials in the first review. The trials compared the efficacy and safety of leflunomide monotherapy with placebo or another DMARD; leflunomide combined with another DMARD (biologic or non-biologic) with DMARD monotherapy; and for different dosages of leflunomide. The ACR20 improvement criteria, demonstrated a 28% absolute difference in improvement in favour of leflunomide compared to placebo. There was no difference in ACR20 response rate between patients treated with leflunomide and sulfasalazine (SSZ) or methotrexate (MTX), at six and 12 months. Other clinical and radiological outcomes were improved significantly in the leflunomide group compared to placebo but were not different from SSZ or MTX. The efficacy of leflunomide combined with MTX was superior to MTX alone. On the other hand, leflunomide plus SSZ was not better than SSZ alone. Half-dose or weekly administration of leflunomide was shown to be as efficacious as regular doses (20 mg/day).

Withdrawals due to adverse events were 10% greater with leflunomide than placebo. Important adverse events included gastrointestinal symptoms, elevated liver function tests, alopecia, allergic reactions and rashes, and infections. Overall, adverse events and withdrawals with leflunomide monotherapy were not significantly different from SSZ or MTX. However, adverse events were reported more frequently in leflunomide plus MTX than with MTX but withdrawal rates were not significantly different.

Authors' conclusions

Leflunomide appears to improve all clinical outcomes and delay radiologic progression at both six and 12 months of treatment compared to placebo. Its efficacy and adverse events are comparable to MTX, SSZ, and cyclosporin A up to two years of treatment. Combined leflunomide and MTX was more efficacious than MTX alone up to three years of treatment and the adverse events did not increase. Different dosages of leflunomide were similar regarding their effectiveness and toxicity.

PLAIN LANGUAGE SUMMARY

Leflunomide for the treatment of rheumatoid arthritis

This summary of a Cochrane review presents what we know from research about the effect of Leflunomide on rheumatoid arthritis. The review shows that in people with rheumatoid arthritis:

- Leflunomide probably improves pain.

-Leflunomide improves number of tender or swollen joints and other outcomes such as pain and disability.
- Leflunomide causes side effects such as diarrhea, upset stomach, elevated liver function tests, and allergic reactions. We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects.

What is rheumatoid arthritis and what is Leflunomide?
When you have rheumatoid arthritis, your immune system, which normally fights infection, becomes over-active and attacks the lining of your joints. This makes your joints swollen, stiff and painful. The small joints of your hands and feet are usually affected first. There is no cure for rheumatoid arthritis at present, so the treatments aim to relieve pain and stiffness and improve your ability to move.

Leflunomide is a disease-modifying antirheumatic drug (DMARD). It works by stabilizing the over-active cells in the immune system that cause inflammation in the joints. Reducing the inflammation can prevent damage to the joints. Leflunomide is taken in pill form. It costs more than other DMARDs, so doctors usually prescribe it if other DMARDs haven't worked well.

Best estimate of what happens to people with rheumatoid arthritis who take Leflunomide after 6 months:

Pain (higher scores mean worse or more severe pain)

- People who took Leflunomide rated their pain to be10 points lower on a scale of 0 to 100 with Leflunomide (10% absolute improvement). This may be due to chance.
- People who took Leflunomide rated their pain to be about 14 points lower on a scale of 0 to 100.
- People who took a placebo rated their pain to be about 4 points lower on a scale of 0 to 100.

ACR 50 (number of tender or swollen joints and other outcomes such as pain and disability).

- 19 people out of 100 who took a placebo experienced improvement. (19% absolute improvement)

- 33 more people out of 100 experienced improvement in the symptoms of their rheumatoid arthritis with Leflunomide
- 14 people out of 100 experienced improvement in the symptoms of their rheumatoid arthritis with a placebo.

Side effects
- 10 more people who took Leflunomide dropped out from the trial because of side effects. (10% absolute difference)

- 16 people out of 100 who took Leflunomide dropped out from the trial because of side effects

- 6 people out of 100 who used a placebo dropped out from the trial because of side effects.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings: leflunomide versus placebo, 6 months

Leflunomide for rheumatoid arthritis versus placebo, 6 months

Patient or population: adult patients with rheumatoid arthritis

Settings: randomized controlled trials

Intervention: leflunomide ± DMARDs

Comparison: comparator (placebo or active treatment)

For outcome	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Absolute differences and NNTs (95% CI)
	Assumed risk	Corresponding risk				
	Control	Leflunomide +/- DMARDs				
ACR 50 response at 6 months	143 per 1000	331 per 1000 (189 to 579)	RR 2.32 (1.32 to 4.05)	221 (1 study)	++++ high	Absolute risk difference: 19% (8 to 30%) NNT: 6 (4 to 13)
HAQ change (0-3 scale) 6 months	Mean change in HAQ score in control groups ranged from 8.1 to 0.07 units lower	The mean change in HAQ score in the LEF was 0.43 lower (0.52 to 0.33 lower)		679 (3 studies)	++++ high	
Pain change (0-100 mm VAS) 6 months	The mean change in pain (0-100 mm VAS) in control groups ranged from 8.8 mm lower to 3 mm higher	The mean change in pain (0-100 mm VAS) in the LEF groups was 13.81 mm lower (15.91 to 11.71 mm lower)		724 (3 studies)	++++ high	
Radiographic change (Change in Sharp score) 12 months	Mean change in Sharp score in control group was 5.88	The mean change in Sharp score in the intervention groups was 1.63 lower (2.78 to 0.48 lower)	RR 1.23 (0.91 to 1.66)	380 (1 study)	++++ high	

Withdrawals due to adverse events	58 per 1000	158 per 1000 (97 to 259)	2.73 (1.67 to 4.47)	727 (3 studies)	++++ high	Absolute risk difference: 10% (6 to 15%) NNH: 10 (7 to 17)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; NNT: Number needed to treat; MTX: Methotrexate; Lef: Leflunomide; Plc: Placebo; ; GRADE: GRADE Working Group grades of evidence (see explanations)

GRADE Working Group grades of evidance
High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality (+++O): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality (++OO): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality (+OOO): We are very uncertain about the estimate.

Summary of findings 2. Summary of findings: leflunomide + methotrexate versus methotrexate, 6 months

Leflunomide + MTX vs MTX for rheumatoid arthritis, 6 months

Patient or population: adult patients with rheumatoid arthritis

Settings: randomized controlled trials

Intervention: leflunomide + MTX

Comparison: MTX

For outcome	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Absolute differences and NNTs (95% CI)
	Assumed risk	Corresponding risk				
	Control	Leflunomide +/- DMARDs				
ACR 50 at 6 months	60 per 1000	261 per 1000 (125 to 542)	RR 4.35 (2.09 to 9.03)	263 (1 study)	++++ high	Absolute risk difference: 20% (7 to 48%) NNT: 5 (4 to 9)

HAQ change Range of HAQ: 0-3 scale (6 months)	The mean change in HAQ score in the LEF group was 0.1 units lower	The mean change in HAQ scores in the LEF+MTX groups was 0.3 lower [0.42 to 0.18 lower]		263 (1 study)	++++ high	
Change in pain (0-100 mm VAS) 6 months	The mean change in the control group was 8.3 mm lower	The mean change in LEF+MTX group was 16.9 mm lower (from 10.10 to 23.7 mm lower)		263 (1 study)	++++ high	
Withdrawals due to adverse events (6 months)	68 per 1000	124 per 1000 (56 to 270)	1.82 (0.83 to 3.97)	263 (1 study)	+++ Moderate	Absolute risk difference: 5% (1 to 20%) NNH: 17 (not statistically significant)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; NNT: Number needed to treat; MTX: Methotrexate; Lef: Leflunomide; Plc: Placebo; ; GRADE: GRADE Working Group grades of evidence (see explanations)

GRADE Working Group grades of evidence
High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality (+++O): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality (++OO): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality (+OOO): We are very uncertain about the estimate.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that causes destruction of the joints. It affects around 1% of the population (Alarcon 1995). RA can cause progressive joint destruction and deformity despite treatment. Several medications, known as disease-modifying antirheumatic drugs (DMARDs), have been shown to decrease inflammation, delay bone erosion, and improve patients' health-related quality of life (HRQoL) (Wolfe 1991; Egsmose 1995; Fries 1996). DMARDs are more effective if administered within two years of disease occurrence (Egsmose 1995). However, not all RA patients benefit from treatment with DMARDs. A number of patients have progressive bone and joint damage although joint inflammation is well suppressed.

DMARDs may be classified into two groups, traditional DMARDs and biologic DMARDs. Traditional DMARDs contain a diverse group of chemical agents. They include methotrexate, antimalarial drugs (chloroquine and hydroxychloroquine), sulphasalazine, gold (injectable and oral forms), azathioprine, and d-penicillamine (Weinblatt 1999a). Newer DMARDs used include cyclosporin A, and leflunomide. These DMARDS may be prescribed either as a single agent or combined. Biologic DMARDs are the new class of DMARDs that act directly on specific mediators of the inflammatory processes in RA. This targeted treatment is more potent than traditional DMARDs and is increasingly prescribed in active RA. However, biologic DMARDs are not effective in all RA patients and may cause serious adverse events. The American College of Rheumatology (ACR) recommends the initiation of traditional DMARDs in all DMARD-naive patients with RA (Saag 2008).

Leflunomide has a different structure and mechanism of action from the other traditional DMARDs. Leflunomide is an isoxazol derivative and its active metabolite, A77 1726, acts as an inhibitor of pyrimidine synthesis (Fox 1998; Rozman 1998; Furst 1999). Since pyrimidine is required for the proliferation of activated autoimmune T-lymphocytes, the reduction of pyrimidine synthesis will decrease these T-cells and hence the autoimmune response, which should result in clinical benefits for RA patients (Fox 1998; Furst 1999).

OBJECTIVES

To determine the efficacy and safety of leflunomide in the treatment of RA. The major endpoints included:
(1) improvement of clinical outcomes, defined by the ACR (Felson 1995) or the European League Against Rheumatism (EULAR) (van der Heijde 1993; van Gestel 1996);
(2) improvement of the patients' HRQoL;
(3) incidence of side effects.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials (RCTs) or controlled clinical trials (CCTs) comparing leflunomide as monotherapy or in combination with another DMARD to placebo or other DMARDs.

Types of participants

Only RCTs or CCTs with patients aged at least 18 years old and clinical diagnosis of RA according to the ACR 1987 revised criteria (Arnett 1988) were included. These patients must have active disease as shown in the following outcomes:
1) number of tender joints;
2) number of swollen joints;
3) duration of morning stiffness;
4) acute phase reactants.

Types of interventions

Studies comparing leflunomide treatment (as monotherapy or in combination with other DMARDs) at a dose of 20 to 25 mg/day (with or without a loading daily dose of 100 mg given in the first one to three days) with placebo or other DMARDs were included. The duration of treatment in the trials must have been at least three months (or 12 weeks).

Types of outcome measures

Primary outcomes

Primary outcome measures were those defined as the ACR core set of disease activity measures for RA for clinical trials, which were endorsed by EULAR and the Outcome Measures in Rheumatology Clinical Trials (OMERACT) (Felson 1993; Felson 1995; Pincus 1999). They included:
(1) number of tender joints;
(2) number of swollen joints;
(3) pain level;
(4) patient global assessment of disease activity;
(5) physician global assessment of disease activity;
(6) functional ability;
(7) acute phase reactants;
(8) radiographic change of bone and joint damage for trials of at least one year of duration.
In addition, the numbers of patients who fulfilled the ACR20, ACR50, and ACR 70 response criteria were included.

The EULAR response criteria are measured as the Disease Activity Score (DAS). If the 28-joint assessment method is used, it is called DAS28. The outcomes include mean change in the DAS28 score from baseline; number of patients with remission (DAS28 score ≤ 2.6); number of patients with low disease activity (2.6 < DAS28 ≤ 3.2); number of patients with moderate disease activity (3.2 < DAS28 ≤ 5.1); number of patients with high disease activity (DAS28 > 5.1); number of patients with good response, moderate response, and no response according to the EULAR response criteria (van Gestel 1996).

Secondary outcomes

Secondary outcome measures included HRQoL of the patients, reported side effects, total number of patients withdrawn from the studies, and withdrawals due to adverse events.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2008); MEDLINE, EMBASE, HEALTHSTAR (1966 to June 2008) and Current Contents. The search strategy was conducted as recommended by Haynes et al (Haynes 1994) and modified for the Cochrane Musculoskeletal Group.

Reference lists were handsearched for further identification of published work and presentations at scientific meetings. Abstracts from the ACR, EULAR, and Asian Pacific League Against Rheumatism (APLAR) Annual Scientific Meetings were manually checked if the information was available. MeSH terms used in the database search included leflunomide, isoxazole, rheumatoid arthritis, and randomized controlled trial. Content experts were also contacted for unpublished data.

The search strategy used in the MEDLINE database is in Appendix 1.

Our search included articles of all languages.

Data collection and analysis

Data selection and extraction

All studies were assessed independently by two review authors (MO, BS) to select the trials that fulfilled the inclusion criteria. Differences were resolved by consensus.
From each selected trial, information regarding the trial design, characteristics of the study population, treatment regimen and duration, and baseline and end-of-study outcome measures was collected. These data were extracted by the same two review authors using standardized forms. Differences in data extraction were resolved by referring back to the original articles and establishing consensus. A third review author (MSA) was consulted to help resolve differences.

Assessment of risk of bias in included studies

Assessment of the trial methodological quality was performed using the recommendations from the Cochrane Musculoskeletal Group and a Delphi list (Higgins 2008, Verhagen 1998). The following criteria were answered as: A (yes), B (not sure), or C (no).

1) Was the allocation concealment adequately generated?

2) Was the allocation sequence adequately concealed?

3) Was knowledge of the allocated interventions adequately prevented during the study?

4) Were incomplete outcome data adequately addressed?

5) Are reports of the study free of suggestions of selective outcome reporting?

6) Was the study apparently free of other problems that could put it at a high risk of bias?

The global quality level was estimated for each study according to the following criteria (Higgins 2008):

Level A (low risk of bias): all of the individual criteria were met (all of them score A);

Level B (moderate risk of bias): one or more individual criteria partially met (one or more individual criteria scored B);

Level C (high risk of bias): one or more individual criteria not met (one or more criteria scored C).

The quality of the included studies was also assessed using a checklist developed by Jadad (Jadad 1996) which included the appropriateness of randomization, appropriateness of blinding, and description of dropouts and withdrawals. Quality was assessed independently by two review authors (MO, BS). Differences were resolved by consensus. A third review author (MSA) was consulted, if necessary. Studies were divided into low and high quality, based on the median quality score, to examine the effect of quality on the outcome measures. The maximum score was 5. Studies with quality scores less than 3 were considered low quality studies, while those that scored 3 or higher were high quality studies.

The grading of evidence used in this systematic review and meta-analysis followed the recommendations by the Cochrane Musculoskeletal Group and appear in the Evidence-based Rheumatology book (Tugwell 2004). They are: Platinum, Gold, Silver, and Bronze.

Platinum level: evidence from a published systematic review that has ≥ two RCTs, each satisfying the following.

- Sample size of ≥ 50 per group. If no statistically significant difference is found, the sample size are adequately powered for a 20% relative difference in the relevant outcome.
- Blinding of patients and assessors for outcomes.
- Handling of withdrawals with > 80% follow up (imputations based on methods such as the last observation carried forward (LOCF) were acceptable).
- Concealment of treatment allocation.

Gold level: Evidence from ≥ one RCT that meets all of the following criteria for the major outcome(s):

- Sample size of ≥ 50 per group. If no statistically significant difference is found, the sample size are adequately powered for a 20% relative difference in the relevant outcome.
- Blinding of patients and assessors for outcomes
- Handling of withdrawals >80% follow up (imputations based on methods such as LOCF acceptable)
- Concealment of treatment allocation

Silver level: evidence from a systematic review or RCT that does not meet the above criteria. Also includes evidence from ≥ one non-randomized cohort study or ≥ one case-control study. Evidence from an RCT with 'head-to-head' comparison of agents is considered Silver level ranking unless a reference is provided to a comparison of one of the agents to placebo showing ≥ 20% relative difference.

Bronze level: evidence from ≥ one case series without controls (including simple before and after studies) or is derived from expert opinion based on clinical experience without reference to any of the foregoing.

In addition, the quality of evidence was assessed by the GRADE approach. The quality of a body of evidence in the GRADE approach is categorized into four levels: high (++++) for RCTs, or double-upgraded observational studies; moderate (+++) for downgraded RCTs, or upgraded observational studies; low (++) for double-downgraded RCTs or observational studies; and very low (+) for triple-downgraded RCTs or downgraded observational studies or case series and case reports (Schünemann 2008).

Analysis

Data on the outcome measures from each trial were pooled to determine the overall estimate efficacy of leflunomide in RA

therapy. Where possible, the analyses were based on the intention-to-treat data from individual trials. A sensitivity analysis was conducted to test the robustness of results based on the trial quality.

For continuous data, results were present as weighted mean differences (WMD). However, when different scales were used to measure the same outcome standardized mean differences (SMD) were used instead. For dichotomous data, relative risks (RR) were calculated. Homogeneity of the data was calculated using the Chi^2 test at n-1 degrees of freedom (n = number of study) with the significance level of $P < 0.05$. Meta-analysis was conducted according to a fixed-effect model. Where heterogeneity existed, a random-effects model was used.

When necessary, the authors of the primary studies were contacted to obtained additional information.

Summary of Findings table

The Summary of Findings (SoF) table for this review presented the efficacy and toxicity outcomes. The efficacy outcome chosen in this SoF table was the ACR 50 response rate, as the ACR50 response represents a clinically relevant change of RA activity (Felson 1995). In studies that did not report the ACR50 response rate, the EULAR good response rate was used. The toxicity outcome chosen was the withdrawal rate due to treatment adverse events. Both the ACR 50 response rate (or EULAR good response rate) and withdrawals due to adverse events were presented as absolute risk differences and their 95% confidence intervals (CIs). The number needed to treat (NNT) and number needed to harm (NNH) with their 95% CIs were also calculated. Also presented in the SoF table were the different comparisons between leflunomide and comparators, levels of evidence quality, and number of participants and studies for each comparison.

Absolute and relative differences

The absolute and relative differences in changes from baseline of the OMERACT core outcomes are shown in Table 1 (additional tables). The absolute difference was calculated as the difference from baseline in the original units of the outcome measured. The relative difference was calculated as a percentage of the baseline mean of all included trials. The baseline mean is shown in the table also. The 95% CIs of the absolute and relative difference were calculated using the pooled estimates. For tender and swollen joints at six months, standardized mean differences(SMD) were converted back to the original units by multiplying the pooled SMD by the standard deviation, in one study (Strand 1999a).

The number needed to treat was calculated as the inverse of the pooled risk difference (Table 2).

RESULTS

Description of studies

The search strategies retrieved 568 articles, of which 26 trials met the inclusion criteria. Handsearching for articles from the ACR, EULAR and APLAR scientific meeting abstract books (to 2008) identified 304 abstracts on leflunomide and RA. Of these, seven abstracts were included in this review. A total of 33 trials were then eligible for systematic review and meta-analysis.

Of these 33 trials, 19 were double-blind RCTs; 2 were single-blind RCTs; nine were open-label RCTs, and the other three were open-label non-randomized CCTs. One study was a phase II study comparing leflunomide at different daily doses (5, 10, 25 mg/day) with placebo (Mladenovic 1995). Two phase III studies compared the efficacy of leflunomide with placebo and active control (three-arm studies); one active control was SSZ (Smolen 1999) and the other was MTX (Strand 1999a). Extension studies of both trials were also included in this review where the placebo arm of each trial was switched to active control (SSZ in Scott 2001 and Kalden 2001; and MTX in Cohen 2001). Eleven trials were head-to-head comparisons between leflunomide and MTX (Emery 1999; Bao 2000; Cohen 2001; Hu 2001; Jiang 2001; Lao 2001; Lau 2002; Reece 2002; Shuai 2002; Bao 2003; Fiehn 2007). Six of them were double-blind RCTs conducted in China (Bao 2000; Jiang 2001; Lao 2001; Lau 2002; Shuai 2002; Bao 2003). Three trials compared leflunomide with SSZ (Kalden 2001; Larsen 2001; Scott 2001). One three-arm study compared the efficacy and safety of leflunomide with cyclosporin A (CsA) and combined leflunomide and CsA (Karanikolas 2006). Four studies compared combined leflunomide and MTX with MTX alone (Amit 2004; Kremer 2002; Lao 2002; Amit 2006) and one trial compared a leflunomide and MTX combination with leflunomide alone (Antony 2006). The open-label extension trial of Kremer et al study (Kremer 2002) compared the efficacy and adverse events of combined leflunomide and MTX with the placebo group switched to leflunomide and MTX (Kremer 2004). The Dougados 2005 trial was a second-phase double-blind study comparing leflunomide and SSZ with SSZ alone in RA patients who had not responded to leflunomide in the first-phase, open-label study. The Gao 2004 study was an open-label trial comparing a leflunomide and MTX combination with triple therapy (MTX+CQ +SSZ). Three studies compared the efficacy of different dosages of leflunomide (Rozman 1994a; Jakez-Ocampo 2002; Poor 2004). Two studies compared leflunomide with anti-tumor necrosis factor agents (anti-TNF) (Mariette 2004; Wislowska 2007). The Mariette 2004 trial was a large cohort study comparing single DMARD, combined DMARDs, adalimumab (ADA), and combined ADA with DMARD. The Wislowska 2007 trial was an open-label, three-arm study that compared leflunomide with MTX and combined anti-TNF with MTX (etanercept and infliximab). With the exception of some Chinese trials, studies reported after the year 2001 were mostly open-label trials with small sample sizes.

Noticeably, several studies included in this review were based on the data from a single trial but outcomes were separately reported by different authors. Strand 1999(a) and Strand 1999(b) reported the data from one trial. The former selectively reported the outcomes in the core set of the ACR response criteria while the latter reported the data on functional ability and quality of life outcomes. Sharp 2000 reported the radiographic changes in the population from both Strand trials. This publication pattern was also observed in the extension study of the Smolen 1999 trial. Three studies (Kalden 2001; Larsen 2001; Scott 2001) reported the data from this extension study with different outcomes. Studies conducted by a group of authors were commonly reported at different time durations. This was evident in the trials by Amit et al (Amit 2004; Amit 2006), Bao et al (Bao 2000; Bao 2003), Strand et al (Strand 1999a; Strand 1999b; Cohen 2001), Smolen et al (Smolen 1999; Kalden 2001; Larsen 2001; Scott 2001), and Kremer et al (Kremer 2002; Kremer 2004). Thus, this meta-analysis stratified the comparison between leflunomide and comparators by outcomes at different lengths of treatment.

Twenty-four studies were excluded. Most of them were single-arm studies without control groups (Jevtic 1997; Mroczkowski 1999; Weinblatt 1999b; Dougados 2003; Kalden 2003; Kuzmanova 2003; Balabanova 2004; Godinho 2004; Hansen 2004; van der Heijde 2004; van Roon 2005; Balabanova 2006; Litinsky 2006; Ju 2007; Sarunhan-Direskeneli 2007). Some studies were subsets of the included studies (Kraan 2004; van der Kooij 2007; Tchetverikov 2008) or the outcomes were not clinical-based (Kraan 2004; Grijalva 2007; Richards 2007; Tchetverikov 2008).

Risk of bias in included studies

From the 33 included studies, according to the global quality level described in the Methods of the review section no trial met level A, 20 trials met level B, and 13 trials met level C.

The median quality score of the included trials was 3. One study scored 0, five scored 1, seven scored 2, 12 scored 3, five scored 4, and three scored 5 using the Jadad score.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: leflunomide versus placebo, 6 months; **Summary of findings 2** Summary of findings: leflunomide + methotrexate versus methotrexate, 6 months

Efficacy of leflunomide compared to placebo

ACR20, ACR50 and ACR70 response rates
RA patients in the leflunomide group were two times more likely to meet the ACR20 response criteria than placebo, at both 6 months (RR 0.51, 95% CI 0.42 to 0.62) and 12 months (RR 0.50, 95% CI 0.36 to 0.70). Similar findings were observed for the patients who met the ACR50 criteria at both 6 months (RR 0.43, 95% CI 0.25 to 0.76) and and 12 months (RR 0.22, 95% CI 0.12 to 0.43) and for the ACR70 at 12 months of treatment (RR 0.21, 95% CI 0.09 to 0.53).

Joint counts
A significant reduction in the number of tender joint count by 26% relative to baseline (SMD -0.57, 95% CI -0.72 to -0.42) was observed in leflunomide-treated patients at 6 months compared to those in the placebo group, and a 13% relative reduction in the number of swollen joint count (SMD -0.49, 95% CI -0.64 to -0.34). The results were similar in the comparison at 12 months with a 29% relative reduction in tender joint count (WMD -4.7 joints, 95% CI -6.59 to -2.81) and a 20% relative reduction in swollen joint count (WMD -8.6 joints, 95% CI -10.05 to -7.15).

Global assessments
Both patient global assessment of disease severity (SMD -0.64, 95% CI -0.79 to -0.49) and physician global assessment (SMD -0.67, 95% CI -0.82 to -0.52) improved significantly in the leflunomide group compared to placebo at 6 months. At 12 months, both patient global assessment in the leflunomide group compared to placebo (WMD -2.2 cm, 95% CI -2.84 to -1.56) and physician global assessment (WMD -1.8 cm, 95% CI -2.41 to -1.19) improved significantly. The relative difference in patient global assessment was 21% and 29% at 6 and 12 months, respectively.

Erythrocyte sedimentation rate (ESR)
ESR decreased significantly more in the leflunomide group than the placebo group, by 15% at 6 months (WMD -7.94 mm/hr, 95% CI -10.96 to -4.92) and by 24% at 12 months (WMD -8.9 mm/hr, 95% CI -13.68 to -4.12) of treatment.

C-reactive protein (CRP)
CRP also decreased significantly in the leflunomide group at both 6 months (WMD -1.24 mg/dl, 95% CI -1.68 to -0.79) and 12 months (WMD -1.09 mg/dl, 95% CI -1.62 to -0.56) of treatment.

Pain severity
Pain severity measured as a visual analog scale in mm improved significantly in the leflunomide group. The relative difference in pain was 23% at 6 months (WMD -13.81 mm, 95% CI -15.91 to -11.71) and 29% at 12 months (WMD -18 mm, 95% CI -24.04 to -11.96).

Functional status and Health related quality of life
1) Health Assessment Questionnaire (HAQ) disability index and modified HAQ (MHAQ) scores
A significant improvement in the HAQ disability scores in the leflunomide-treated group were observed at 6 months with a relative difference of 39% (WMD -0.43 points, 95% CI -0.52 to -0.33); and a relative difference of 56% at 12 months (WMD - 0.48 points, 95% CI -0.60 to -0.36). The improvements of the MHAQ scores after 6 and 12 months of leflunomide were also significant (WMD -0.35 points, 95% CI -0.46 to -0.24; WMD -0.36 points, 95% CI -0.48 to -0.24, respectively).

2) Problem Elicitation Technique (PET) scores
The scores of the top 5 items of the PET improved significantly in the leflunomide-treated patients compared to placebo, by 29% relative to baseline (WMD -6.24 points, 95% CI -8.46 to -4.02) at 12 months.

3) Short Form-36 health survey (SF-36)
A significant improvement in the physical component scores of the SF-36 of 22% relative to baseline was observed in the leflunomide group (WMD -6.6 points, 95% CI -8.91 to -4.29); but not in the mental component (WMD -0.7 points, 95% CI -3.53 to 2.13).

4) Work productivity
Work productivity scores were also significantly improved in the leflunomide group compared to the placebo group at 12 months of treatment (WMD -9.5 points, 95% CI -14.25 to -4.75).

Radiographic changes
Changes of hand radiographs, measured as a Sharp score, favoured leflunomide treatment in all categories (total score, erosion, and joint space narrowing subscores) at both 6 months (WMD of total Sharp score -4.65 points, 95% CI -7.21 to -2.09) and 12 months (WMD of total score -1.63 points, 95% CI -2.78 to -0.48). Delay in progression of joint damage, as measured by the Larsen score, was also observed when leflunomide was compared to placebo at 6 months (WMD -0.04 points, 95% CI -0.06 to -0.02).

Evidence level: Gold

Efficacy of leflunomide compared to methotrexate (MTX)

There were 11 clinical trials comparing the efficacy of leflunomide to MTX. The trial duration ranged from 3 months to 2 years. A test of homogeneity showed that the results from several studies were significantly different from the others. Thus, the comparison of outcomes between leflunomide and MTX from more than one study was based on a random-effects model.

ACR20, ACR50 and ACR70 response rates
There was no difference in ACR20 response rates between RA patients treated with leflunomide and those treated with MTX at 3, 4, 6, 12, and 24 months.
For the ACR50 response rate, no significant difference in the number of ACR50 responders was found between the leflunomide and MTX groups at 12 and 24 months.
A significantly greater number of patients met the ACR70 response criteria in the leflunomide group compared to MTX at 12 months (RR 0.44, 95% CI 0.26 to 0.77) but not at 2 years (RR 0.72, 95% CI 0.44 to 1.18).

Joint counts
There was no significant difference between leflunomide and MTX in the reduction of tender joint count or swollen joint count at any time point of assessment.

Global assessments
No significant difference between leflunomide and MTX was observed in the change of physician global assessment at 3, 4, 12 months, and 2 years. A significant difference was observed at 6 months for patient and physician global assessment, with a WMD of -0.60 mm (95% CI -0.95 to -0.26) and -0.48 mm (95% CI -0.82 to -0.15), respectively.

ESR
No significant difference in the improvement of ESR after treatment with leflunomide or MTX at any time point of assessment.

CRP
A significant reduction in CRP level was found after 3 months of treatment with leflunomide compared to MTX (WMD -3.02 mg/dl, 95% CI -5.94 to -0.09).

Pain severity
Leflunomide was not significantly different from MTX in pain reduction at any time point of evaluation.

Functional status and health-related quality of life (HRQoL)
1) HAQ disability index and MHAQ scores
The HAQ scores in the leflunomide-treated group did not improve more than in the MTX group at 3, 6, 12, or 24 months of treatment. The MHAQ scores improved significantly in the leflunomide group compared to MTX at 6, 12, and 24 months, but not at 4 months.

2) PET scores
The scores of the PET top 5 improved significantly in the leflunomide-treated patients when compared to MTX (WMD -3.5 points, 95% CI -5.62 to -1.38) at 12 months.

3) SF-36 scores
The changes of the SF-36 scores when leflunomide was compared to MTX were similar to those observe when leflunomide was compared to placebo, that is a significant improvement in the physical component (WMD -3.0 points, 95% CI -5.41 to -0.59) but not the mental component (WMD -0.6 points, 95% CI -3.01 to 1.81).

4) Work productivity
Work productivity did not improve significantly in the leflunomide group when compared to MTX (WMD -2.3 points, 95% CI -6.37 to 1.77).

5) Disability index in Chinese studies
The Chinese leflunomide studies compared the disability index between patients taking leflunomide and MTX. A significant difference in the disability index was observed at 3 months (WMD -0.09 points, 95% CI -0.18 to -0.001) but not at 6 months (WMD -0.05 points, 95% CI -0.20 to 0.10).

Radiographic changes
Changes in the total Sharp score were not significant when leflunomide was compared to MTX at 12 and 24 months of treatment. However, a significant change in magnetic resonance imaging (MRI) initial rate of enhancement of the patients' inflamed knee joints was observed in the leflunomide group compared to MTX.

Treatment response rate in Chinese leflunomide studies

Therapeutic efficacy of leflunomide compared with MTX in Chinese studies at both three and six months showed that leflunomide was comparable to MTX. No statistical significance in efficacy was detected between groups.

EULAR response criteria

The EULAR response criteria measured as Disease Activity Score (DAS) were used for assessing response to treatment in RA. The DAS28 assesses the number of tender and swollen joint on a 28-joint assessment basis as well as patient global assessment of disease activity and ESR or CRP. The mean change of DAS28 score at 4 months of treatment was significantly better for MTX than leflunomide (WMD 0.57 points, 95% CI 0.24 to 0.90). However, the EULAR good and moderate response rates and EULAR remission rate at four months were not significantly different between leflunomide and MTX. At six months, mean changes of DAS28; DAS28 remission rate; number of patients with DAS28 low, moderate, and high disease activity were not significantly different for patients treated with leflunomide and those with MTX.

Evidence level: Gold

Efficacy of leflunomide compared to sulfsalazine (SSZ)

ACR20, ACR50 and ACR70 response rates
There were no differences in response rates between the RA patients treated with leflunomide and those treated with SSZ at 6 and 12 months. Only at 24 months the ACR20 response rate in the leflunomide group was significantly better than for SSZ (RR 0.73, 95% CI 0.57 to 0.93).
For the ACR50 response rate, a significantly greater number of patients treated with leflunomide met the ACR50 response criteria compared to SSZ, at 24 months (RR 0.48, 95% CI 0.28 to 0.80).
The number of ACR70 responders in the leflunomide and SSZ groups were not significantly different at any time point of assessment.

Joint counts
Reductions in the number of tender joint or swollen joint were not significantly different in leflunomide-treated patients compared to SSZ at both 6 and 12 months. However, at 24 months, leflunomide was significantly more efficacious than SSZ in decreasing the number of tender joints (WMD -3.33 joints, 95% CI -5.83 to -0.83) and swollen joints (WMD -2.62 joints, 95% CI -4.67 to -0.57).

Global assessments

No significant differences in the change of patient global and physician global assessments were observed when leflunomide was compared to SSZ at 6 and 12 months. At 24 months, both patient and physician global assessments improved significantly in the leflunomide group (WMD for patient global -0.68 points, 95% CI -1.35 to -0.01; WMD for physician global -0.7 points, 95% CI -1.37 to -0.03) compared to SSZ.

ESR
ESR improved less in the leflunomide group than with SSZ (WMD 9.2 mm/hr, 95% CI 3.47 to 14.93) at 6 months. There was no difference in the change of ESR between leflunomide and SSZ at 12 and 24 months.

CRP
Leflunomide decreased the CRP level significantly at 6, 12, and 24 months of treatment when compared to SSZ. The WMD of CRP changes at 6 months was -1.20 mg/dl (95% CI -1.98 to -0.42). The WMD of CRP changes at 12 and 24 months were -1.10 (95% CI -2.17 to -0.03) and -1.40 (95% CI -2.77 to -0.33), respectively.

Pain severity
Pain severity decreased significantly in the leflunomide group compared to SSZ at all time points. Changes in pain severity measured by VAS at 6, 12, and 24 months in the leflunomide group were better than SSZ with the WMD of -7.5 mm (95% CI -14.21 to -0.79); WMD -11.4 mm (95% CI -20.35 to -2.45); and WMD -15.1 mm (95% CI -25.16 to -5.04), respectively.

Functional status and health-related quality of life (HRQoL)
At 6 and 24 months, leflunomide improved the HAQ disability index significantly when compared to SSZ (WMD -0.25 points, 95% CI -0.42 to -0.08; WMD -0.29 points, 95% CI -0.57 to -0.01, respectively). The difference in HAQ score was not observed at 12 months.

Radiographic changes
Changes in total Sharp score were not significantly different when leflunomide was compared to SSZ, at 6 or 12 months. Larsen scores, both total scores and erosion scores of the hands and feet, were not delayed significantly in the leflunomide group when compared to SSZ at 6, 12, and 24 months.

Evidence level: Gold

Efficacy of leflunomide compared to cyclosporin A (CsA)

ACR20, ACR50, and ACR70 response rates

The ACR20, ACR50, and ACR70 response rates in RA patients receiving leflunomide were not significantly different from those receiving CsA, at 12 months of treatment.

EULAR response criteria

The mean change of DAS28 score from baseline was significantly better for patients taking CsA than those taking leflunomide at 12 months of treatment (WMD 0.25 points, 95% CI 0.15 to 0.35). However, the number of patients who met the EULAR low disease activity criteria (DAS28 < 3.2) was not significantly different between the two treatment groups.

Evidence level: Silver

Efficacy of leflunomide+MTX compared to MTX

ACR20, ACR50, and ACR70 response rates
A significantly greater number of RA patients taking leflunomide +MTX met the ACR20, ACR50, and ACR70 criteria compared to MTX +placebo, at 24 weeks. The RR for ACR20 responders was 0.42 (95% CI 0.29 to 0.63); for ACR50 responders, RR 0.23 (95% CI 0.11 to 0.48); and for ACR70 responders, RR 0.23 (95% CI 0.07 to 0.77). At 48 weeks, the extension study showed that the ACR20, ACR50, and ACR70 response rates for RA patients taking leflunomide+MTX were not significantly different from those taking placebo switched to leflunomide+MTX.

Joint counts
A significant reduction in the number of tender and swollen joints was observed in RA patients treated with leflunomide+MTX compared to MTX+placebo, at 24 weeks. The WMD of tender joint counts was -7.6 joints (95% CI -10.59 to -4.61) and the WMD of swollen joint counts was -3.6 joints (95% CI -5.47 to -1.73). At 48 weeks when patients receiving MTX+placebo were switched to leflunomide+MTX, the changes in joint counts were not different from those receiving leflunomide+MTX at study entry.

Global assessments
Combined leflunomide and MTX improved both patient and physician global assessments more than with MTX, at 24 weeks of treatment. The WMD of patient global assessment measured by VAS was -15.5 mm (95% CI -21.86 to -9.14) and the WMD of physician global assessment was -17.1 mm (95% CI -22.71 to -11.49). At 48 weeks both patient and physician global assessments were not significantly different between the two groups; MTX+placebo was changed to leflunomide+MTX in the control group.

ESR
Improvement of ESR from baseline in the leflunomide+MTX and MTX groups was not significantly different, at both 24 and 48 weeks.

CRP
Leflunomide+MTX decreased the CRP level significantly more at 24 weeks of treatment compared to MTX. The WMD of CRP change was -12.1 mg/l (95% CI -19.84 to -4.36). At 48 weeks, when both groups were assigned leflunomide+MTX treatment, mean changes of CRP in the two groups were not significantly different.

Pain severity
Pain severity decreased significantly in the leflunomide+MTX group compared to MTX, at 24 weeks. The WMD of change in pain severity measured by VAS was -16.9 mm (95% CI -23.7 to -10.1). This difference was not observed in the 48-week extension study when both groups were treated with leflunomide+MTX.

Functional status and health-related quality of life (HRQoL)
At 24 weeks, leflunomide+MTX improved the HAQ disability index significantly when compared to MTX (WMD -0.3 points, 95% CI -0.42 to -0.18). At 48 weeks, when both patient groups were treated with leflunomide+MTX, there were no significant differences in the HAQ score, and SF-36 physical and mental components between the two groups.

Treatment response rate in Chinese and Indian leflunomide studies

The number of patients with a remarkable improvement in both clinical and laboratory parameters in a Chinese leflunomide study was significantly higher for leflunomide+MTX treatment than for

MTX, at 24 weeks. The RR was 0.43 (95% CI 0.27 to 0.68). In Indian studies, the number of patients with significant improvements was higher for leflunomide+MTX than for MTX at both two and three years. The RR at 2 years was 0.69 (95% CI 0.52 to 0.91) and the RR at 3 years was 0.73 (95% CI 0.62 to 0.86).

Evidence level: Gold

Efficacy of leflunomide+MTX compared to leflunomide

EULAR response rate
The EULAR good and moderate responders, non responders, and EULAR remission rate at 3 months were not significantly different between RA patients taking leflunomide+MTX and leflunomide alone.

Evidence level: Silver

Efficacy of leflunomide+SSZ compared to SSZ

ACR20, ACR50 and ACR70 response rates
There was no difference in the ACR20 or ACR50 response rate between the RA patients treated with leflunomide+SSZ and those treated with SSZ, at 24 weeks. The ACR70 response rate in both treatment groups could not be estimated because no patients reached the ACR70 response criteria.

Joint counts
Reductions in the number of tender joints or swollen joints were not significant between leflunomide+SSZ and SSZ groups, at 24 weeks.

ESR
There was no significant difference in ESR after treating with leflunomide+SSZ or SSZ, at 24 weeks.

CRP
Leflunomide+SSZ reduced the CRP but the reduction was not significantly different from the SSZ group, at 24 weeks.

Pain severity
Pain severity did not significantly decrease in the leflunomide+SSZ group compared to SSZ, at 24 weeks.

Functional status and health-related quality of life (HRQoL)
At 24 weeks, changes in HAQ-DI and mean HAQ score were not significantly different between the leflunomide+SSZ group and SSZ group.

EULAR response criteria

The number of patients who met the EULAR good and moderate response for both intention-to-treat groups and completers, at 24 weeks, was not significantly different for those treated with leflunomide+SSZ and with SSZ. The mean change of DAS28 scores from baseline was also not different between the two groups.

Evidence level: Gold

Efficacy of leflunomide+CsA compared to leflunomide

ACR20, ACR50, and ACR70 response rates

The ACR20 and ACR50 response rates in RA patients receiving leflunomide+CsA were not significantly different from those in patients receiving leflunomide, at 12 months of treatment. On the other hand, the ACR70 response rate was significantly higher for patients receiving leflunomide+CsA than for those receiving leflunomide alone (RR 1.96, 95% CI 1.12 to 3.44).

EULAR response criteria

The mean change of DAS28 score from baseline was significantly better for patients taking leflunomide+CsA than for those taking leflunomide, at 12 months of treatment (WMD 0.46 points, 95% CI 0.35 to 0.57). However, the number of patients who met the EULAR low disease activity criteria (DAS28 < 3.2) was not significantly different between the two treatment groups.

Evidence level: Gold

Efficacy of leflunomide compared to anti-tumor necrosis factor agents (ANTI-TNF)+MTX

ACR 20, ACR50, and ACR70 response rates

The ACR20 and ACR50 response rates in patients taking anti-TNF +MTX were marginally higher than for those taking leflunomide, at 24 weeks, but this difference was not statistical significant. The ACR70 response rate was significantly higher for the anti-TNF+MTX treated group than for the leflunomide group (RR 3.75, 95% CI 1.35 to 10.43).

Joint counts

A significant improvement in the number of tender and swollen joints was observed in the combination anti-TNF+MTX group compared with leflunomide, at 24 weeks. The WMD of tender joint counts was 3.3 joints (95% CI 1.88 to 4.72) and the WMD of swollen joint counts was 1.4 joints (95% CI 0.22 to 2.58).

ESR

Mean ESR changes from baseline were not significantly different between the two treatment groups.

Pain severity

Anti-TNF+MTX reduced the pain intensity measured by VAS more efficiently than leflunomide, at 24 weeks (WMD 11 mm, 95% CI 1.29 to 20.71).

EULAR response criteria

Mean change from baseline of the DAS28 score was significantly higher for anti-TNF+MTX treatment group than for the leflunomide group, at 24 weeks (WMD 0.80 points, 95% CI 0.43 to 1.17). The number of patients who met the EULAR remission criteria (DAS28 < 2.6) was not significantly different between the two groups (RR 1.67, 95% CI 0.38 to 7.39). The patients treated with anti-TNF+MTX were significantly more likely to meet the EULAR low disease activity criteria (DAS28 < 3.2) than those treated with leflunomide (RR 3.33, 95% CI 1.17 to 9.51). The number of patients in the leflunomide group who met the EULAR moderate and high disease activity criteria was not significantly different to the number in the anti-TNF +MTX group.

Evidence level: Silver

Efficacy of leflunomide+adalimumab (ADA) compared to ADA

ACR20 and ACR50 response rates

The ACR20 response rate in the leflunomide+ADA group was significantly better than in the ADA group, at 12 weeks (RR 0.83, 95% CI 0.89 to 0.99). There was no significant difference in the ACR50 response rate between the two treatment groups.

EULAR response criteria

The number of patients who met the EULAR good response criteria was not significantly different between the two groups, while fewer patients in the leflunomde+ADA group met the EULAR moderate response criteria than in the ADA group (RR 0.83, 95% CI 0.73 to 0.93).

Evidence level: Silver

Efficacy of leflunomide 10 mg/day compared to leflunomide 20 mg/day

ACR20, ACR50, and ACR70 response rates
There was no significant difference in the ACR20, ACR50, and ACR70 response rate between the RA patients treated with leflunomide 10 mg/day and those treated with leflunomide 20 mg/day, at 24 months.

Joint counts
There was no significant difference in the mean change from baseline of tender and swollen joint counts between leflunomide 10 mg/day and leflunomide 20 mg/day, at 24 months of treatment.

Functional status and health-related quality of life (HRQoL)
At 24 months, no difference in the change of HAQ scores between leflunomide 10 and 20 mg/day.

Evidence level: Gold

Efficacy of weekly leflunomide compared to daily leflunomide

ACR20, ACR50, and ACR70 response rates

No significant difference in the ACR20, ACR50, and ACR70 response rate was observed between the two groups at both 6 and 12 months of treatment.

Evidence level: Silver

Efficacy of leflunomide 100 mg/week compared to leflunomide 200 mg/week

Joint counts

There was no significant difference in the mean changes from baseline of the number of tender and swollen joints between the two treatment groups, at 6 months.

Global assessments

No significant difference in both patient and physician global assessments at six months of treatment with leflunomide 100 mg/week or 200 mg/week.

Evidence level: Silver

Adverse events

1. ***Leflunomide monotherapy versus placebo, MTX, SSZ, or CsA***

An important adverse event with leflunomide is an elevation of liver function test results. The risk ratio of elevated liver function tests as a reported adverse event was significantly higher for leflunomide compared with placebo at 6 months (RR 2.45, 95%CI 1.02 to 5.87), 12 months (RR 5.84, 95% CI 1.81 to 18.8), and 2 years (RR 3.23, 95% CI 1.27 to 8.25). However, this adverse event was not significantly different between leflunomide and MTX or SSZ.

RA patients receiving leflunomide were less likely to discontinue treatment when compared to placebo (RR 0.70, 95% CI 0.59 to 0.83) but was not different from SSZ (RR 0.75, 95% CI 0.53 to 1.07). On the other hand, patients taking leflunomide were more likely to withdraw when compared to MTX (RR 1.26, 95% CI 1.08 to 1.48) at 12 months, but not at 2 years. The withdrawal rate was also significantly higher for leflunomide than for CsA at 12 months of treatment (RR 4.38, 95% CI 1.02 to 18.84). The number of withdrawals due to drug-related adverse events in the leflunomide group was significantly higher than with placebo (RR 2.73, 95% CI 1.67 to 4.47); and MTX at 12 months (RR 1.43, 95% CI 1.13 to 1.83); but not for MTX at 2 years (RR 1.15, 95% CI 0.83 to 1.61) or with SSZ (RR 0.77, 95% CI 0.45 to 1.33) or CsA (RR 8.76, 95% CI 0.49 to 156.85). Withdrawals due to adverse events related to leflunomide were significantly fewer than with MTX at 6 months in the Chinese leflunomide studies (RR 0.24, 95% CI 0.10 to 0.57).

Major reported adverse events from leflunomide included gastrointestinal (GI) symptoms (diarrhea, dyspepsia, nausea and vomiting, abdominal pain, oral ulcers), elevated liver function tests, allergic reactions, alopecia, infections, weight loss, and hypertension. Heterogeneity was significant for several adverse events (random-effects model).

GI symptoms were more likely to occur in the leflunomide group than in the placebo group (RR 1.60, 95% CI 1.28 to 1.99) but less likely to occur compared with the MTX group (RR 0.50, 95% CI 0.28 to 0.92) and not different from SSZ (RR 0.88, 95% CI 0.63 to 1.22).

Elevation of liver function tests, more than 3 times the upper normal values, was more likely in the leflunomide group when compared to placebo (RR 3.74, 95% CI 1.86 to 7.54) but was not different from SSZ (RR 0.60, 95% CI 0.15 to 2.46) or MTX (RR 0.66, 95% CI 0.31 to 1.39).

Mild allergic reactions were more likely to occur in the leflunomide group when compared to placebo (RR 1.72, 95% CI 1.08 to 2.74) or MTX (RR 1.51, 95% CI 1.19 to 1.92) but were not different from SSZ (RR 1.00, 95% CI 0.52 to 1.92).

Reversible alopecia was more likely to occur in the leflunomide group than in the placebo group (RR 6.60, 95% CI 2.36 to 18.44) or MTX group (RR 1.72, 95% CI 1.32 to 2.24) but was no different in the SSZ group (RR 1.57, 95% CI 0.63 to 3.93).

Infection rates and significant weight loss were not significantly different between leflunomide, placebo, SSZ, and MTX.

Hypertension in the leflunomide group was not different from placebo (RR 3.36, 95% CI 0.58 to 19.32) or SSZ (RR 1.00, 95% CI 0.21 to 4.87) but was more likely to occur than in the MTX-treated group (RR 2.29, 95% CI 1.42 to 3.69).

2. ***Leflunomide combination with another DMARD compared to DMARD monotherapy***

The total withdrawal rate and withdrawal rate due to treatment-related adverse events were not significantly different in patients receiving leflunomide+MTX compared with patients receiving MTX, at 24 weeks. A similar result was observed in the 48-week extension study. After the patients in the placebo+MTX group were switched to leflunomide+MTX (without a loading dose of leflunomide), from week 24 to week 48, certain adverse events were observed more frequently in the placebo switched to leflunomide+MTX group than in patients already taking leflunomide+MTX from the beginning of the trial. These adverse events included diarrhea (RR 5.33, 95% CI 1.61 to 17.71) and alopecia (RR 8.0, 95% CI 1.02 to 62.74). The risk of nausea, skin rash, infection, or elevated liver enzymes was not significantly different between the two treatment groups. Serious adverse events were also not different at 48 weeks of treatment. However, the risk of reported adverse events in patients taking leflunomide+MTX was significantly higher than in patients taking MTX as reported by the Chinese Leflunomide Study Group, at 24 weeks (RR 3.5, 95% CI 1.29 to 9.49). The total withdrawal rate and withdrawal rate due to leflunomide+MTX treatment were not significantly higher than in the MTX-treated group at both 24 and 36 months of treatment in the Indian leflunomide studies.

For the adverse events in the trial comparing leflunomide+SSZ with SSZ, at 24 weeks the reported adverse events, serious adverse events, total number of withdrawals, and withdrawal rate from treatment-related adverse events, were not significantly different between the two groups.

Total withdrawals and withdrawals due to treatment-related adverse events in RA patients taking leflunomide+CsA were not significantly different from those in patients taking CsA, at 12 months. Similarly, withdrawals due to adverse events in the leflunomide+MTX were not higher than in the leflunomide group, at three months of treatment.

3. ***Comparisons between leflunomide at different doses***

Reported adverse events and withdrawals due to treatment-related adverse events in RA patients taking leflunomide 10 mg/day and 20 mg/day were not significantly different. Patients taking weekly leflunomide were at a lower risk of developing adverse events and withdrawing from the study due to adverse events compared with patients taking daily leflunomide, but this difference did not reach statistical significance (RR 3.0, 95% CI 0.85 to 10.63; RR 5.0, 95% CI 0.28 to 90.18, respectively). In addition, a study comparing leflunomide at 100 mg/week with 200 mg/week did not show a significant difference in the number of withdrawals due to adverse events, at 6 months of treatment.

Sensitivity analysis

Methodological quality
The median quality scores of the included trials were moderate (Jadad score = 3). Studies with poor blinding quality were compared to those with higher scores in blinding quality. A significant difference in the number of patients who met the ACR20 criteria was observed in studies with blinding quality > 1.

RA duration
Trials including patients with a mean duration of RA less than five years were more likely to report a better response with MTX (RR 1.28, 95% CI 1.15 to 1.43) while the trials involving patients with a mean disease duration of 5 years or more tended to favor leflunomide (RR 0.87, 95% CI 0.72 to 1.05).

Concomitant steroid use
A significant difference in ACR20 response rate between studies with baseline steroid use less than 50% (RR 0.52, 95% CI 0.40 to 0.66) and those with steroid use 50% or more (RR 0.72, 95% CI 0.51 to 1.03) was observed.

Withdrawal rate
Studies with a withdrawal rate of 50% or more did not show a significant difference in ACR20 response rate compared with studies with withdrawal rates less than 50%.

DISCUSSION

Leflunomide is a novel DMARD with a different structure and mechanism of action from the other DMARDs. It is an isoxazole derivative that is converted to the active form A77 1726 once ingested. The primary mode of action is to inhibit the enzyme dihydro-orotate dehydrogenase, which activates the rate-limiting step in the pathway for de novo synthesis of pyrimidines (Fox 1998; Simon 2000; Smolen 2000). Pyrimidine nucleotides are required for the proliferation of T lymphocytes. The autoreactive T lymphocytes are more sensitive to the depletion of pyrimidine pools than other types of lymphocytes and cells in the body (Fox 1998). This leads to suppression of autoimmune T-cell proliferation with a minimum effect on the other cells. Since most of the cells that infiltrate the RA synovium are activated CD4+ T-cells, leflunomide helps improve the inflammation of synovium in RA patients as well as their clinical symptoms (Fox 1998; Simon 2000; Smolen 2000).

Leflunomide was approved by the United States FDA in August 1998 for the treatment of adult RA. It has shown a beneficial result in many RCTs and CCTs. Earlier studies were high quality RCTs evaluating the efficacy and adverse events of leflunomide compared to placebo, MTX, or SSZ. MTX and SSZ are the most widely used DMARDs in North America and Europe, respectively (Mladenovic 1995; Emery 1999; Smolen 1999; Strand 1999a; Cohen 2001; Scott 2001). These six trials had the same objectives and similar primary outcome measures, which included in the core set of disease activity measures for RA clinical trials established by OMERACT and the ACR (Felson 1993; Felson 1995; Pincus 1999). However, differences in the outcome measures did exist. The Mladenovic study (Mladenovic 1995) based the number of joint counts on the evaluation of 66 or 68 joints while the others based the counts on the 28-joint evaluation. In functional evaluation, the Mladenovic 1995 trial used total HAQ scores in their study while the others used the HAQ disability index. There was also a difference in the patients recruited to the studies. The RA patients in Strand 1999(a) had a mean duration of disease at recruitment of 6.5 to 7 years while the patients in Emery 1999 had a shorter duration of disease of 3.7 to 3.8 years. More than 99% of the patients from Strand et al (Strand 1999a) were prescribed folic acid supplement while folic acid was not mandatory in the Emery study (Emery 1999). These differences would explain the heterogeneity of the pooled estimates from both studies.

The pooled estimates of the clinical efficacy of leflunomide have shown this agent to be significantly better than placebo at both six months and 12 months, in all outcome measures for disease activity. The pooled relative differences show a relative benefit in change from baseline of over 20%, compared to placebo, for most

of the OMERACT core set of outcomes. At six and 12 months, the clinical benefits from leflunomide were not significantly different from SSZ; except for pain severity, which leflunomide significantly improved more than SSZ. At 24 months, leflunomide was shown to be more efficacious than SSZ in improving most of the outcome measures. Thus, the efficacy of leflunomide appeared to be sustained over at least two years of treatment. It might still be efficacious in longer-term treatment, as MTX is. For the comparison between leflunomide and MTX, leflunomide efficacy was not significantly different from MTX in most of the outcome measures, in six trials. However, additional RCTs from China showed that leflunomide was significantly more efficacious than MTX in pooled efficacy outcomes and mean changes of DAS28 scores.

For the functional status and HRQoL, leflunomide improved the health status in almost every aspect for RA patients. The exception was the mental component of the SF-36, for which the treated group did no better than the placebo group. This was also observed when leflunomide was compared to MTX where the improvement of the mental component of the SF-36 was not significant. There may be other factors that influenced the mental component, for example adverse events from the treatment, inability to perform normal social activity, or inadequate length of time to evaluate the improvement of mental status of the patients. The improvement of the MHAQ scores in the RA patients treated with leflunomide was significantly superior to that for the patients treated with MTX but the changes of the HAQ disability index in both groups were not significantly different. This might be explained by the heterogeneity of the results of the included studies. In the study by Strand and colleagues (Strand 1999b) the patients responded better to leflunomide than MTX in term of MHAQ scores, but not the HAQ disability index; while in the study by Emery and colleagues (Emery 1999) the patients treated with MTX tended to improve better in the HAQ disability index.

Progression of radiographic changes was also significantly slower in the leflunomide-treated group than the placebo group. The effects of leflunomide in retarding the radiographic changes were not significantly different from those of SSZ or MTX; the results from the study by Strand and colleagues (Sharp 2000) tended to favour leflunomide over MTX and the results from Emery study favoured MTX (Sharp 2000). From the available data to date, leflunomide is not superior to MTX or SSZ in delaying bone erosions or joint damage in RA patients.

Later trials included RCTs and CCTs comparing leflunomide combined with another DMARD (mostly MTX) to DMARD monotherapy, and leflunomide as monotherapy or in combination with biologic agents (anti-TNF agents). These trials comprised heterogeneous groups of trials with low to moderate quality and varied levels of biases. The majority of trials compared the efficacy of leflunomide+MTX with MTX alone (Kremer 2002; Lao 2002; Amit 2004, Amit 2006). Combined leflunomide and MTX was superior to MTX in almost all efficacy outcomes. When placebo was replaced with leflunomide in the 48-week extension study of an RCT, the patients in both treatment groups (leflunomide and leflunomide+MTX, placebo and leflunomide+MTX) responded similarly in all efficacy outcomes (Kremer 2002; Kremer 2004). An open-label, CCT conducted in India showed that the patients' responses to combined leflunomide and MTX were not significantly different from those to leflunomide alone (Antony 2006). Although combined leflunomide+MTX was more efficacious than MTX, this combination was no better than leflunomide. This might be explained by the shorter length of the study (three months), small sample size, different patient characteristics and baseline disease activity, or the dose of MTX used in this study (only 5 to 7.5 mg/week) (Antony 2006). In an RCT conducted in RA patients with inadequate responses to leflunomide, combined leflunomide and SSZ was superior to SSZ in only one outcome, the number of ACR50 responders art 24 weeks. The other efficacy outcomes were not significantly different between the two groups (Dougados 2005). Thus, when an RA patient needs a combination of DMARDs, leflunomide+MTX is a better combination than leflunomide+SSZ in improving disease activity. Another DMARD combination with leflunomide that was shown to be more efficacious than leflunomide alone was leflunomide+CsA. The ACR50 and ACR70 response rates and mean changes of DAS28 score were significantly better for combined leflunomide and CsA than leflunomide (Karanikolas 2006).

Leflunomide efficacy was also compared with that of anti-TNF agents in two studies (Mariette 2004; Wislowska 2007). ADA +leflunomide was not significantly better than ADA in improving activity outcomes in patients with RA. Anti-TNF agents (etanercept and infliximab) combined with MTX were significantly better than leflunomide in the majority of activity and quality of life outcomes.

Three trials explored the efficacy and safety of different doses and preparations of leflunomide. These included leflunomide 10 mg/day versus 20 mg/day (Poor 2004), leflunomide 20 mg/day versus 100 mg/week (Jakez-Ocampo 2002), and leflunomide 100 mg/week versus 200 mg/week (Rozman 1994a). The data showed that no significant difference was observed in the efficacy and safety outcomes of these trials. This information suggests that leflunomide may be prescribed as a daily dose (either half or full dose) or weekly dose, which may be suitable for certain patients.

Adverse events in leflunomide-treated patients that were significantly increased compared to placebo included alopecia, gastrointestinal symptoms, and elevated liver function tests. However, infections, hypertension, and weight loss were not significantly different from those in the placebo group. All adverse events in the leflunomide group were not different from those with SSZ. Alopecia, gastrointestinal symptoms, allergic reactions, and hypertension were significantly increased in the leflunomide group compared to MTX. Elevated liver function tests were significantly higher in the MTX group while infection and weight loss were not different between treatment groups.

As expected, the number of withdrawals due to adverse events in the leflunomide group was significantly higher than that in the placebo group. However, the total withdrawal rate in the leflunomide group was lower. This was because the number of withdrawals due to a lack of treatment efficacy was higher in the placebo group. Total withdrawal rates in the SSZ and MTX groups were not different from those in the leflunomide group. Withdrawals due to adverse events were not different between leflunomide and SSZ, but were significantly higher in the leflunomide group compared with the MTX group.

For the year two follow-up studies comparing leflunomide with SSZ and MTX, the adverse events in the leflunomide-treated group were not different from those in the MTX and SSZ groups (Cohen 2001; Scott 2001). A follow-up study that extended from the Mladenovic

1995 trial confirmed leflunomide's efficacy and tolerability after 18 months of treatment (Rozman 1994b).

The reported adverse events that occurred in patients treated with combined leflunomide and MTX were higher than with MTX alone but the rate of serious adverse events and the number of patients who withdrew from studies because of treatment-related adverse events were not significant different between the two groups. Similarly, reported adverse events, total withdrawal rate, and the withdrawal rate from treatment-related adverse events were not significantly higher for combined leflunomide and another DMARD (MTX, SSZ, or CsA) than for DMARD monotherapy (leflunomide, SSZ, or CsA). These findings suggest that the use of combination DMARDs is more efficacious than single DMARDs and does not result in higher rates of adverse events.

AUTHORS' CONCLUSIONS

Implications for practice

Leflunomide has shown to be efficacious in the treatment of active RA, for up to two years. Patients treated with leflunomide can expect to achieve approximately 20% greater improvements than with placebo in all OMERACT core set outcomes (pain, tender and swollen joints, patient and physician global assessments, function and ESR) relative to baseline. Its efficacy is comparable to SSZ and MTX and is shown to be better than SSZ at 24 months of treatment. Leflunomide is considered a new choice of DMARD therapy in patients with active RA who do not respond to SSZ or MTX, or cannot tolerate these drugs. Leflunomide combined with MTX is more efficacious than MTX alone with additional adverse events. This combination may be recommended in RA patients with active disease despite treatment with DMARD monotherapy. An economic analysis of adding leflunomide to DMARDs for RA treatment showed that leflunomide was cost effective, with the additional cost of 13,000 USD per year of ACR20 response (Maetzel 2002).

Implications for research

(1) Some studies included in this systematic review did not contain the data essential for pooling in the meta-analysis. Thus, it might be useful to consider including all of the essential data in clinical trials. This would avoid the need to obtain additional data and analyses from the original investigators, which is often hard to obtain after the study is published.

(2) Leflunomide may be a substitute for MTX in RA patients who cannot tolerate or are allergic to MTX. Head-to-head studies of the combination of leflunomide and another DMARD versus MTX and another DMARD (such as antimalarials, SSZ, triple therapy, CsA) should be conducted to evaluate the possibility of using leflunomide instead of MTX.

(3) RCTs on the efficacy of leflunomide+anti-TNF agent should be conducted to assess the additional effect of leflunomide on anti-TNF agent activity, as evident in combined MTX and anti-TNF agent studies.

(4) The efficacy of leflunomide combined with another DMARD should be evaluated compared with combining with biologic agents. Since biologic agents are expensive and may be not affordable in RA patients in developing countries, the need for combination DMARDs with comparable efficacy to anti-TNF agents is crucial for these patients.

ACKNOWLEDGEMENTS

We would like to thank Jessie McGowan for her help with the electronic search strategy; Catherine Dorrier for providing additional data on the functional outcomes in the article by Strand et al (Strand 1999b); Barbara Stephenson, Karen Simpson, and Bhakti Kshatriya for providing the data of Strand 1999 (a) study at six months; and the Cochrane Musculoskeletal Editorial team and the Musculoskeletal Consumer group for reviewing our proposal.

REFERENCES

References to studies included in this review

Amit 2004 *{published data only}*

Amit M. A comparative 2-year clinical study of combined leflunomide and methotrexate vs methotrexate alone as DMARD in rheumatoid arthritis. Abstract book, the 11th APLAR meeting, Jeju, South Korea. Seoul, Sep 2004:93.

Amit 2006 *{published data only}*

Amit M, Rakhee M. A comparative 3-year clinical study of combined leflunomide and methotrexate vs methotrexate alone as DMARD in rheumatoid arthritis. *The Journal of Rheumatology* 2006;**9 Suppl 1**:A190.

Antony 2006 *{published data only}*

Antony T, Jose VM, Paul BJ, Thomas T. Efficacy and safety of leflunomide alone and in combination with methotrexate in the treatment of refractory rheumatoid arthritis. *Indian Journal of Medical Sciences* 2006;**60**(8):318-26.

Bao 2000 *{published data only}*

Bao CD, Huang WQ, Chen SL, Gu YY. Treatment of rheumatoid arthritis with leflunomide: a double blind, randomised controlled study. *China Journal of Rheumatology* 2000;**4**:44-6.

Bao 2003 *{published data only}*

Bao C, Chen S, Gu Y, Lao Z, Ni L, Yu Q, et al. Leflunomide, a new disease-modifying drug for treating active rheumatoid arthritis in methotrexate-controlled phase II clinical trial. *Chinese Medical Journal* 2003;**116**(8):1228-34.

Cohen 2001 *{published data only}*

Cohen S, Cannon GW, Schiff M, Weaver A, Fox R, Olsen N, et al. for the Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group, Strand V. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. *Arthritis and Rheumatism* 2001;**44**(9):1984-92.

Dougados 2005 *{published data only}*

Dougados M, Emery P, Lemmel EM, Zerbini CAF, Brin S, van Riel P. When a DMARD fails, should patients switch to sulfasalazine or add sulfasalazine to continuing leflunomide?. *Annals of the Rheumatic Diseases* 2005;**64**(5):44-51.

Emery 1999 *{published and unpublished data}*

Emery P, Breedveld FC, Jubb RW, Sorensen H, Oed C, Loew-Friedrich I. Efficacy and safety of leflunomide vs. methotrexate in rheumatoid arthritis (RA): results of a double-blind, randomized, 2-year trial. *Arthritis and Rheumatism* 1999;**42 Suppl**(9):271.

Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, Gomor B, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;**39**(6):655-65.

Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Data on file, Hoechst Marion Roussel (Bridgewater) Nov 2, 1999.

United States Food, Drug Administration. Summary basis of approval, leflunomide: NDA 20-905. Summary basis of approval, United States Department of Health and Human Services. Vol. **ND 20-905**, 1997:2-22.

Fiehn 2007 *{published data only}*

Fiehn C, Jacki S, Heilig B, Lampe M, Wiesmuller G, Richter C, et al. Eight versus 16-week re-evaluation period in rheumatoid arthritis patients treated with leflunomide or methotrexate accompanied by moderate dose prednisone. *Rheumatology International* 2007;**27**(10):975-9.

Gao 2004 *{published data only}*

Gao JS, Wu H, Chen YJ, Li F, Tian J, Xie X. Observation on the short-term curative effect and safety on combination use of LEF plus MTX in the treatment of active and severe RA. Abstract book, the 11th APLAR meeting, Jeju, South Korea. Seoul, Sep 2004:92.

Hu 2001 *{published data only}*

Hu Y, Tu S, Liu P. A randomized, controlled, single-blind trial of leflunomide in the treatment of rheumatoid arthritis. *Journal of Tongji Medical University* 2001;**21**(1):72-4.

Jakez-Ocampo 2002 *{published data only}*

Jakez-Ocampo J, Richaud-Patin Y, Simón A, Llorente L. Weekly dose of leflunomide for the treatment of refractory rheumatoid arthritis: an open pilot comparative study. *Joint, Bone, Spine: Revue du Rhumatisme* 2002;**69**:307-11.

Jiang 2001 *{published data only}*

* Jiang LD, Yu Q, Mei ZW. Efficacy in Active Rheumatoid Arthritis Treated by Leflunomide in Comparison with Methotrexate: A Randomized and Controlled Trial. *Clinical Medical Journal of China* 2001;**8**(2):157-8.

Kalden 2001 *{published data only}*

Kalden JR, Scott DL, Smolen JS, Schattenkirchner M, Rozman B, Williams BD, et al. for the Eurpoean Leflunomide Study Group. Improved functional ability in patients with rheumatoid arthritis - long term treatment with leflunomide versus sulfasalazine. *The Journal of Rheumatology* 2001;**28**(9):1983-91.

Karanikolas 2006 *{published data only}*

Karanikolas G, Charalambopoulos D, Andrianakos A, Antoniades C, Katsilambros N. Combination of cyclosporine and leflunomide versus single therapy in severe rheumatoid arthritis. *The Journal of Rheumatology* 2006;**33**(3):486-9.

Kremer 2002 *{published data only}*

Kremer JM, Genovese MC, Cannon GW, Caldwell JR, Cush JJ, Furst DE, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 2002 Nov 5;**137**(9):726-33.

Kremer 2004 *{published data only}*

Kremer J, Genovese M, Cannon GW, Caldwell J, Cush J, Furst DE, et al. Combination leflunomide and methotrexate therapy for patients with active rheumatoid arthritis failing MTX monotherapy: open-label extension of a randomized, double-blind, placebo controlled trial. *The Journal of Rheumatology* 2004;**31**(8):1521-31.

Lao 2001 *{published data only}*

Lao ZY, Ni LQ, Zhang ZF, Zhou JL, et al. Leflunomide in treating rheumatoid arthritis: a double-blind study. *Chinese Journal of New Drugs and Clinical Remedies* 2001;**20**(2):94-7.

Lao 2002 *{published data only}*

Lao ZY, Chen JH. Leflunomide combined with MTX in the treatment of rheumatoid arthritis. Abstract book, the 10th APLAR congress, Bangkok, Thailand. Bangkok, Dec 2002:140.

Larsen 2001 *{published data only}*

Larsen A, Kvien T, Schattenkirchner M, Rau R, Scott DL, Smolen JS, et al. European Leflunomide Study Group. Slowing of disease progression in rheumatoid arthritis patients during long-term treatment with leflunomide or sulfasalazine. *Scandinavian Journal of Rheumatology* 2001;**30**(3):135-42.

Lau 2002 *{published data only}*

Lau CS, on behalf of the ARAVA Asia Study Group. Leflunomide (LEF) versus low dose methotrexate (MTX) in adult Asian patients with active rheumatoid arthritis (RA). Abstract book, the 10th APLAR congress, Bangkok, Thailand. Bangkok, Dec 2002:141.

Mariette 2004 *{published data only}*

Mariette X, Bijlsma JWJ, Herold M, Eiselstein J, Spencer-Green GT, Kupper H. Efficacy evaluation of adalimumab (Humira®) in combination with single and multiple disease modifying antirheumatic drugs in the REACT trial. *Annals of the Rheumatic Diseases* 2004;**63 Suppl 1**:278.

Mladenovic 1995 *{published data only}*

* Mladenovic V, Domljan Z, Rozman B, Jajic I, Mihajlovic D, Dordevic J, Popovic M, et al. Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis. *Arthritis and Rheumatism* 1995;**38**(11):1595-603.

Poor 2004 *{published data only}*

Poor G for the Leflunomide Multinational Study Group, Strand V. Efficacy and safety of leflunomide 10 mg vs 20 mg once daily in patients with active rheumatoid arthritis: multinational double-blind, randomized trial. *Rheumatology (Oxford)* 2004;**43**(6):744-9.

Reece 2002 *{published data only}*

Reece RJ, Kraan MC, Radjenovic A, Veale DJ, O'Connor PJ, Ridgway JP, et al. Comparative assessment of leflunomide and methotrexate for the treatment of rheumatoid arthritis, by dynamic enhanced magnetic resonance imaging. *Arthritis and Rheumatism* 2002;**46**(2):366-72.

Rozman 1994a *{published data only}*

Rozman B, Domijan Z, Popovic M, Mladenovic V, Mihajlovic D, Jajic I, Zivkovic M, Leflunomide Study Group, Croatia, Slovenia, Yugoslavia. Low-Friedrich I, Oed Ch, Seifert H, Strand V. Weekly administration of leflunomide to patients with active rheumatoid arthritis. *Arthritis and Rheumatism* 1994;**37 Suppl 9**:339.

Scott 2001 *{published data only}*

Scott DL, Smolen JS, Kalden JR, van de Putte LBA, Larsen A, Kvien TK, et al for the European Leflunomide Study Group. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. *Annals of the Rheumatic Diseases* 2001;**60**(10):913-23.

Sharp 2000 *{published data only}*

* Sharp JT, Strand V, Leung H, Hurley F, Loew-Friedrich I, on behalf of the Leflunomide Rheumatoid Arthritis Investigators Group. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis. *Arthritis and Rheumatism* 2000;**43**(3):495-505.

Shuai 2002 *{published data only}*

Shuai ZW, Liu S, Shun GH, Xue JH, Xue SY. The phase II clinical trial of leflunomide in treatment of rheumatoid arthritis. *Acta Universitatis Medicinalis Anhui* 2002;**37**(1):41-4.

Smolen 1999 *{published data only}*

Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. *Lancet* 1999;**353**:259-66.

Strand 1999a *{published and unpublished data}*

Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Archives in Internal Medicine* 1999;**159**:2542-50.

Strand 1999b *{published data only}*

Strand V, Tugwell P, Bombardier C, Maetzel A, Crawford B, Dorrier C, et al. Function and health-related quality of life: results form a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. *Arthritis and Rheumatism* 1999;**42**(9):1870-8.

Wislowska 2007 *{published data only}*

Wislowska M, Jakubicz D. Preliminary evaluation in rheumatoid arthritis activity in patients treated with TNF-α blocker plus methotrexate versus methotrexate or leflunomide alone. *Rheumatology International* 2007;**27**:641-7.

References to studies excluded from this review

Balabanova 2004 *{published data only}*

Balabanova RM, Makolkin VI, Shostak NA, Chichasova NV, Olyunin YuA, Goryachev DV, et al. Changes in indices of inflammatory activity in patients with rheumatoid arthritis

during early stages of basic therapy with leflunomide. *Terapevticheskii Arkhiv* 2004;**76**(5):28-32.

Balabanova 2006 *{published data only}*

Balabanova RM, Kashevarov RIu, Oliunin IuA, Smirnov AV, Aleksandrova EN. An antidestructive effect of leflunomide in early rheumatoid arthritis. *Terapevticheskii Arkhiv* 2006;**78**(6):6-10.

Dougados 2003 *{published data only}*

Dougados M, Emery P, Lemmel EM, de la Serna R, Zerbini CA, Brin S, van Riel P. Efficacy and safety of leflunomide and predisposing factors for treatment response in patients with active rheumatoid arthritis: RELIEF 6-month data. *The Journal of Rheumatology* 2003;**30**(12):2572-9.

Godinho 2004 *{published data only}*

Godinho F, Godfrin B, El Mahou S, Navaux F, Zabraniecki L, Cantagrel A. Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis. *Clinical and Experimental Rheumatology* 2004;**22**(3):328-30.

Grijalva 2007 *{published data only}*

Grijalva CG, Chung CP, Arbogast PG, Stein CM, Mitchel EF Jr, Griffin MR. Assessment of adherence to and persistence on disease- modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. *Medical Care* 2007;**45 Suppl 2**(10):66-76.

Hansen 2004 *{published data only}*

Hansen KE, Cush J, SInghal A, Cooley DA, Cohen S, Patel SR, et al. The safety and efficacy of leflunomide in combination with infliximab in rheumatoid arthritis. *Arthritis and Rheumatism* 2004;**51**(2):228-32.

Jevtic 1997 *{published data only}*

Jevtic V, Watt I, Rozman B, Kos-Golja M, Praprotnik S, Logar D, et al. Contrast enhanced Gd-DTPA magnetic resonance imaging in the evaluation of rheumatoid arthritis during a clinical trial with DMARDs. A prospective two-year follow-up study on hand joints in 31 patients. *Clinical and Experimental Rheumatology* 1997;**15**:151-6.

Ju 2007 *{published data only}*

Ju JH, Kim SI, Lee JH, Lee SI, Yoo WH, Choe JY, et al. Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. *Arthritis and Rheumatism* 2007 Jun;**56**(6):2094-6.

Kalden 2003 *{published data only}*

Kalden JR, Schattenkirchner M, Sorensen H, Emery P, Deighton C, Rozman B. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study. *Arthritis and Rheumatism* 2003;**48**(6):1513-20.

Kraan 2004 *{published data only}*

Kraan MC, Smeets TJ, van Loon MJ, Breedveld FC, Dijkmans BA, Tak PP. Differential effects of leflunomide and methotrexate on cytokine production in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2004;**63**(9):1056-61.

Kuzmanova 2003 *{published data only}*

Kuzmanova SI, Solakov PT, Batalov AZ, Staikova ND, Andreev SA, Russafov PB. Leflunomide in the treatment of refractory rheumatoid arthritis. *Folia Medica (Plovdiv)* 2003;**45**(3):43-7.

Litinsky 2006 *{published data only}*

Litinsky I, Paran D, Levartovsky D, Wigler I, Kaufman I, Yaron I, et al. The effect of leflunomide on clinical parameters and serum levels of IL-6, IL-10, MMP-1, and MMP-3 in patients with resistant rheumatoid arthritis. *Cytokine* 2006;**33**(2):106-10.

Mroczkowski 1999 *{published data only}*

Mroczkowski PJ, Weinblatt ME, Kremer JM. Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis. *Clinical and Experimental Rheumatology* 1999;**17 Suppl 18**(6):66-8.

Popovic 1998 *{published data only}*

Popovic M, Stefanovic D, Pejnovic N, Popovic R, Glisic B, Obradovic S, et al. Comparative study of the clinical efficacy of four DMARDs (leflunomide, methotrexate, cyclosporin, and levamisole) in patients with rheumatoid arthritis. *Transplantation Proceedings* 1998;**30**(8):4135-6.

Richards 2007 *{published data only}*

Richards BL, Spies J, McGill N, Richards GW, Vaile J, Bleasel JF, Youssef PP. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. *Internal Medicine Journal* 2007;**37**(2):101-7.

Rozman 1994b *{published data only}*

Rozman B, Domljan Z, Popovic M, Mladenovic D, Mihajlovic I, Jajic M, Zivkovic M, Leflunomide Study Group, Croatia, Slovenia, Yugoslavia. Low-Friedrich I, Oed Ch, Seifert H, Strand V. Long term administration of leflunomide to patients with rheumatoid arthritis (RA). *Arthritis and Rheumatism* 1994;**37 Suppl**(9):339.

Sarunhan-Direskeneli 2007 *{published data only}*

Saruhan-Direskeneli G, Inanc M, Fresko I, Akkoc N, Dalkilic E, Erken E, et al. The role of HLA-DRB1 shared epitope alleles in predicting short-term response to leflunomide in rheumatoid arthritis. *Rheumatology* 2007;**46**(12):1842-4.

Strand 2005 *{published data only}*

Strand V, Scott DL, Emery P, Kalden JR, Smolen JS, Cannon GW, et al. Leflunomide Rheumatoid Arthritis Investigators Groups. Physical function and health related quality of life: analysis of 2-year data from randomized, controlled studies of leflunomide, sulfasalazine, or methotrexate in patients with active rheumatoid arthritis. *The Journal of Rheumatology* 2005;**32**(4):590-601.

Tchetverikov 2008 *{published data only}*

Tchetverikov I, Kraan MC, van El B, Hanemaaijer R, DeGroot J, Huizinga TW. Leflunomide and methotrexate reduce levels of activated matrix metalloproteinases in complexes with alpha2 macroglobulin in serum of rheumatoid arthritis patients. *Annals of the Rheumatic Diseases* 2008;**67**(1):128-30.

van der Heijde 2004 *{published data only}*

van der Heijde D, Kalden J, Scott D, Smolen J, Strand V. Long term evaluation of radiographic disease progression in a subset of patients with rheumatoid arthritis treated with leflunomide beyond 2 years. *Annals of the Rheumatic Diseases* 2004 Jun;**63**(6):737-9.

van der Kooij 2007 *{published data only}*

van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, van Zeben D, Kerstens PJ, Gerards AH, et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Annals of the Rheumatic Diseases* 2007;**66**(10):1356-62.

van Riel 2003 *{published data only}*

van Riel P. Lelfunomide improves the clinical response in patients with active rheumatoid arthritis treated with methotrexate. *Clinical and Experimental Rheumatology* 2003;**21**(6):695-6.

van Roon 2005 *{published data only}*

van Roon EN, Jansen TL, van de Laar MA, Janssen M, Yska JP, Keuper R, et al. Therapeutic drug monitoring of A77 1726, the active metabolite of leflunomide: serum concentrations predict response to treatment in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2005 Apr;**64**(4):569-74.

Weinblatt 1999b *{published data only}*

Weinblatt ME, Kremer JM, Coblyn JS, Maier AL, Helfgott SM, Morrell M, et al. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arthritis and Rheumatism* 1999;**42**(7):1322-8.

References to studies awaiting assessment

Raczkiewicz-Papierska2007 *{published data only}*

Raczkiewicz-Papierska A, Dudek A, Bachta A, Thustochowicz M, Zawadyl B, Sulek M. Leflunomide as a second choice treatment in patients with rheumatoid arthritis. *Polski Merkuriusz Lekarski* 2007;**22**(132):547-50.

Shevchuk 2003 *{published data only}*

Shevchuk SV, Stanislavchuk MA, Pentiuk OO. Efficacy and safety of treatment with methotrexate, leflunomide, detralex, and their combination of patients with rheumatoid arthritis. *Likarska Sprava* 2003, (3-4):34-41.

Zhang 2004 *{published data only}*

Zhang X, Cui Y, Luo Q, Yao RY, Zhou H. Methotrexate combined with leflunomide or hydroxychloroquine in the treatment of rheumatoid arthritis. *Zhonghua Yi Xue Za Zhi* 2004;**84**(12):1038-40.

Zhao 2006 *{published data only}*

Zhao YX, Liu Y. Clinical observation on effects of leflunomide and total glucosides of paeony on rheumatoid arthritis. *Chinese Journal of Integrated Traditional and Western Medicine* 2006;**26**(4):355-7.

Additional references

Alarcon 1995

Alarcon GS. Epidemiology of rheumatoid arthritis. *Rheumatic Diseases Clinics of North America* 1995;**21**:589-604.

Arnett 1988

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism* 1988;**31**:315-24.

Egsmose 1995

Egsmose C, Lund B, Borg G, Pettersson H, Berg E, Brodin U, et al. Patients with rheumatoid arthritis benefit from early second line therapy: 5-year follow up of a prospective, double blind, placebo controlled study. *The Journal of Rheumatology* 1995;**22**:2208-13.

Felson 1993

Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis. *Arthritis and Rheumatism* 1993;**36**:729-40.

Felson 1995

Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith D, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis & Rheumatism* 1995;**38**:727-35.

Fox 1998

Fox RI. Mechanism of action of leflunomide in rheumatoid arthritis. *The Journal of Rheumatology* 1998;**25 Suppl**(53):20-6.

Fries 1996

Fries JF, Williams CA, Morfield D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. *Arthritis and Rheumatism* 1996;**39**:616-22.

Furst 1999

Furst DE. Leflunomide, mycophenolic acid and matrix metalloproteinase inhibitors. *Rheumatology* 1999;**38 Suppl 2**:14-8.

Haynes 1994

Haynes R, Wilczynski N, McKibbon KA, Walker CJ, Sinclair JC. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *Journal of the American Medical Informatics Association* 1994;**1**:447-58.

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Jadad 1996

Jadad A, Moore A, Carrol D. Assessing the quality of randomized trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12.

Maetzel 2002

Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C. Cost effectiveness of adding leflunomide to a 5-year strategy of conventional disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. *Arthritis and Rheumatism* 2002;**47**(6):655-61.

Pincus 1999

Pincus T, Stein CM. ACR20: clinical or statistical significance?. *Arthritis and Rheumatism* 1999;**42**(8):1572-6.

Rozman 1998

Rozman B for the Leflunomide Investigators Group. Clinical experience with leflunomide in rheumatoid arthritis. *The Journal of Rheumatology* 1998;**25 Suppl**(53):27-32.

Saag 2008

Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis and Rheumatism* 2008;**59**(6):762-84.

Schünemann 2008

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, and Guyatt GH on behalf of the Cochrane Applicability and Recommendations Methods Group. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S editor(s). Cochrane handbook for systematic reviews of interventions. Version 5.0.1. The Cochrane Collaboration, Updated Sep 2008.

Simon 2000

Simon LS, Yocum D. New and future drug therapies for rheumatoid arthritis. *Rheumatology (Oxford)* 2000;**39 Suppl 1**:36-42.

Smolen 2000

Smolen JS, Emery P. Efficacy and safety of leflunomide in active rheumatoid arthritis. *Rheumatology (Oxford)* 2000;**39 Suppl 1**:48-56.

Tugwell 2004

Tugwell P, Shea B, Boers M, Brooks P, Simon L, Strand V, Wells G (editors). Evidence-based Rheumatology. London: BMJ Books, 2004.

van der Heijde 1993

van der Heijde DM, van Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. *The Journal of Rheumatology* 1993;**20**:573-81.

van Gestel 1996

van Gestel AM, Prevoo ML, van Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. *Arthritis and Rheumatism* 1996;**39**:34-40.

Verhagen 1998

Verhagen AP, de Vet HCW, de Bie RA, Kessels AGH, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomized controlled trials for conducting systematic review developed by Delphi consensus. *Journal of Clinical Epidemiology* 1998;**51**(12):1235-41.

Weinblatt 1999a

Weinblatt ME. The role of current strategies in the future treatment of rheumatoid arthritis. *Rheumatology* 1999;**38 Suppl 2**:19-23.

Wolfe 1991

Wolfe F, Hawley DJ, Cathey MA. Clinical and health status measures over time: prognosis and outcome assessment in rheumatoid arthritis. *The Journal of Rheumatology* 1991;**18**:1290-7.

References to other published versions of this review

Osiri 2003a

Osiri M, Shea B, Robinson V, Suarez-Almazor M, Strand V, Tugwell P, Wells G. Leflunomide for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. *The Journal of Rheumatology* 2003;**30**(6):1182-90.

Osiri 2003b

Osiri M, Shea B, Welch V, Suarez-Almazor ME, Strand V, Tugwell P, Wells GA. Leflunomide for the treatment of rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858.CD002047]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Amit 2004

Methods	Open-label, randomized, active controlled, parallel group clinical trial
	Sample size at entry: total 166, Lef+MTX 83, MTX 83

Amit 2004 *(Continued)*

	WIthdrawals: Lef+MTX 8, MTX 10
	Trial duration: 24 months
Participants	Patients who met the ACR classification criteria of RA were included
Interventions	Group A: MTX 7.5 mg/week + folic acid 5 mg/week + Lef 20 mg/d
	Group B: MTX 7.5 mg/week + folic acid 5 mg/week
Outcomes	Primary outcomes: improvement of each item of ACR core set
	Secondary outcomes: duration of morning stiffness, grip strength, RF, ESR, CRP, CBC, LFT, hands X-Ray
Notes	Quality score = 1 (R0, B0,W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Unclear risk	B-unclear
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	High risk	C-no
Free of selective reporting?	High risk	C-no
Free of other bias?	Unclear risk	B-unclear

Amit 2006

Methods	Open-label, randomized, active controlled, parallel group clinical trial
	Sample size at entry: total 466, Lef+MTX 233, MTX 233
	WIthdrawals: Lef+MTX 20, MTX 15
	Trial duration: 36 months
Participants	Patients who met the ACR classification criteria of RA were included
Interventions	Group A: MTX 10 mg/week + folic acid 5 mg/week + Lef 20 mg/day
	Group B: MTX 10 mg/week + folic acid 5 mg/week
Outcomes	Improvement of each item of ACR core set
Notes	Quality score = 2 (R1, B0, W1)

Amit 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Unclear risk	B-unclear
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	High risk	C-no
Free of selective reporting?	High risk	C-no
Free of other bias?	Unclear risk	B-unclear

Antony 2006

Methods	Open-label, non-randomized, active controlled, parallel group clinical trial Sample size at entry: total 60, Lef 49, Lef+MTX 11 WIthdrawals: Lef 4, Lef+MTX 0 Trial duration: total 6 months
Participants	Patients, aged 18-65 years old, with active RA not responded to antimalarials, SSZ, MTX after 3-6 months of treatment. Excluded patients with: 1. uncontrolled HT 2. hepatic, renal, pulmonary and hematologic diseases 3. overlap syndrome 4. pregnancy and lactation 4. reproductive age with unwilling to use contraception Wash-out period: 2 weeks Stable dose of prednisolone ≤ 10 mg/day of prednisolone
Interventions	All patients received leflunomide loading dose of 100 mg/day for 3 days then 20 mg/day. After 3 months of treatment, if improvement was observed, the patients continued taking leflunomide until 6 months. If no significant improvement was not seen, MTX 5-7.5 mg/week was added on baseline leflunomide
Outcomes	1. DAS28 response criteria 2. Physician and patient global assessment of disease activity

Antony 2006 *(Continued)*

	3. Remission rate
Notes	Quality score = 1 (R0, B0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	High risk	C-no
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Bao 2000

Methods	Randomized, double-blind, active controlled, parallel group trial Sample size at entry: total 60, leflunomide 30, MTX 30 Withdrawals: leflunomide: 0, MTX: 4 (serious GI symptoms) Trial duration: 6 months
Participants	Patients who were 18-65 years of age, met the ACR criteria with active RA Active RA, at least 4 of 5: 1) 5 or more tender joints 2) 3 or more swollen joints 3) morning stiffness lasted at least 1 hour 4) Westergren ESR at least 28 mm/hr 5) Moderate resting pain Exclusion criteria: 1. taking other DMARDs during the last 6 months 2. serious hepatic, renal, hematologic disorders 3. history of gastrointestinal ulcer 4. women who were pregnant, breastfeeding 5. history of allergy to drugs
Interventions	Leflunomide: 20 mg once daily (no loading dose) MTX: 15 mg/ week
Outcomes	1. pain level 2. duration of morning stiffness (min) 3. grip strength (Kpa) 4. tender joint count

Bao 2000 *(Continued)*

	5. swollen joint count 6. HAQ 7. patient global assessment of disease activity 8. physician global assessment of disease activity 9. ESR (mm/h) 10. CRP (ug/ml) Improvement of each of the 10 indices = (value before treatment-value after treatment)/value before treatment x100% Response rate = average of improvement of the ten indices Ineffective = improvement <30% Effective = improvement 30-50% Improvement = improvement 51-75% Remarkable improvement = improvement >75% Total response rate = (number of patients with effective+improvement+ remarkable improvement)/total patientsx100% Obvious response rate = (number of patients with improvement+ remarkable improvement)/total patientsx100%
Notes	Quality score = 4 (R1, B2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-yes
Allocation concealment?	Low risk	A-yes
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Bao 2003

Methods	Randomized, double-blind, active controlled, parallel group, multicenter trial Sample size at entry: total 566, Lef 323, MTX 243 Withdrawals: Lef 32, MTX 30 Trial duration: 24 weeks
Participants	Patients who were ≥18 years old, met the ACR criteria with active RA

Bao 2003 *(Continued)*

	Active RA: at least 4 of 5: 1) moderate resting pain 2) morning stiffness ≥ 1 hour 3) 3 or more swollen joints 4) 5 or more tender joints 5) Westergren ESR at least 28 mm/hr Exclusion criteria: 1. any acute or chronic illness in heart, liver, renal, GI and other vital organs 2. history of sensitivity to trial drugs or allergies 3. pregnant women or breast-feeding women 4. previous treatment with gold
Interventions	Leflunomide: 20 mg once daily (no loading dose) MTX: 15 mg/ week NSAIDs (Neptlung 0.4 g/day) was permitted in the first 4-6 weeks of the trial Glucocorticoids and other DMARDs were not allowed in the trial and the washout period was at least 1 month
Outcomes	1. resting pain level 2. duration of morning stiffness (min) 3. grip strength (Kpa) 4. tender joint count 5. swollen joint count 6. HAQ 7. patient global assessment of disease activity 8. physician global assessment of disease activity 9. ESR (mm/h) 10. CRP (ug/ml) Improvement of each of the 10 indices = (value before treatment-value after treatment)/ value before treatment x100% General effective rate Ineffective = improvement <30% Effective = improvement 30 to <50% Remarkable improvement = improvement ≥50% Total response rate = (number of patients with effective+ remarkable improvement) / total patients x100% ACR20 response rate
Notes	Quality score = 4 (R1, B2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-yes
Allocation concealment?	Low risk	A-yes
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B - unclear

Bao 2003 *(Continued)*

Free of selective reporting?	Unclear risk	B - unclear
Free of other bias?	Unclear risk	B - unclear

Cohen 2001

Methods	Randomized, double-blind, active controlled, parallel group, multinational trial Sample size at entry; total 199, leflunomide 98, MTX 101. Withdrawals: leflunomide 15, MTX 21 Trial duration: 12 months (year 2 extension from Strand 1999 (a) study
Participants	Patients who were 18-75 years of age, met the ACR criteria for 6 months or more, with active RA and never been treated with MTX. Active RA, at least 3 of 4: 1) 9 or more tender joints 2) 6 or more swollen joints 3) morning stiffness lasted at least 45 minutes 4) Westergren ESR at least 28 mm/hr No other DMARD treatment within the last 30 days Stable dose of NSAID and/or prednisone (not more than 10 mg/day) for at least 30 days Required contraceptions during the study and continued at least 6 months after the study ended All patients who continued treatment into the second year and received at least 1 dose of study medication and attended 1 follow-up visit after week 52 were included in the year-2 cohort, regardless of the ACR responder status
Interventions	Leflunomide: 20 mg/day if the problems with tolerability occurred, the dose was reduced to 10 mg/day MTX: 15-17.5-20 mg/week Almost all patients received 1-2 mg folate daily
Outcomes	Tender and swollen joint counts (28 joints), patient global and physician global assessments using 10 cm VAS, patient assessment of pain on 10-cm VAS, modified HAQ score, Westergren ESR, CRP, HAQ DI, PET, SF-36, work productivity index Hands and feet X-ray: modified Sharp score Number of patients met the ACR20, ACR50, ACR70 response criteria
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-yes
Allocation concealment?	Low risk	A-yes
Blinding?	Low risk	A-yes

Cohen 2001 *(Continued)*

All outcomes		
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Dougados 2005

Methods	Randomized, double-blind, active controlled, parallel group, multinational trial Sample size at entry: total 106, leflunomide+SSZ 56, placebo+SSZ 50 Withdrawals: leflunomide+SSZ 32 (57%) placebo+SSZ 27 (54%) Trial duration: 24 weeks
Participants	Patients who were 18-75 years of age, with active RA as defined by a DAS28 >3.2 and ARA functional class I,II, or III. FIrst open label phase: No other DMARD treatment for at least 4 weeks. Stable NSAIDs dose and prednisone dose <=10 mg/day. No intraarticular steroid injection within 4 weeks. Second double blind phase: Patients not responded to leflunomide after 24 weeks of the first open label phase Stable dose of NSAID and/or prednisone (not more than 10 mg/day) for at least 30 days. Required contraceptions.
Interventions	First open label phase: leflunomide loading 100 mg/d for 3 days followed by 20 mg/d for 24 weeks in all patients Second double blind phase: Patients not responded adequately to leflunomide 20 mg/d (DAS28 > 3.2) were randomized to received either leflunomide 20 mg/d plus SSZ 2 g/d or SSZ 2 g/d plus placebo for 24 weeks Second open label phase: Patients who were good or moderate responders in the first open label phase entered a second open label phase of 24 weeks leflunomide monotherapy.
Outcomes	1. DAS28 response rate (sum of good and moderate responders) every 4 weeks 2. number of patients with sustained DAS28 responders at week 24 3. ACR20, 50, and 70 response rates every 4 weeks 4. Sustained responders for ACR criteria at week 24
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement

Dougados 2005 *(Continued)*

Adequate sequence generation?	Low risk	A-yes
Allocation concealment?	Low risk	A-yes
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Emery 1999

Methods	Randomized, double-blind, active controlled, parallel group, multinational trial Sample size at entry: total 999, leflunomide 501, MTX 498 Withdrawals: leflunomide 152, MTX 111 Trial duration: 52 weeks
Participants	Patients who met the 1987 ACR criteria for RA, had active disease as defined by all of the followings: 6 or more tender joints; 6 or more swollen joints; patient global assessment of RA condition as fair, poor, or very poor; physician global assessment as fair, poor, or very poor; CRP.2.0 mg/dl or ESR.28 mm/hr Excluded: women who were pregnant, breastfeeding, or of childbearing potential; men wishing to father a child; previous therapy with leflunomide or MTX at any time Total 1244 patients were enrolled, 999 were randomized Patients completed treatment phase: leflunomide 349, MTX 387 Mean (SD) age: lef 58.3 (10.12), MTX 57.79 (10.8) Men/women: lef 354/147, MTX 348/150 Mean (SD) duration of RA in years: lef 3.7 (3.16), MTX 3.8 (3.49) Mean (SD) at RA onset: lef 54.6 (10.64), MTX 54.0 (11.21) Mean (SD) number of DMARDs failed: lef 1.1 (1.09), MTX 1.1 (1.12)
Interventions	Leflunomide: loading 100 mg once daily for 3 days followed by a 20-mg daily maintenance dose MTX: single doses of 7.5 mg on days 1, 8, 15, and 22 followed by 10 mg/week and increase to 15 mg/week on or after week 12
Outcomes	Primary outcomes: tender joint count, swollen joint count, patient global assessment, physician global assessment

Emery 1999 *(Continued)*

	Secondary outcomes: responder rates defined as Paulus criteria and ACR20 criteria, joint tenderness score, swollen joint score, duration of morning stiffness, pain intensity, HAQ, X-ray of both hands and feet, ESR, CRP, RF, Safety outcomes: standard adverse events, laboratory and clinical safety variables
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-yes
Allocation concealment?	Low risk	A-yes
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Fiehn 2007

Methods	Prospective, open-label, randomized controlled trial Sample size at entry: leflunomide 19, MTX 21 Withdrawals: leflunomide 3, MTX 4 Trial duration: 16 weeks
Participants	Patients who fulfilled the ACR criteria of RA and were MTX-naive with age less than 70 years old All received prednisone at the initial dose of 20 mg/d with weekly dose reduction by 5 mg/d to 10 mg/d, then prednisone dose was reduced by 2.5 mg/d every week Allowed previously used DMARDs included sulfasalazine and hydroxychloroquine Exclusion criteria: renal insufficiency, liver disease, hypertension, and other severe organ disease Mean (SD) age in years: leflunomide 53 (13), MTX 56 (12) Female gender: leflunomide 17, MTX 14 Mean disease duration in years: leflunomide 2.46, MTX 2.43 Baseline mean (SD) DAS28: leflunomide 5.46 (0.8), MTX 5.36 (0.8)
Interventions	Leflunomide loading dose 100 mg/d for 3 days and then 20 mg/d MTX 25 mg/week intramuscularly

Fiehn 2007 *(Continued)*

	All patients received oral prednisone
Outcomes	Disease activity score (DAS)28 at 8 and 16 weeks Serum C-reactive protein (CRP) level at 8 and 16 weeks
Notes	Quality score = 3 (R2, B0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Gao 2004

Methods	Randomized, open-label, active-controlled, parallel group, clinical trial Sample size at entry: 162, MTX+Lef 84, MTX+CQ+SSZ 78 Withdrawals: not mentioned Trial duration: 12 weeks
Participants	Chinese patients with active and severe RA Definition of active and severe RA: rest pain VAS ≥ 8.0 cm, ESR > 60 mm/hr, duration of morning stiffness > 1 hour, Steinbrocker damage score ≥ grade III, tender joint count > 8, swollen joint count ≥ 3
Interventions	Active treatment group: MTX + Lef Control group: MTX+CQ+SSZ Doses were not mentioned
Outcomes	Rest pain, duration of morning stiffness, grip strength, tender joint count, tender joint index, swollen joint count, swollen joint index, patient global assessment, physician global assessment, functional class, ESR, CRP, RF, CBC, liver function, renal function
Notes	Quality score = 1 (R1, B0, W0)

Risk of bias

Gao 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	High risk	C-no
Free of selective reporting?	High risk	C-no
Free of other bias?	Unclear risk	B-unclear

Hu 2001

Methods	Randomized, single-blind, active controlled, parallel group trial Sample size at entry: total 81 leflunomide 56, MTX 25 Withdrawals: leflunomide: 1, MTX: 0 Trial duration: 12 weeks
Participants	Patients who were 18-65 years of age, met the ACR criteria with active RA and FC I, II Exclusion criteria: 1. Taking other DMARDs during the last 1 month 2. Clinical evidence of cardiac, hepatic, renal, stomach or duodenal disorders 3. Previous use of gold salts 4. Women who were pregnant, breastfeeding 5. History of allergy to drugs Oxaprozin 0.4 g/d was allowed for 4-6 weeks after study entry
Interventions	Leflunomide: 20 mg once daily (no loading dose) MTX: 15 mg/ week
Outcomes	Efficacy outcomes: 1. resting pain 2. morning stiffness 3. swollen joint count 4. swollen joint score 5. tender joint count 6. tender joint score 7. grip strength 8. joint function 9. activity of daily living 10. physician global assessment 11. patient global assessment 12. ESR 13. CRP

Hu 2001 *(Continued)*

	14. rheumatoid factor 15. improvement rate (IR) 16. general therapeutic efficacy Improvement of each of the 10 indices (IR) = (value before treatment-value after treatment)/ value before treatment x100% Response rate = average of improvement rate of the 10 indices Ineffective = improvement <30% Effective = improvement 30-<50% Improvement = improvement 50-<75% Remarkable improvement = improvement ≥75% Total response rate = (number of patients with effective+improvement+ remarkable improvement) / total patientsx100% Adverse reactions assessment: 1. slight 2. mild 3. severe 4. dangerous 5. side reaction rate
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Unclear risk	B-unclear
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Jakez-Ocampo 2002

Methods	Open-label, randomized, active control, parallel group, clinical trial Sample size at entry: total 16, weekly Lef 8, daily Lef 8 Withdrawals: weekly Lef 1, daily Lef 2 Trial duration: 12 months
Participants	Patients who fulfilled the ACR classification criteria for RA

Jakez-Ocampo 2002 *(Continued)*

	All had positive rheumatoid factor Active disease: 1. TJC ≥ 8 2. SJC ≥ 8 3. duration of morning stiffness ≥ 45 minutes 4. ESR ≥ 28 mm/hr Refractory to ≥ 4 DMARDs (chloroquine, d-penicillamine, cyclophosphamide, MTX, SSZ, and glucocorticoids) at a conventional dosage for ≥ 8 months Exclusion criteria: pregnancy, nursing, hypertension, infection, abnormal LFT, HIV positive test, hepatitis B and C, GI disturbance, and presence of other inflammatory and/or chronic diseases
Interventions	Weekly Lef: Lef 100 mg/week without loading dose Daily Lef: Lef 100 mg/day for 3 days then Lef 20 mg/day
Outcomes	ACR20,/50/70 response criteria
Notes	Quality score = 2 (R1, B0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Jiang 2001

Methods	Randomized, double-blind, active controlled, parallel group, trial Sample size at entry: total 60 leflunomide 30, MTX 30 Withdrawals: none Trial duration: 3 months
Participants	Patients who were 18-65 years of age, met the ACR criteria with active RA Active RA: at least 4 of 5: 1) 5 or more tender joints 2) 3 or more swollen joints 3) morning stiffness lasted at least 1 hour 4) Westergren ESR at least 28 mm/hr Exclusion criteria: 1. taking other DMARDs during the last 6 months

Jiang 2001 *(Continued)*

	2. serious hepatic, renal, hematologic disorders 3. history of gastrointestinal ulcer 4. women who were pregnant, breastfeeding 5. history of allergy to drugs
Interventions	Leflunomide: 20 mg once daily (no loading dose) MTX: 15 mg/ week
Outcomes	1. pain level 2. duration of morning stiffness (min) 3. grip strength (Kpa) 4. tender joint count 5. tender joint score 6. swollen joint count 7. swollen joint score 8. HAQ 9. patient global assessment of disease activity 10. physician global assessment of disease activity 11. ESR (mm/h) 12. CRP (ug/ml) 15. RF
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-yes
Allocation concealment?	Low risk	A-yes
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Kalden 2001

Methods	Randomized, double-blind, active controlled, parallel group, multicenter study Sample size at entry (6-12 months): total 197, leflunomide 80, placebo-switch-to-SSZ 41, sulphasalazine 76 Withdrawals (6-12 months): lef 9, pl-SSZ 12, SSZ 8 Sample size at entry (12-24 months): total 146, leflunomide 60, pl-SSZ 26, sulphasalazine 60

Kalden 2001 *(Continued)*

	Withdrawals (12-24 months): lef 11, pl-SSZ 5, SSZ 14 Trial duration: 18 months (month 6 to 24 extension of Smolen study) (complementary data with Scott 2001 study)
Participants	Patients aged at least 18 years with active RA based on ACR criteria and ACR functional class I, II, III Tender joint count at least 6; swollen joint count at least 6; patient and doctor global assessment as fair, poor, or very poor; CRP more than 20 mg/l or ESR more than 28 mm/hr Excluded women who were pregnant, breast feeding, or of childbearing potential not taking oral contraceptives Permitted concomitant stable dose of NSAIDs, oral prednisone (less than 10 mg/day), not more than 3 IA injections or 60 mg of triamcinolone. No IA steroid injection within the first six months
Interventions	Leflunomide 20 mg/day, SSZ 2 g/day
Outcomes	Tender joint counts, swollen joint counts, patient global assessment and doctor global assessment, pain intensity, duration of morning stiffness, Westergren ESR, CRP, RF, functional disability (HAQ-DI and mean HAQ score), number of patients met the ACR20, ACR50 and ACR 70 response criteria
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Karanikolas 2006

Methods	Randomized, open-label, active controlled, parallel group, 2-center trial Sample size at entry: total 106 Lef 36, CsA 35, Lef+CsA 35 Withdrawals: Lef 9, CsA 2, Lef+CsA 4 Trial duration: 12 months

Karanikolas 2006 *(Continued)*

Participants	Patients with RA refractory to at least one DMARD (MTX compulsorily)
Interventions	Leflunomide (Lef) 20 mg/day (with 100-mg loading dose for 3 days) Cyclosporin (CsA) 2.5-5 mg/kg/day Combination Lef and CsA dose as above, not mentioned whether loading dose of Lef were prescribed
Outcomes	Primary outcomes: ACR20, ACR50, ACR70 response rate at 12 months Secondary outcomes: Assessed at 12 months 1. DAS28 remission rate 2. Change in DAS28 index at 12 months Assessed at 6 and 12 months 1. Number of tender joints 2. Number of swollen joints 3. Patient global assessment of disease activity 4. Physician global assessment of disease activity 5. Pain score 6. Disability 7. Duration of morning stiffness 8. Hemoglobin 9. ESR 10. CRP Adverse events and withdrawal rates due to adverse events at 12 months
Notes	Quality score = 2 (R1, B0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear

Karanikolas 2006 *(Continued)*

Free of other bias?	Unclear risk	B-unclear

Kremer 2002

Methods	Randomized, double-blind, active controlled, parallel group, multinational trial Sample size at entry: total 263, Lef+MTX 130, MTX 133 Withdrawals: Lef+MTX 30, MTX 33 Trial duration: 24 weeks
Participants	Patients who were 18-75 years of age, met the ACR criteria, with active RA despite ≥ 6 months of MTX treatment. Active RA: at least 3 of 4: 1) 9 or more tender joints 2) 6 or more swollen joints 3) morning stiffness lasted at least 45 minutes 4) Westergren ESR at least 28 mm/hr. Stable dose of MTX for ≥ 8 weeks Stable dose of NSAID and/or prednisone (not more than 10 mg/day) for at least 30 days.
Interventions	Leflunomide: loading 100 mg once daily for 2 days followed by 10-20 mg/day if the problems with tolerability occurred, the dose was reduced to 10 mg alternate day. MTX: 10-15-20 mg/week Almost all patients received 1-2 mg folate daily.
Outcomes	Primary outcomes: ACR20 response rate at the end of study Secondary outcomes: 1. ACR50 response rate at week 24 2. ACR70 response rate at week 24 3. Changes from baseline to week 24 in each component of the ACR response criteria 4. Changes from baseline to week 24 in RF levels 5. Adverse events
Notes	Quality score = 5 (R2, B2, W1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed?	Low risk	A-yes

Kremer 2002 *(Continued)*

All outcomes		
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Kremer 2004

Methods	Open-label extension of study Kremer 2002 Sample size at entry: total 192 Lef/Lef+MTX 96, Plc/Lef+MTX 96 Withdrawals: Lef/Lef+MTX 10 Plc/Lef+MTX 14 Trial duration: 24 weeks
Participants	Patients who completed the Kremer 2002 study at 24 weeks
Interventions	Leflunomide: 10 mg/day at study initiation then adjusted between 10 mg qid and 20 mg/ day+stable MTX dose Placebo+MTX: placebo was switched to leflunomide 10 mg/day. Leflunomide dosage was adjusted between 10 mg qid and 20 mg/ day + stable dose of MTX No loading dose of Lef
Outcomes	Same as Kremer 2002 study
Notes	Quality score = 2 (R1, B0, W1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Unclear risk	B-unclear
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Lao 2001

Methods	Randomized, double-blind, active controlled, parallel group, trial Sample size at entry: total 80 leflunomide 40, MTX 40 Withdrawals: leflunomide: 4, MTX: 5 Trial duration: 6 months
Participants	Patients who were 18-65 years of age, met the ACR criteria with active RA Active RA: at least 4 of 5: 1) 5 or more tender joints 2) 3 or more swollen joints 3) morning stiffness lasted at least 1 hour 4) Westergren ESR at least 28 mm/hr. Exclusion criteria: 1. taking other DMARDs during the last 6 months 2. serious hepatic, renal, hematologic disorders 3. history of gastrointestinal ulcer 4. women who were pregnant, breastfeeding 5. history of allergy to drugs
Interventions	Leflunomide: 20 mg once daily (no loading dose) MTX: 15 mg/ week
Outcomes	1. pain level 2. duration of morning stiffness (min) 3. grip strength (Kpa) 4. tender joint count 5. tender joint score 6. swollen joint count 7. swollen joint score 8. HAQ 9. patient global assessment of disease activity 10. physician global assessment of disease activity 11. ESR (mm/h) 12. CRP (ug/ml) 15. RF
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed?	Unclear risk	B-unclear

Lao 2001 *(Continued)*

All outcomes		
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Lao 2002

Methods	Randomized, open-label, active controlled, parallel group, clinical trial Sample size at entry: 64, Lef+MTX 32, MTX 32 Withdrawals: not mentioned Trial duration: 24 weeks
Participants	Patients with RA Group I: female gender 23, male 9; mean (SD) age 45.88 (12.22) years; mean (SD) disease duration 61.25 (45.08) months Group II: female gender 25, male 7; mean (SD) age 44.31 (8.39) years; mean (SD) disease duration 40.22 (42.42) months
Interventions	NSAIDs were withdrawn one week before starting treatment Group I: Lef 20 mg/d + MTX 7.5 mg/week, four weeks later, Lef dose was reduced to 10 mg/d No data on the loading dose of Lef Group II: MTX 15 mg/week One NSAID was allowed as needed
Outcomes	Morning stiffness, grip strength, tender joint count, swollen joint count, rest pain, activity of daily living, patient's and physician's global assessment of disease activity, CBC, UA, LFT, Cr, ESR, CRP, RF
Notes	Quality score = 1 (R1, B0, W0)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	High risk	C-no

Lao 2002 *(Continued)*

Free of other bias?	Unclear risk	B-unclear

Larsen 2001

Methods	Randomized, open-label, active controlled, parallel group, multinational trial Sample size at entry: 358 leflunomide n = 133 at 6 mos n = 80 at 12 mos n = 60 at 24 mos SSZ n = 133 at 6 mos n = 76 at 12 mos n = 60 at 24 mos Placebo n = 92 at 6 mos Plc --> SSZ n = 41 at 12 mos n = 26 at 24 mos Withdrawals: leflunomide 28%, 11%, 18% at 6, 12, 24 mos SSZ 38%, 11%, 23% at 6, 12, 24 mos Trial duration: 6, 12, 24 months
Participants	Consenting patients aged = or > 18 years who fulfilled the ACR criteria with active RA and ARA FC I, II, III 1. tender joint count ≥6 2. swollen joint count ≥6 3. patient and physician global assessment fair, poor or very poor 4. CRP > 2.0 g/dl or ESR > 28 mm/hr Excluded women who were pregnant or breast feeding, or of childbearing potential without appropriate contraceptions
Interventions	Leflunomide loading 100 mg once daily for 3 days followed by 20 mg once daily SSZ 0.5 g-->1.0 g --> 1.5 g --> 2.0 g per day Patients receiving placebo in the first 24 weeks were switched to SSZ after 24 weeks until study completion.
Outcomes	Primary outcomes: radiographic analysis of both hands and feet in the intention-to-treat population. Larsen scores Erosion scores Secondary outcomes: ACR response rate, physician and patient global assessments, pain intensity, duration of morning stiffness, HAQ, ESR, CRP, RF and safety
Notes	Quality score = 2 (R1, B0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement

Larsen 2001 *(Continued)*

Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-yes
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Lau 2002

Methods	Randomized, double-blind, placebo-controlled, multicenter study Sample size at entry: 301, Lef 151, MTX 150 Withdrawals: not mentioned (no withdrawals due to alopecia) Trial duration: 16 weeks
Participants	Adult Asian patients with active RA (DAS28 of > 3.2)
Interventions	Leflunomide 20 mg/d (loading dose was not mentioned) MTX 7.5-10 mg/week
Outcomes	EULAR response criteria, tender joint count, swollen joint count, patient's global assessment of disease activity, physician global assessment of disease activity, duration of morning stiffness, general health assessment, pain, ESR, clinical and laboratory adverse reactions
Notes	Quality score = 2 (R1, B1, W0)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear

Lau 2002 *(Continued)*

Free of selective reporting?	High risk	C-no
Free of other bias?	Unclear risk	B-unclear

Mariette 2004

Methods	Open-label, non-randomized, active controlled, parallel group, multicenter, clinical trial Sample size at entry: Lef+ADA 115, ADA 242 Withdrawals: not mentioned Trial duration: 12 weeks
Participants	Patients with long-standing, moderate to severe RA, despite their concomitant DMARDs Mean age at study entry: 53 years, mean disease duration 11 years
Interventions	Adalimumab 40 mg sc every other week Leflunomide 20 mg/day
Outcomes	1. ACR20 response rate 2. ACR50 response rate 3. EULAR moderate response rate 4. EULAR good response rate 5. Mean change of DAS28 6. Mean change of tender joint count 7. Mean change of swollen joint count 8. Mean change of HAQ
Notes	Quality score =0 (R0, B0, W0)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	C-no
Allocation concealment?	High risk	C-no
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear

Mariette 2004 *(Continued)*

Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Mladenovic 1995

Methods	Randomized, placebo-controlled, phase II study Sample size at entry: placebo 102, leflunomide 5mg/day 95, leflunomide 10 mg/day 101, leflunomide 25 mg/day 104 Withdrawals: placebo 13, lef5 8, lef10 11, lef25 13 Trial duration: 24 weeks
Participants	Patients who met the ACR classification criteria for RA, active disease: 3 in 4 of 1) tender joints ≥8 2) swollen joints ≥8 3) morning stiffness ≥45 minutes 4) Westergren ESR ≥40 mm/hr With stable dose of NSAIDs ≥4 weeks and/or stable corticosteroid dose at ≤ 10 mg/day prednisone or equivalent for ≥8 weeks Stop gold, methotrexate, azathioprine ≥ 3 months Mean age: 51 years (20-76) Male/female: 68/334 Mean RA duration: 8.3 years (0.8-37.8) Mean number of failed DMARDs: 1.1 NSAIDs used: 95% Steroid used: 35%
Interventions	Leflunomide loading 50 mg once and then 5 mg/day Leflunomide loading 100 mg once and then 10 mg/day Leflunomide 100 mg loading once and then 25 mg/day Placebo
Outcomes	Primary outcomes: tender joint count, swollen joint count, tender joint score, swollen joint score, patient global assessment, physician global assessment Secondary outcomes: duration of morning stiffness, grip strength, HAQ, pain score (VAS), ESR, CRP, Paulus criteria >20%, ACR 20
Notes	Quality score =4 (R2, B1, W1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	A-adequate

Mladenovic 1995 *(Continued)*

Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Low risk	A-yes
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Poor 2004

Methods	Randomized, double-blind, active controlled, parallel group, multinational trial Sample size at entry: total 402, Lef10: 202, Lef20: 200 Withdrawals: Lef10: 50, Lef20: 36 Trial duration: 24 weeks
Participants	Patients who were 18-75 years of age, met the ACR criteria, with active RA Active RA: at least 3 of 4: 1) 6 or more tender joints 2) 6 or more swollen joints 3) physician and patient global assessment not better than 'fair' 4) Westergren ESR > 28 mm/hr or CRP > 2.0mg/dl Stable dose of NSAID and/or prednisone (not more than 10 mg/day) for at least 4 weeks.
Interventions	Leflunomide loading 100 mg once daily for 3 days followed by 10 or 20 mg once daily
Outcomes	Primary outcomes: tender joint count, swollen joint count, HAQ-DI Secondary outcomes: ACR20, ACR50, ACR70 response rates and adverse events
Notes	Quality score =4 (R2, B1, W1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear

Poor 2004 *(Continued)*

Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Reece 2002

Methods	Randomized, double-blind, active controlled, parallel group trial Sample size at entry: total 39 Leflunomide 18, MTX 21 Withdrawals: Lef 0 MTX 1 (died from acute MI) paired MRI scans were available in 34 patients (data lost in 4) Trial duration: 4 months
Participants	Patients aged ≥18 years, met the 1987 ACR revised criteria, with active RA were enrolled from 2 centers Active RA: ≥ 6 swollen or tender joints and moderate or worse patient and physician global assessment. At least 1 knee joint with active disease, defined by clinically detectable synovitis Stable dose of NSAID and/or prednisone (not more than 10 mg/day) for at least 4 weeks. No IA steroid injection was allowed during the trial period No previous treatment with MTX or leflunomide. Other DMARD therapy had to be stopped at least 28 days
Interventions	Leflunomide loading 100 mg/d for 3 days followed by 20 mg/d MTX initial dose of 7.5 mg/week and was increased to 15 mg/week over 12 weeks
Outcomes	Clinical assessment: 1. swollen and tender joint counts (28-joint assessment) 2. Duration of morning stiffness 3. Patient and physician global assessment of disease activity (VAS) 4. Patient pain (VAS) 5. ESR 6. CRP 7. RF level 8. modified Health Assessment Questionnaire (mHAQ) 9. ACR20 response rate Dynamic MRI scans (DEMRI): Measurement of inflamed synovium at knee joint 1. Initial rate of enhancement (IRE) 2. Maximal signal intensity enhancement (ME)
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-adequate

Reece 2002 *(Continued)*

Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Rozman 1994a

Methods	Randomized, single blind, active controlled, parallel group, clinical trial Sample size at entry: 49, Lef 100mg/week 24, Lef 200 mg/week 23 Withdrawals: 2 Trial duration: 6 months
Participants	Patients with active RA with 3 of 4 of the following: 1) ≥ 8 tender joints 2) ≥ 8 swollen joints 3) Duration of morning stiffness ≥ 45 minutes 4) ESR ≥ 40 mm/hr 47 patients were enrolled, with 15 men and 34 women Mean disease duration: 9.6 years Mean number of failed DMARDs: 1.1
Interventions	Leflunomide 100 mg weekly and 200 mg weekly A loading dose of 200 mg was given
Outcomes	Number of tender joints, number of swollen joints, patient assessment of disease activity, physician assessment of disease activity, Paulus20 response rate, adverse events, number of withdrawals due to adverse events and lack of efficacy
Notes	Quality score=3 (R1, B1, W1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate

Rozman 1994a *(Continued)*

Blinding? All outcomes	Low risk	A-Yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Scott 2001

Methods	Randomized, double-blind, active controlled, parallel group, multicenter study Sample size at entry (6-12 months): total 197, leflunomide 80, placebo-switch-to-SSZ 41, sulphasalazine 76 Withdrawals (6-12 months): lef 9, pl-SSZ 12, SSZ 8 Sample size at entry (12-24 months): total 146, leflunomide 60, pl-SSZ 26, sulphasalazine 60 Withdrawals (12-24 months): lef 11, pl-SSZ 5, SSZ 14 Trial duration: 18 months (month 6 to 24 extension of Smolen study)
Participants	Patients aged at least 18 years with active RA based on ACR criteria and ACR functional class I, II, III. Tender joint count at least 6; swollen joint count at least 6; patient and doctor global assessment as fair, poor, or very poor; CRP more than 20 mg/l or ESR more than 28 mm/hr Excluded women who were pregnant, breast feeding, or of childbearing potential not taking oral contraceptives Permitted concomitant stable dose of NSAIDs, oral prednisone (less than 10 mg/day), not more than 3 IA injections or 60 mg of triamcinolone. No IA steroid injection within the first six months
Interventions	Leflunomide 20 mg/day, SSZ 2 g/day
Outcomes	Tender joint counts, swollen joint counts, patient global assessment and doctor global assessment, pain intensity, duration of morning stiffness, Westergren ESR, CRP, RF, functional disability (HAQ-DI and mean HAQ score), number of patients met the ACR20, ACR50 and ACR 70 response criteria
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes

Scott 2001 *(Continued)*

Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Sharp 2000

Methods	Combined data from the studies Smolen 1999, Strand 1999 (a), and FDA 1997 (or MN302)
Participants	All patients from the studies Smolen 1999, Strand 1999 (a), and FDA 1997
Interventions	In all 3 studies, a 3-day loading dose of leflunomide (100 mg/day) was followed by 20-mg daily doses. Smolen 1999: sulphasalazine was started at 500 mg/day and increased to 2000 mg/day in weekly increment of 500 mg Strand 1999 (a): MTX was started at 7.5 mg/week and increased to 15 mg/week over week 6-9 in 60% of the patients FDA1997: MTX was initiated at 7.5 mg/week, increased to 10 mg/week at week 4 and to 15 mg/week at week 12, in 53% of the patients
Outcomes	Sharp scores obtained from the radiographs of hands and feet at baseline and follow-up (6 months, 12 months, or at early exit) - total Sharp score (summation of erosion and joint space narrowing subscores) - erosion subscore (34 hand joints and 12 foot joints, on a scale of 0-5) - joint space narrowing subscore (36 hand joints and 12 foot joints, on a scale of 0-4)
Notes	Quality score = 2 (R1, B1, W0)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	B-unclear
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Shuai 2002

Methods	Randomized, double-blind, active controlled, parallel group, trial Sample size at entry: total 80 leflunomide 40, MTX 40 Withdrawals: leflunomide: 0 MTX: 2 Trial duration: 6 months
Participants	Patients who were 18-65 years of age, met the ACR criteria with active RA Active RA: at least 4 of 5: 1) 5 or more tender joints 2) 3 or more swollen joints 3) morning stiffness lasted at least 1 hour 4) Westergren ESR at least 28 mm/hr. Exclusion criteria 1. taking other DMARDs during the last 6 months 2. serious hepatic, renal, hematologic disorders 3. history of gastrointestinal ulcer 4. women who were pregnant, breastfeeding 5. history of allergy to drugs
Interventions	Leflunomide: 20 mg once daily (no loading dose) MTX: 15 mg/ week
Outcomes	1. pain level 2. duration of morning stiffness (min) 3. grip strength (Kpa) 4. tender joint count 5. tender joint score 6. swollen joint count 7. swollen joint score 8. HAQ 9. patient global assessment of disease activity 10. physician global assessment of disease activity 11. ESR (mm/h) 12. CRP (ug/ml) 15. RF
Notes	Quality score = 3 (R1, B1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed?	Unclear risk	B-unclear

Shuai 2002 *(Continued)*

All outcomes

Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Smolen 1999

Methods	Double-blind, randomized controlled, multicenter study Sample size at entry: leflunomide 133, placebo 92, sulphasalazine 132 Withdrawals: lef 37, placebo 41, SSZ 50 Trial duration: 24 weeks
Participants	Met the ACR classification criteria for RA, ACR functional class I, II, III, Active disease: 1) tender joints ≥6 2) swollen joints ≥6 3) global assessment of fair, poor, or very poor 4) CRP ≥20 or ESR ≥28 mm/hr Age =>18 years, if women must have adequate contraception, and not pregnant Stable doses of NSAIDs and/or corticosteroid (≤10 mg/day of prednisolone) for ≥30 days Discontinue SSZ ≥1 year or other DMARDs => 28 days Mean (SD) age: lef 58.3 (10.6), placebo 58.8 (12.2), SSZ 58.9 (11.4) Male/female: lef 32/101, placebo 23/69, SSZ 41/92 Mean (SD) RA duration: lef 7.6 (8.6), placebo 5.7 (6.5), SSZ 7.4 (10.0) % never used DMARDs: lef 40, placebo 53, SSZ 51 % NSAIDs used: lef 85, placebo 83, SSZ 82 % corticosteroid used: lef 29, placebo 25, SSZ 28
Interventions	Leflunomide 100 mg loading for 3 days, follow by 20 mg/day SSZ 0.5, 1.0, 1.5 g OD or bid on week 1,2,3 and then 2 g/day Placebo
Outcomes	Primary outcomes: tender joint count, swollen joint count, patient global assessment, physician global assessment, ACR20, ACR50, Paulus criteria ≥20% Other outcomes: tender joint score, swollen joint score, duration of morning stiffness, pain (VAS), ESR, CRP, RF, HAQ, radiographic changes using Larsen method, and safety
Notes	Quality score = 5 (R2, B2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement

Smolen 1999 *(Continued)*

Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Low risk	A-yes
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Strand 1999a

Methods	Randomized, double-blind, placebo and active controlled, multicentre study Sample size at entry: leflunomide 182, placebo 118, methotrexate 182 Withdrawals: lef 86, placebo 81, MTX 77 Trial duration: 12 months
Participants	Met the ACR classification criteria for RA ≥6 months, Active disease: 3 in 4 of 1) tender joints ≥9 2) swollen joints ≥6 3) morning stiffness ≥45 minutes 4) ESR ≥28 mm/hr Age ≥18 years, must have adequate contraception 6 months before and after the trial Stable doses of NSAIDs and/or corticosteroid (≤10 mg/day of prednisolone) for ≥30 days No previous MTX use or discontinue other DMARDs ≥ 30 days No history or clinical of drug or alcohol abuse or take > 1 alcoholic drink/day. Laboratory: Hb ≥ 10 or Hct ≥ 30, WBC ≥ 3,000, platelet ≥ 100,000, Cr < 2UNL, albumin ≥ 3.5 g/dl, normal LFT (AST, ALT, AP, bilirubin ≤1.2 UNL for ≥ 3 times) Mean (SD) age: lef 54.1 (12.0), placebo 54.6 (10.7), MTX 53.5 (11.8) % female: lef 72.5, placebo 70.3, MTX 75.3 Mean (SD) RA duration: lef 7.0 (8.6), placebo 6.9 (8.0), MTX 6.5 (8.1) % no previous DMARDs used: lef 44.5, placebo 39.8, MTX 44.0 % with NSAIDs use: lef 75.2, placebo 65.2, MTX 69.7 % with corticosteroid use: lef 53.8, placebo 55.1, MTX 52.7 Mean (SD) number of failed DMARDs: lef 0.8 (1.0), placebo 0.9 (0.9), MTX 0.9 (1.0)

Strand 1999a *(Continued)*

Interventions	Leflunomide 100 mg loading for 3 days and then 20 mg/day MTX increased to 15 mg/week in week 7-9 Placebo
Outcomes	Primary outcomes: ACR20 and complete 52 weeks of initial therapy (ACR success), ACR50, ACR70 at 12 months Secondary outcomes: mean change of tender joint count, swollen joint count, patient global, physician global, pain (VAS), ESR, hand and feet X-Ray films, physical function and quality of life (HAQ, PET, SF-36), duration of morning stiffness, RF titers Adverse events will also be reported.
Notes	Quality score = 5 (R2, B2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Low risk	A-yes
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Strand 1999b

Methods	Same as Strand 1999 (a)
Participants	Same as Strand 1999 (a)
Interventions	Same as Strand 1999 (a)
Outcomes	Primary outcomes: tender joint count, swollen joint count, patient and physician global assessments of disease activity, pain intensity (VAS), MHAQ scores, Westergren ESR, CRP Physical function and HRQoL measures: HAQ, PET top-5, SF-36, and questionnaire related to work productivity
Notes	Quality = 4 (R1, B2, W1)

Risk of bias

Strand 1999b *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A-adequate
Allocation concealment?	Low risk	A-adequate
Blinding? All outcomes	Low risk	A-yes
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

Wislowska 2007

Methods	Open-label, controlled clinical trial Sample size at entry: MTX 30, Lef 30, anti-TNF+MTX 18 Withdrawals: 1 Trial duration: 24 weeks
Participants	Met the ACR classification criteria for RA, Steinbrocker stage II, III, IV Stable doses of NSAIDs and/or corticosteroid (<=10 mg/day of prednisolone) Exclude patients with concomitant other connective tissue diseases or contraindications to treatment interventions Mean (SD) age: MTX 61.0 (11.8), Lef 56.6 (9.9), anti-TNF 52.9 (13.2) years Number (%) female: MTX 25 (83), Lef 27 (90%), anti-TNF 11 (61) Mean (SD) RA duration: MTX 14.6 (7.5), Lef 12.6 (10.1), anti-TNF 13.0 (9.0) years
Interventions	Group I: MTX 15 mg/week Group II: Lef 20 mg/d Group III: MTX 15 mg/week + Anti-TNF (infliximab 3 mg/kg week 0, 2, 6 and then every 8 weeks in 12 patients; etanercept 25 mg twice weekly in 6 patients)
Outcomes	Tender joint count, swollen joint count, duration of morning stiffness, HAQ, pain intensity (VAS), patient and physician global assessment of disease activity (VAS), ESR, CRP, DAS28, ACR20/ACR50/ACR70 response rate, X-Ray of hands and feet
Notes	Quality = 1 (R0, B0, W1)

Wislowska 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	C-no
Allocation concealment?	High risk	C-no
Blinding? All outcomes	High risk	C-no
Incomplete outcome data addressed? All outcomes	Unclear risk	B-unclear
Free of selective reporting?	Unclear risk	B-unclear
Free of other bias?	Unclear risk	B-unclear

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

Study	Reason for exclusion
Balabanova 2004	Single-arm study, no comparator
Balabanova 2006	Single-arm study without control group
Dougados 2003	Open-label, single-arm study, no comparator
Godinho 2004	Retrospective, single-arm study without control group
Grijalva 2007	Outcomes do not meet the inclusion criteria of the review
Hansen 2004	Retrospective, single-arm study without control group
Jevtic 1997	Open-label study, no comparator
Ju 2007	Retrospective study without control group
Kalden 2003	Single-arm study without control group
Kraan 2004	Subset of Emery 1999 study and outcomes are not clinical-based ones
Kuzmanova 2003	Single-arm study without control group
Litinsky 2006	Single-arm study without control group
Mroczkowski 1999	Single-arm study
Popovic 1998	Contained pool data from open and/or double-blind studies with different duration of studies and dosages of treatment. (28 patients were treated with leflunomide 10-25 mg per day for 30 weeks. 81 patients were treated with MTX 7.5-15 mg per week for 12-84 weeks)

Study	Reason for exclusion
Richards 2007	Outcomes were neurophysiologic findings from nerve conduction velocity
Rozman 1994b	Open-label study comparing the adverse events from different doses of leflunomide (5-25 mg/day)
Sarunhan-Direskeneli 2007	Single-arm study, no control group
Strand 2005	Pooled data on year 2 extension studies from 3 RCTs comparing leflunomide with sulfasalazine or methotrexate. These data were already presented in included studies
Tchetverikov 2008	Subset of Emery 1999 trial with non-clinical based outcomes
van der Heijde 2004	Single-arm study, no control group
van der Kooij 2007	Subset of BeSt study without direct comparison between leflunomide and other options
van Riel 2003	Comments on Kremer 2002 study (Evidence-based Rheumatology)
van Roon 2005	Single-arm study without control group
Weinblatt 1999b	Single-arm study, no comparator

Characteristics of studies awaiting assessment *[ordered by study ID]*

Raczkiewicz-Papierska2007

Methods	Open-label, controlled clinical trial Sample size at entry: MTX+Lef 49, Lef 32 Trial duration: 5 months
Participants	Met the ACR criteria for the classification of RA Mean (SD) age 57.6 (11.7) years, mean (SD) disease duration 7.7 (7.1) years Active disease: Disease activity score (DAS)28 > 3.2 With contraindication to MTX or inadequate response to MTX for ≥ 3 months 66 (77.7%) were prescribed stable dose of prednisolone (daily dose 5-15 mg)
Interventions	MTX (mean (SD) weekly dose 17 (4.2) mg) + Lef 20 mg/d (without loading dose) Lef 100 mg/d for 3 days then 20 mg/d
Outcomes	Tender joint count, swollen joint count, pain score (VAS), global assessments of disease activity (VAS), ESR, CRP, blood count, aminotransferase level, adverse events The assessment was performed monthly until 5 months
Notes	Await for data from full article

Shevchuk 2003

Methods	Open-label, controlled clinical trial Sample size at entry: 189 Withdrawals: Trial duration: 6 months
Participants	Patients with RA
Interventions	1) Leflunomide 20 mg/day (with loading dose?) 2) MTX 7.5-10 mg/week 3) Combined MTX and leflunomide 4) Combined MTX and detralex
Outcomes	Efficacy: clinical and laboratory outcomes Functional ability: HAQ Adverse events
Notes	Await data from full article and authors

Zhang 2004

Methods	Open-label, randomized controlled trial Sample size at entry: MTX+Lef 20, MTX+HCQ 20 Withdrawals: MTX+Lef 0, MTX+HCQ 1 Trial duration: 12 months
Participants	Met the ACR criteria for the classification of RA Age 19-65 years, RA disease duration < 2 years Active disease: at least 3 out of 4 activity indices 1) tender joint count > 5 2) swollen joint count > 3 3) ESR > 30 mm/hr 4) morning stiffness duration > 30 minutes
Interventions	MTX 10-15 mg/week + Lef 20 mg/d (with loading dose?) MTX 10-15 mg/week + HCQ 400 mg/d NSAIDs or low dose prednisolone (<10 mg/d) was administered in the first 3 months
Outcomes	Tender joint count, tender joint score, swollen joint count, swollen joint score, patient global assessment of disease activity, physician global assessment of disease activity, pain score, HAQ, duration of morning stiffness, grip strength, ESR, CRP, ACR20, ACR50

Zhang 2004 *(Continued)*

	Assessment at baseline, 3, 6, and 12 months
Notes	Await for data from full article

Zhao 2006

Methods	Open-label, randomized controlled trial Sample size at entry: leflunomide 40, leflunomide + total glycosides of paeony (TGP) 40 Withdrawals: await for data from full article Trial duration: 12 weeks
Participants	Await for data from full article
Interventions	Leflunomide Leflunomide +TGP
Outcomes	Total effectiveness
Notes	Await data from full article

DATA AND ANALYSES

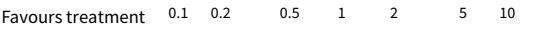
Comparison 1. Treatment responder - ACR20

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	3	724	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.42, 0.62]
2 leflunomide vs. placebo, at 12 months	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.36, 0.70]
3 leflunomide vs. methotrexate, at 3 months	1	566	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.10]
4 leflunomide vs. methotrexate, at 4 months	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.50, 1.81]
5 leflunomide vs. methotrexate, at 6months (24 weeks)	3	988	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.87, 1.06]
6 leflunomide vs. methotrexate, at 12 months	2	1348	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.75, 1.55]
7 leflunomide vs. methotrexate, at 2 years	2	980	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.81, 1.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 leflunomide vs. sulfasalazine, at 6 months	1	262	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.28]
9 leflunomide vs. sulfasalazine, at 12 months	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.29]
10 leflunomide vs. sulfasalazine, at 24 months	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.93]
11 leflunomide+MTX vs MTX, at 24 weeks	1	263	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.29, 0.63]
12 leflunomide10mg vs leflunomide 20 mg, at 24 weeks	1	399	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.06]
13 leflunomide+SSZ vs. placebo+SSZ, at 24 weeks	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.49, 1.88]
14 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.33]
15 leflunomide vs. anti-TNF+MTX, at 24 weeks	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.97, 1.34]
16 Lef vs. CsA, at 12 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.87, 1.56]
17 Lef vs. Lef+CsA, at 12 months	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.85, 1.55]
18 Lef+ADA vs. ADA, at 12 weeks	1	357	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 0.99]
19 Weekly Lef vs. daily Lef, at 6 months	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.63, 1.23]
20 Weekly Lef vs. daily Lef, at 12 months	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.76, 1.31]

Analysis 1.1. Comparison 1 Treatment responder - ACR20, Outcome 1 leflunomide vs. placebo, at 6 months.

Study or subgroup	placebo n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mladenovic 1995	31/102	60/101		30.42%	0.51[0.37,0.72]
Smolen 1999	26/91	71/130		29.5%	0.52[0.36,0.75]
Strand 1999a	32/118	101/182		40.08%	0.49[0.35,0.68]
Total (95% CI)	**311**	**413**		**100%**	**0.51[0.42,0.62]**
Total events: 89 (placebo), 232 (leflunomide)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=2(P=0.96); I^2=0%					
Test for overall effect: Z=6.82(P<0.0001)					

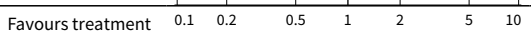


Analysis 1.2. Comparison 1 Treatment responder - ACR20, Outcome 2 leflunomide vs. placebo, at 12 months.

Study or subgroup	placebo n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Strand 1999a	31/118	95/182		100%	0.5[0.36,0.7]
Total (95% CI)	**118**	**182**		**100%**	**0.5[0.36,0.7]**
Total events: 31 (placebo), 95 (leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.04(P<0.0001)					

Analysis 1.3. Comparison 1 Treatment responder - ACR20, Outcome 3 leflunomide vs. methotrexate, at 3 months.

Study or subgroup	MTX n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bao 2003	146/243	202/323		100%	0.96[0.84,1.1]
Total (95% CI)	**243**	**323**		**100%**	**0.96[0.84,1.1]**
Total events: 146 (MTX), 202 (leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.55)					



Analysis 1.4. Comparison 1 Treatment responder - ACR20, Outcome 4 leflunomide vs. methotrexate, at 4 months.

Study or subgroup	MTX n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Reece 2002	10/21	9/18		100%	0.95[0.5,1.81]
Total (95% CI)	**21**	**18**		**100%**	**0.95[0.5,1.81]**
Total events: 10 (MTX), 9 (leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.15(P=0.88)					

Analysis 1.5. Comparison 1 Treatment responder - ACR20, Outcome 5 leflunomide vs. methotrexate, at 6months (24 weeks).

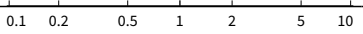
Study or subgroup	MTX n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bao 2003	149/243	207/323		58.34%	0.96[0.84,1.09]
Strand 1999a	92/180	101/182		32.97%	0.92[0.76,1.12]
Wislowska 2007	30/30	26/30		8.7%	1.15[0.99,1.34]

Study or subgroup	MTX n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**453**	**535**		**100%**	**0.96[0.87,1.06]**
Total events: 271 (MTX), 334 (leflunomide)					
Heterogeneity: Tau^2=0; Chi^2=5.56, df=2(P=0.06); I^2=64.04%					
Test for overall effect: Z=0.77(P=0.44)					

Favours treatment — Favours control

Analysis 1.6. Comparison 1 Treatment responder - ACR20, Outcome 6 leflunomide vs. methotrexate, at 12 months.

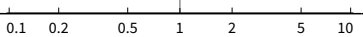
Study or subgroup	MTX n/N	leflunomide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Emery 1999	317/489	250/495		52.99%	1.28[1.15,1.43]
Strand 1999a	84/182	95/182		47.01%	0.88[0.72,1.09]
Total (95% CI)	**671**	**677**		**100%**	**1.08[0.75,1.55]**
Total events: 401 (MTX), 345 (leflunomide)					
Heterogeneity: Tau^2=0.06; Chi^2=9.61, df=1(P=0); I^2=89.59%					
Test for overall effect: Z=0.4(P=0.69)					



Favours treatment — Favours control

Analysis 1.7. Comparison 1 Treatment responder - ACR20, Outcome 7 leflunomide vs. methotrexate, at 2 years.

Study or subgroup	MTX n/N	leflunomide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2001	91/190	100/190		44.89%	0.91[0.74,1.11]
Emery 1999	241/314	185/286		55.11%	1.19[1.07,1.32]
Total (95% CI)	**504**	**476**		**100%**	**1.05[0.81,1.37]**
Total events: 332 (MTX), 285 (leflunomide)					
Heterogeneity: Tau^2=0.03; Chi^2=5.57, df=1(P=0.02); I^2=82.04%					
Test for overall effect: Z=0.38(P=0.7)					



Favours leflunomide — Favours MTX

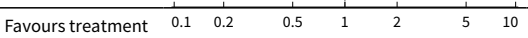
Analysis 1.8. Comparison 1 Treatment responder - ACR20, Outcome 8 leflunomide vs. sulfasalazine, at 6 months.

Study or subgroup	SSZ n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Smolen 1999	74/132	71/130		100%	1.03[0.83,1.28]
Total (95% CI)	**132**	**130**		**100%**	**1.03[0.83,1.28]**
Total events: 74 (SSZ), 71 (leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					

Favours treatment — Favours control

Analysis 1.9. Comparison 1 Treatment responder - ACR20, Outcome 9 leflunomide vs. sulfasalazine, at 12 months.

Study or subgroup	SSZ n/N	Leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	51/74	52/78		100%	1.03[0.83,1.29]
Total (95% CI)	**74**	**78**		**100%**	**1.03[0.83,1.29]**
Total events: 51 (SSZ), 52 (Leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.3(P=0.77)					



Analysis 1.10. Comparison 1 Treatment responder - ACR20, Outcome 10 leflunomide vs. sulfasalazine, at 24 months.

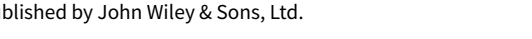
Study or subgroup	SSZ n/N	Leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	34/57	49/60		100%	0.73[0.57,0.93]
Total (95% CI)	**57**	**60**		**100%**	**0.73[0.57,0.93]**
Total events: 34 (SSZ), 49 (Leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.51(P=0.01)					

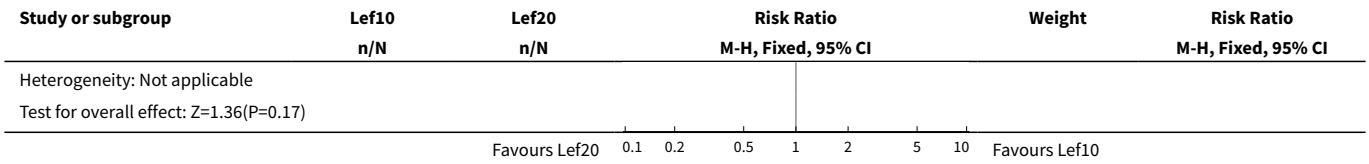
Analysis 1.11. Comparison 1 Treatment responder - ACR20, Outcome 11 leflunomide+MTX vs MTX, at 24 weeks.

Study or subgroup	MTX n/N	Lef+MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kremer 2002	26/133	60/130		100%	0.42[0.29,0.63]
Total (95% CI)	**133**	**130**		**100%**	**0.42[0.29,0.63]**
Total events: 26 (MTX), 60 (Lef+MTX)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.3(P<0.0001)					

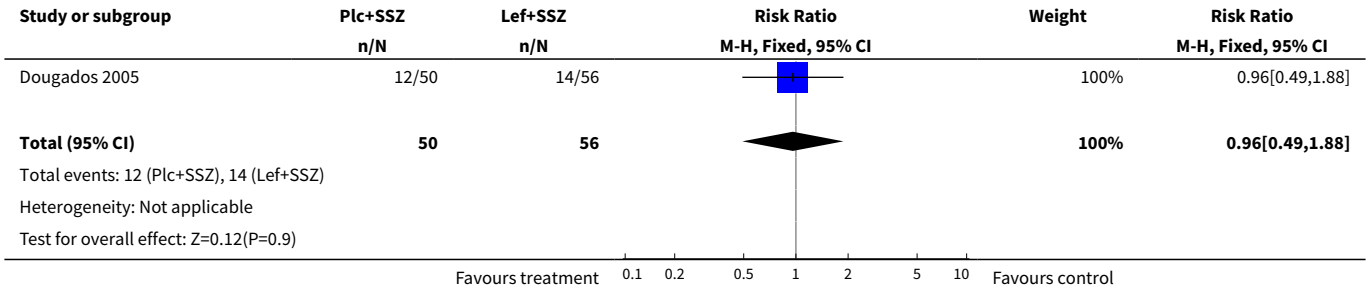
Analysis 1.12. Comparison 1 Treatment responder - ACR20, Outcome 12 leflunomide10mg vs leflunomide 20 mg, at 24 weeks.

Study or subgroup	Lef10 n/N	Lef20 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Poor 2004	100/201	112/198		100%	0.88[0.73,1.06]
Total (95% CI)	**201**	**198**		**100%**	**0.88[0.73,1.06]**
Total events: 100 (Lef10), 112 (Lef20)					

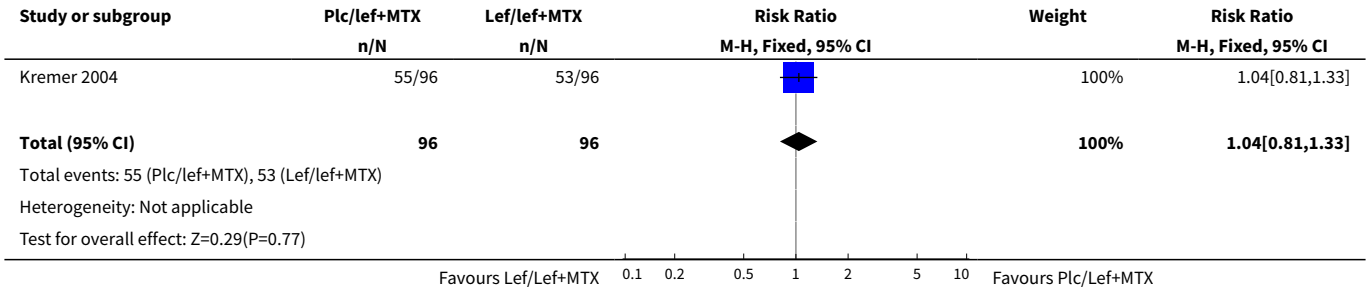




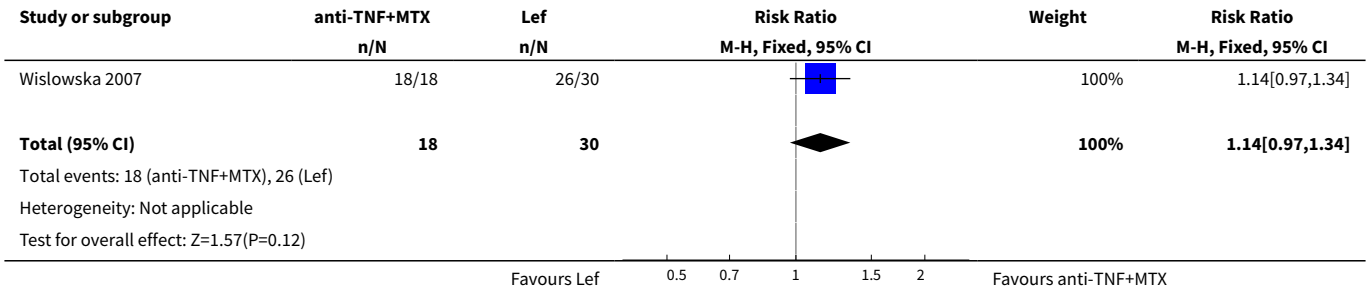
Analysis 1.13. Comparison 1 Treatment responder - ACR20, Outcome 13 leflunomide+SSZ vs. placebo+SSZ, at 24 weeks.



Analysis 1.14. Comparison 1 Treatment responder - ACR20, Outcome 14 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 1.15. Comparison 1 Treatment responder - ACR20, Outcome 15 leflunomide vs. anti-TNF+MTX, at 24 weeks.

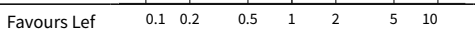


Analysis 1.16. Comparison 1 Treatment responder - ACR20, Outcome 16 Lef vs. CsA, at 12 months.

Study or subgroup	CsA n/N	Lef n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Karanikolas 2006	27/33	19/27		100%	1.16[0.87,1.56]
Total (95% CI)	**33**	**27**		**100%**	**1.16[0.87,1.56]**
Total events: 27 (CsA), 19 (Lef)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					

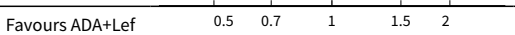
Analysis 1.17. Comparison 1 Treatment responder - ACR20, Outcome 17 Lef vs. Lef+CsA, at 12 months.

Study or subgroup	Lef+CsA n/N	Lef n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Karanikolas 2006	25/31	19/27		100%	1.15[0.85,1.55]
Total (95% CI)	**31**	**27**		**100%**	**1.15[0.85,1.55]**
Total events: 25 (Lef+CsA), 19 (Lef)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.89(P=0.37)					



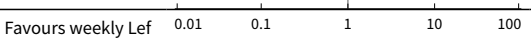
Analysis 1.18. Comparison 1 Treatment responder - ACR20, Outcome 18 Lef+ADA vs. ADA, at 12 weeks.

Study or subgroup	ADA n/N	Lef+ADA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mariette 2004	129/242	74/115		100%	0.83[0.69,0.99]
Total (95% CI)	**242**	**115**		**100%**	**0.83[0.69,0.99]**
Total events: 129 (ADA), 74 (Lef+ADA)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.05(P=0.04)					

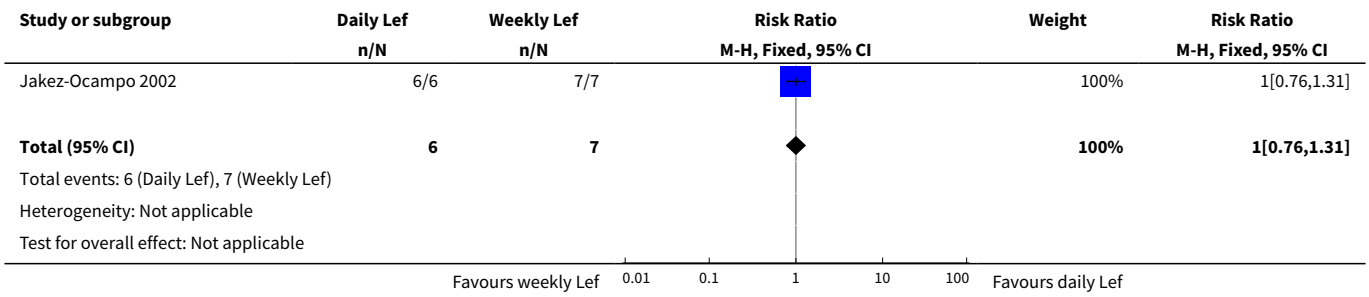


Analysis 1.19. Comparison 1 Treatment responder - ACR20, Outcome 19 Weekly Lef vs. daily Lef, at 6 months.

Study or subgroup	Daily Lef n/N	Weekly Lef n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Jakez-Ocampo 2002	7/8	8/8		100%	0.88[0.63,1.23]
Total (95% CI)	**8**	**8**		**100%**	**0.88[0.63,1.23]**
Total events: 7 (Daily Lef), 8 (Weekly Lef)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.74(P=0.46)					



Analysis 1.20. Comparison 1 Treatment responder - ACR20, Outcome 20 Weekly Lef vs. daily Lef, at 12 months.

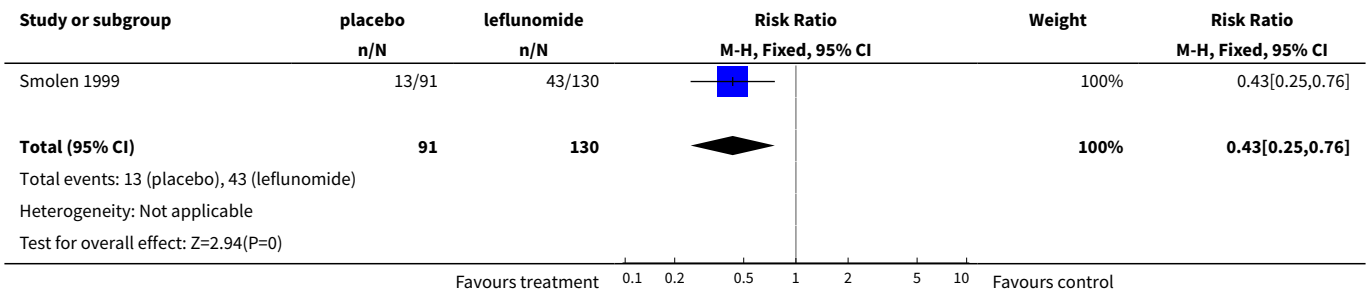


Comparison 2. Treatment responder - ACR50

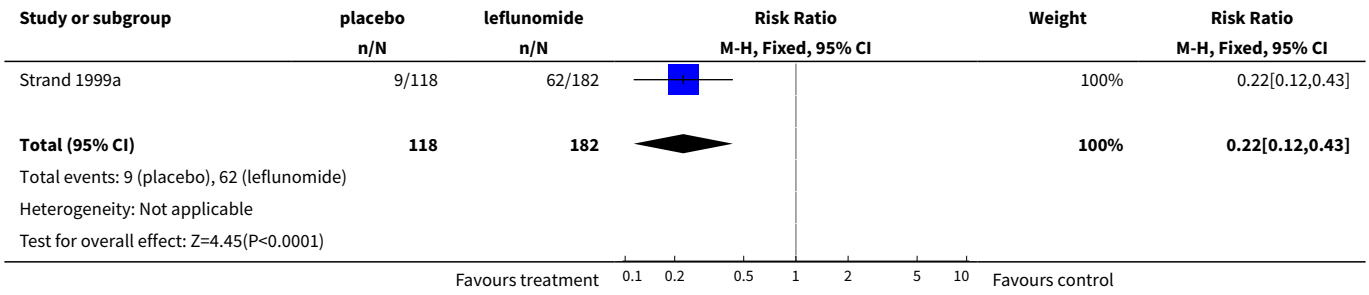
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.25, 0.76]
2 leflunomide vs. placebo, at 12 months	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.12, 0.43]
3 leflunomide vs. methotrexate, at 12 months	2	935	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.52, 1.44]
4 leflunomide vs. methotrexate, at 2 years	1	380	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.60, 1.10]
5 leflunomide vs. sulfasalazine, at 6 months	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.31]
6 leflunomide vs. sulfasalazine, at 12 months	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.63, 1.36]
7 leflunomide vs. sulfasalazine, at 24 months	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.28, 0.80]
8 leflunomide+MTX vs MTX, at 24 weeks	1	263	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.11, 0.48]
9 leflunomide10mg vs leflunomide 20 mg, at 24 weeks	1	399	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.55, 1.14]
10 leflunomide+SSZ vs. placebo+SSZ, at 24 weeks	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.79]
11 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.52, 1.21]
12 leflunomide vs. methotrexate, at 24 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.53, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 leflunomide vs. anti-TNF+MTX, at 24 weeks	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.97, 1.99]
14 Lef vs. CsA, at 12 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.43, 1.33]
15 Lef vs. Lef+CsA, at 12 months	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.04, 2.33]
16 Lef+ADA vs. ADA, at 12 weeks	1	357	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.58, 1.20]
17 Weekly Lef vs. daily Lef, at 6 months	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.27, 1.20]
18 Weekly Lef vs. daily Lef, at 12 months	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.77, 1.69]

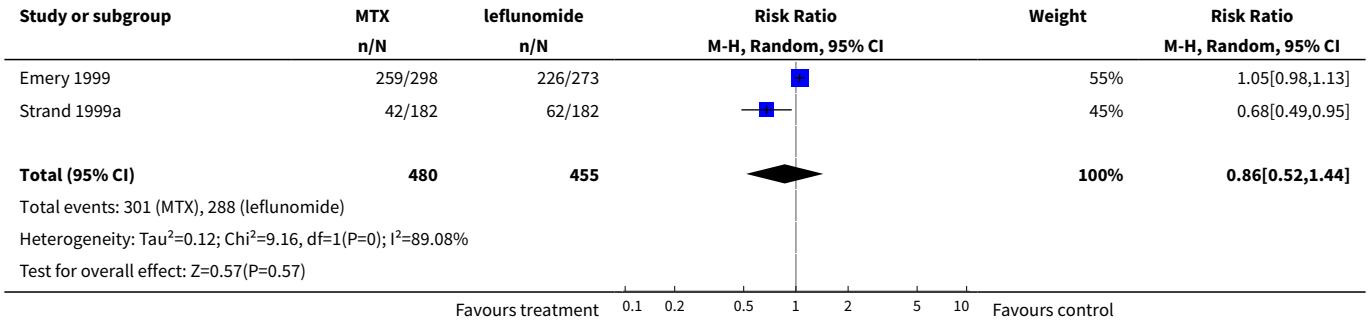
Analysis 2.1. Comparison 2 Treatment responder - ACR50, Outcome 1 leflunomide vs. placebo, at 6 months.



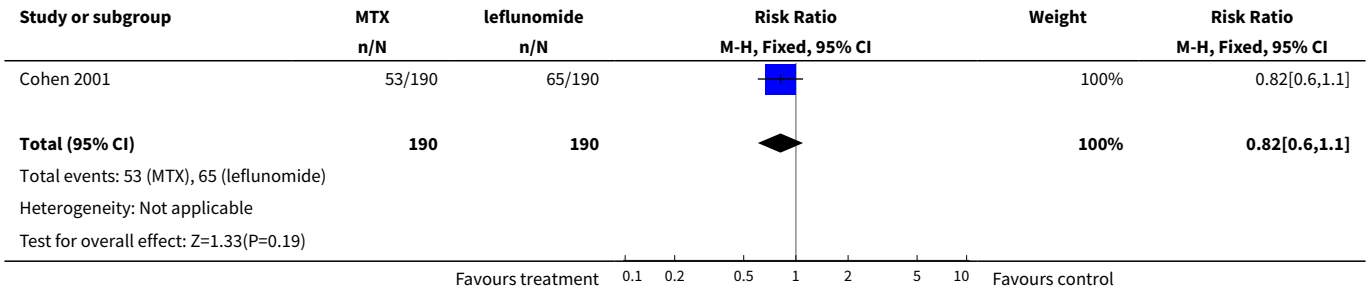
Analysis 2.2. Comparison 2 Treatment responder - ACR50, Outcome 2 leflunomide vs. placebo, at 12 months.



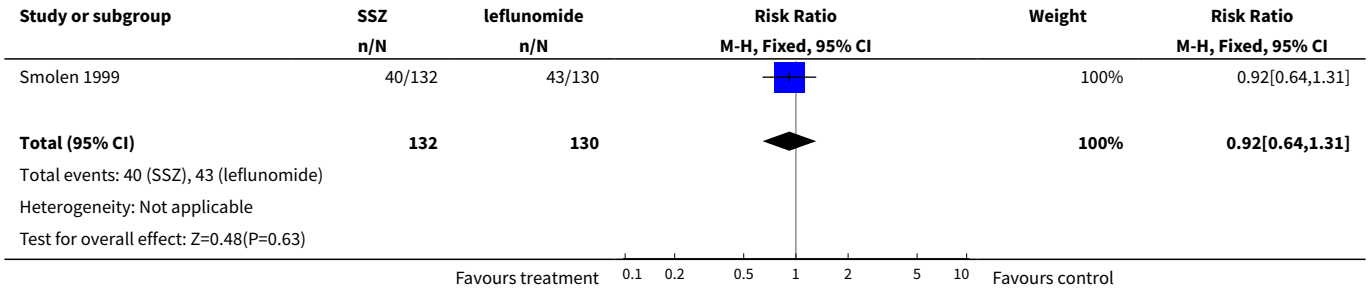
Analysis 2.3. Comparison 2 Treatment responder - ACR50, Outcome 3 leflunomide vs. methotrexate, at 12 months.



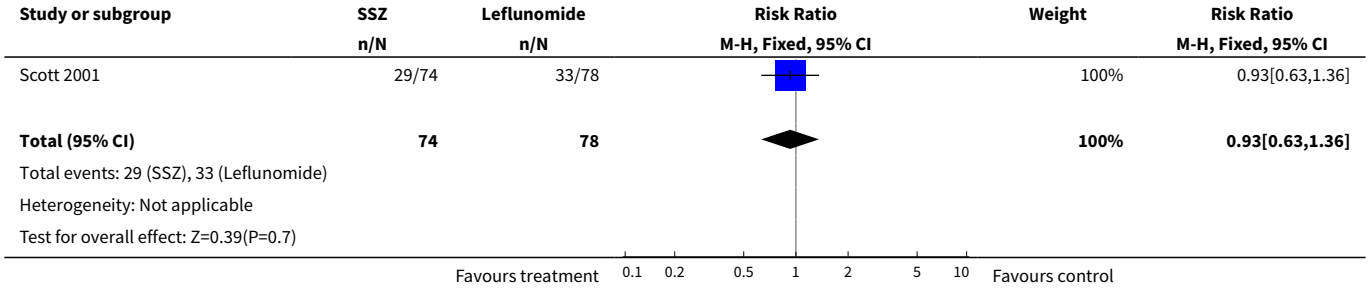
Analysis 2.4. Comparison 2 Treatment responder - ACR50, Outcome 4 leflunomide vs. methotrexate, at 2 years.



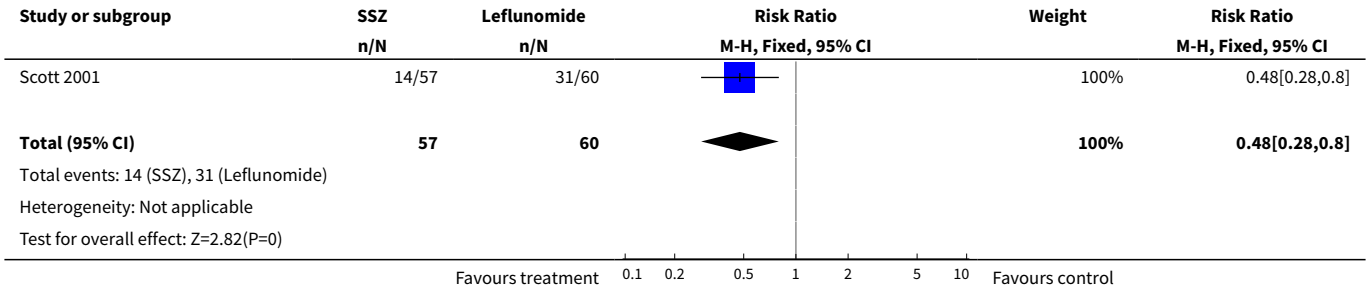
Analysis 2.5. Comparison 2 Treatment responder - ACR50, Outcome 5 leflunomide vs. sulfasalazine, at 6 months.



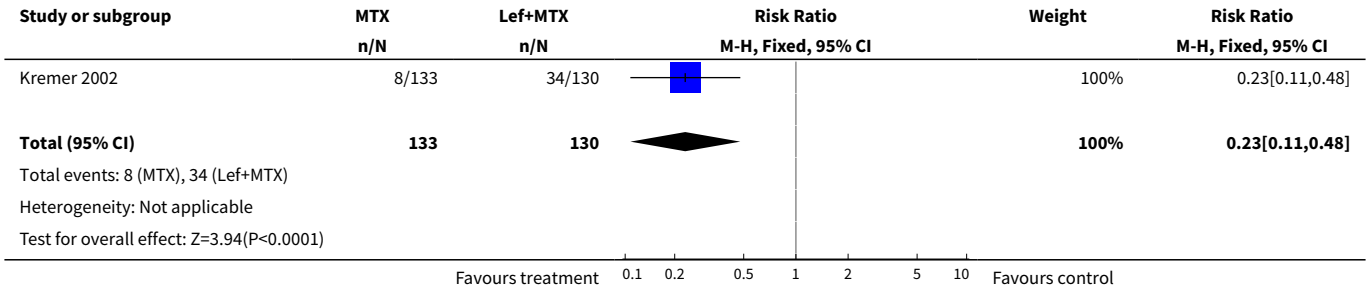
Analysis 2.6. Comparison 2 Treatment responder - ACR50, Outcome 6 leflunomide vs. sulfasalazine, at 12 months.



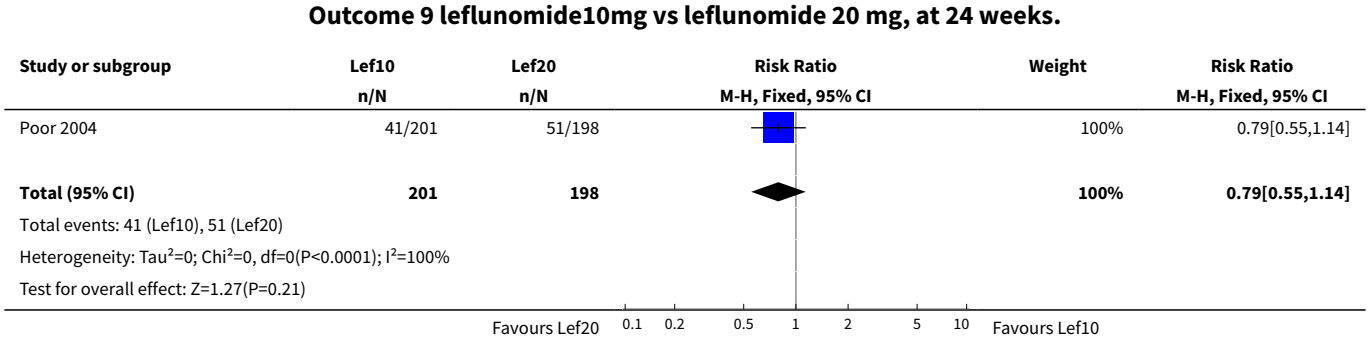
Analysis 2.7. Comparison 2 Treatment responder - ACR50, Outcome 7 leflunomide vs. sulfasalazine, at 24 months.



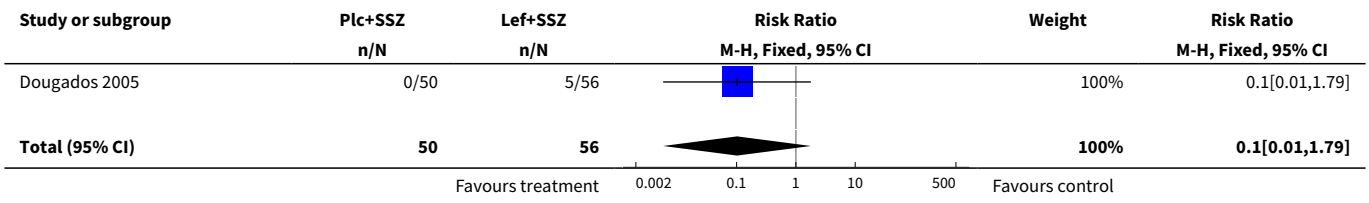
Analysis 2.8. Comparison 2 Treatment responder - ACR50, Outcome 8 leflunomide+MTX vs MTX, at 24 weeks.

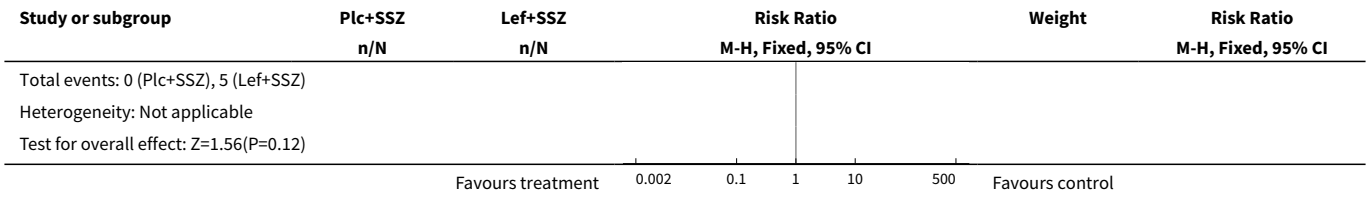


Analysis 2.9. Comparison 2 Treatment responder - ACR50, Outcome 9 leflunomide10mg vs leflunomide 20 mg, at 24 weeks.

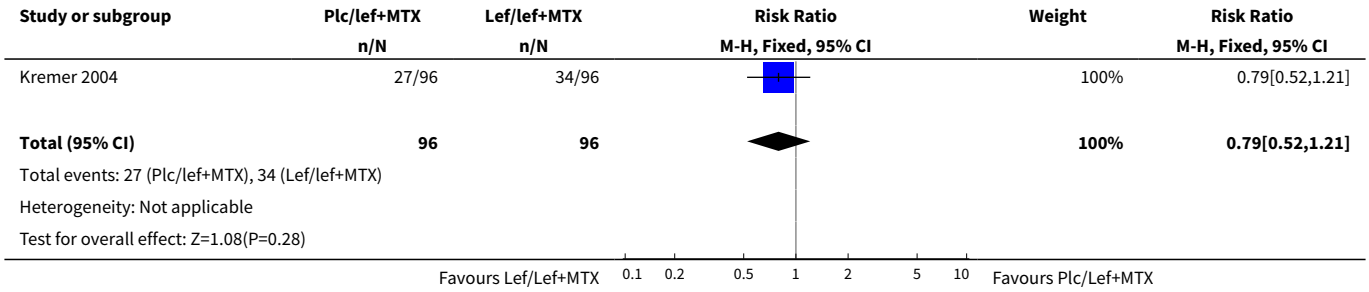


Analysis 2.10. Comparison 2 Treatment responder - ACR50, Outcome 10 leflunomide+SSZ vs. placebo+SSZ, at 24 weeks.

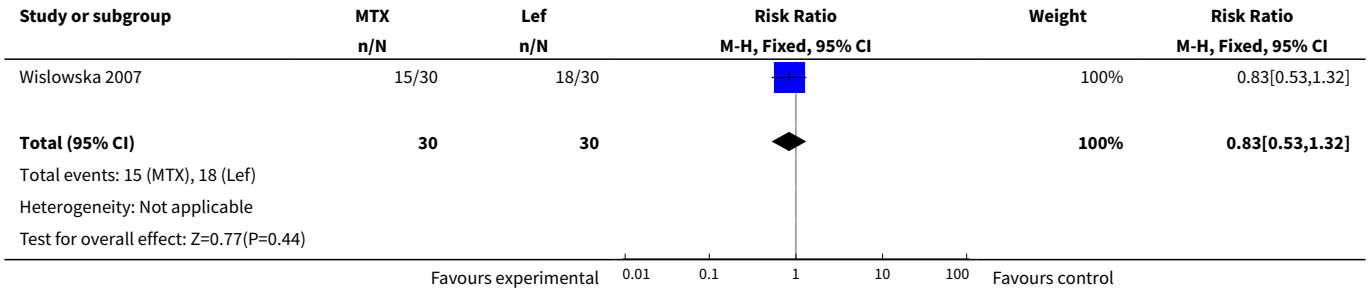




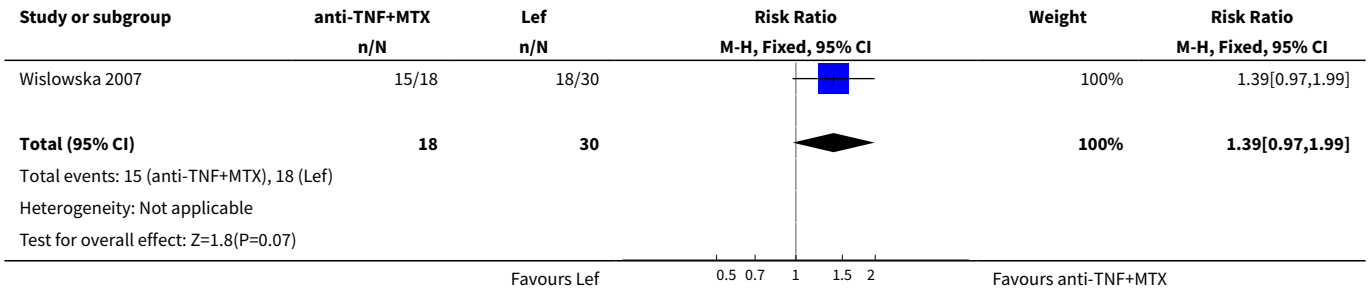
Analysis 2.11. Comparison 2 Treatment responder - ACR50, Outcome 11 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



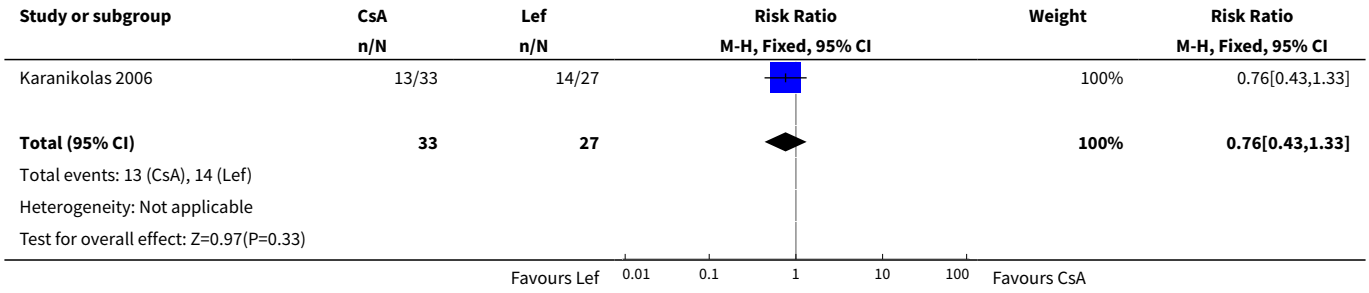
Analysis 2.12. Comparison 2 Treatment responder - ACR50, Outcome 12 leflunomide vs. methotrexate, at 24 weeks.



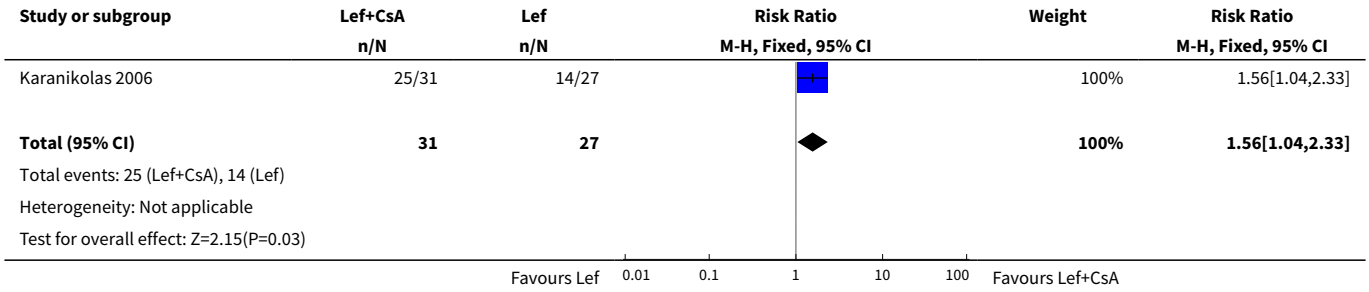
Analysis 2.13. Comparison 2 Treatment responder - ACR50, Outcome 13 leflunomide vs. anti-TNF+MTX, at 24 weeks.



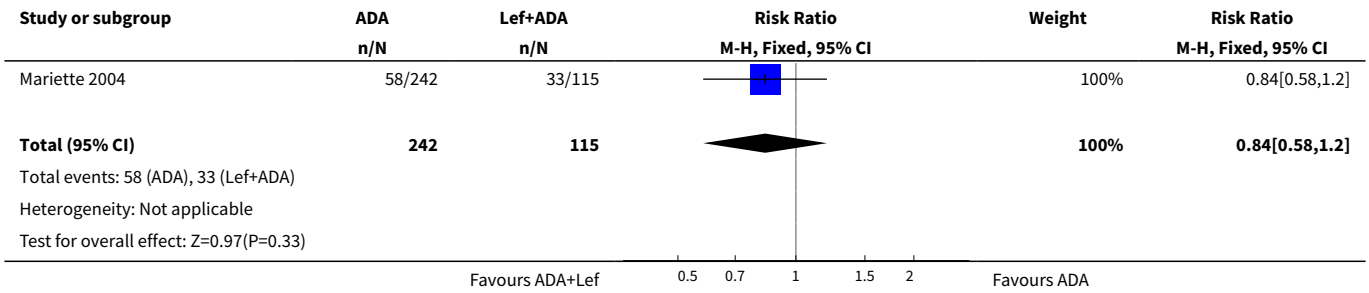
Analysis 2.14. Comparison 2 Treatment responder - ACR50, Outcome 14 Lef vs. CsA, at 12 months.



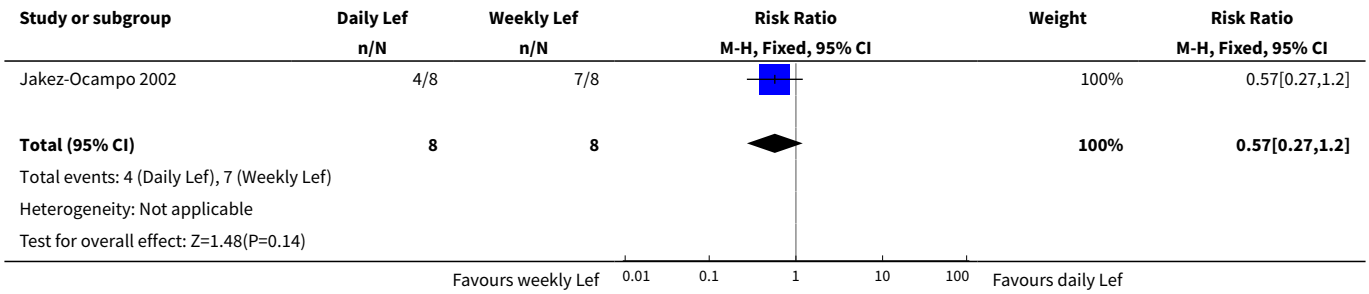
Analysis 2.15. Comparison 2 Treatment responder - ACR50, Outcome 15 Lef vs. Lef+CsA, at 12 months.



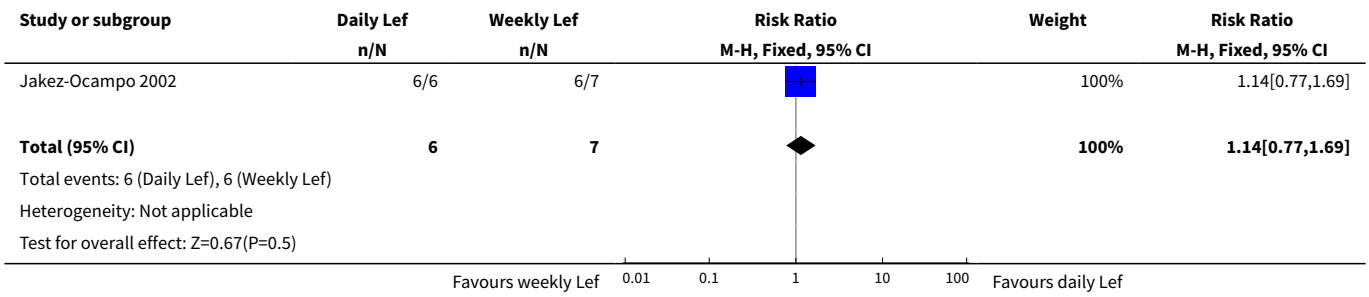
Analysis 2.16. Comparison 2 Treatment responder - ACR50, Outcome 16 Lef+ADA vs. ADA, at 12 weeks.



Analysis 2.17. Comparison 2 Treatment responder - ACR50, Outcome 17 Weekly Lef vs. daily Lef, at 6 months.



Analysis 2.18. Comparison 2 Treatment responder - ACR50, Outcome 18 Weekly Lef vs. daily Lef, at 12 months.

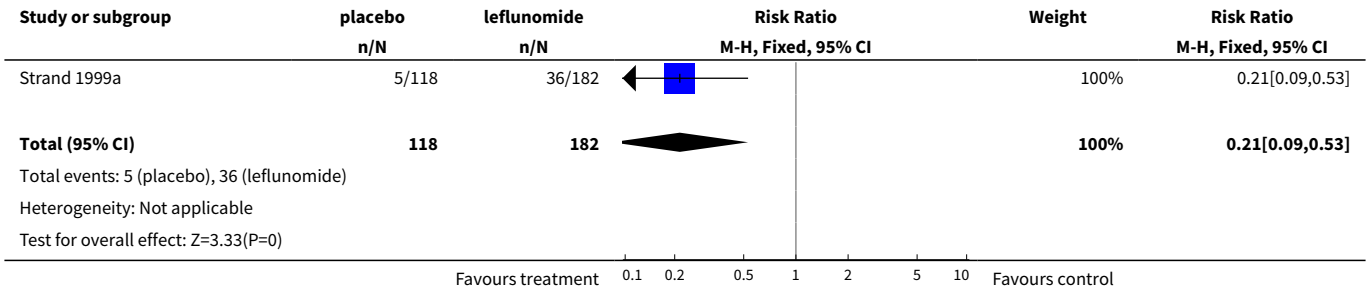


Comparison 3. Treatment responder - ACR70

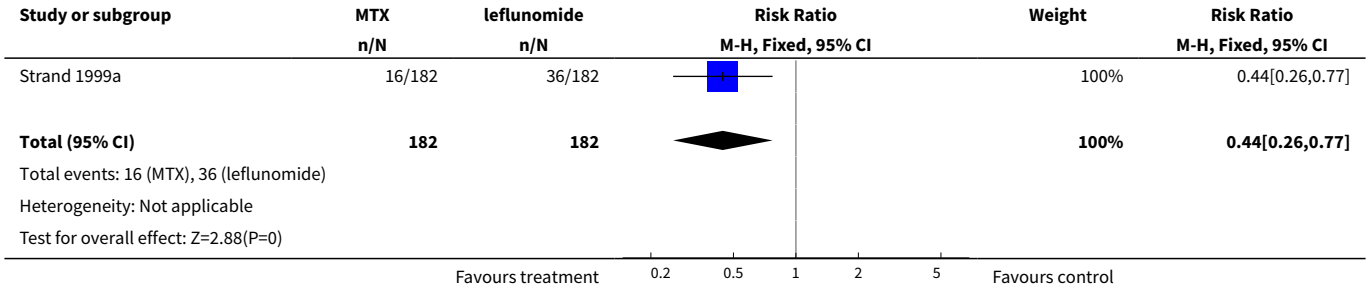
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 12 months	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.09, 0.53]
2 leflunomide vs. methotrexate, at 12 months	1	364	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.26, 0.77]
3 leflunomide vs. methotrexate, at 2 years	1	380	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.44, 1.18]
4 leflunomide vs. sulfasalazine, at 6 months	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.28, 1.55]
5 leflunomide vs. sulfasalazine, at 12 months	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.57, 2.25]
6 leflunomide vs. sulfasalazine, at 24 months	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.34, 1.43]
7 leflunomide+MTX vs MTX, at 24 weeks	1	263	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.77]
8 leflunomide10mg vs leflunomide 20 mg, at 24 weeks	1	399	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.37, 1.41]
9 leflunomide+SSZ vs. placebo+SSZ, at 24 weeks	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.34, 1.40]
11 leflunomide vs. methotrexate, at 24 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.10, 2.53]
12 leflunomide vs. anti-TNF+MTX, at 24 weeks	1	48	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [1.35, 10.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Lef vs. CsA, at 12 months	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.57, 2.20]
14 Lef vs. Lef+CsA, at 12 months	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.12, 3.44]
15 Weekly Lef vs. daily Lef, at 6 months	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.34, 6.70]
16 Weekly Lef vs. daily Lef, at 12 months	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.42, 7.23]

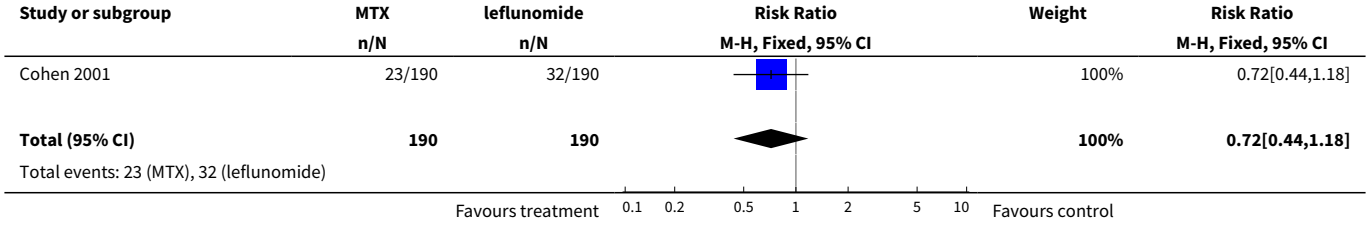
Analysis 3.1. Comparison 3 Treatment responder - ACR70, Outcome 1 leflunomide vs. placebo, at 12 months.



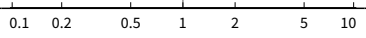
Analysis 3.2. Comparison 3 Treatment responder - ACR70, Outcome 2 leflunomide vs. methotrexate, at 12 months.



Analysis 3.3. Comparison 3 Treatment responder - ACR70, Outcome 3 leflunomide vs. methotrexate, at 2 years.

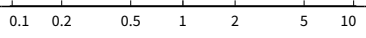


Study or subgroup	MTX n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					



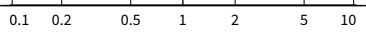
Analysis 3.4. Comparison 3 Treatment responder - ACR70, Outcome 4 leflunomide vs. sulfasalazine, at 6 months.

Study or subgroup	SSZ n/N	Leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	8/132	12/130		100%	0.66[0.28,1.55]
Total (95% CI)	**132**	**130**		**100%**	**0.66[0.28,1.55]**
Total events: 8 (SSZ), 12 (Leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					



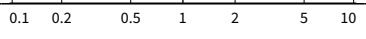
Analysis 3.5. Comparison 3 Treatment responder - ACR70, Outcome 5 leflunomide vs. sulfasalazine, at 12 months.

Study or subgroup	SSZ n/N	Leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	14/74	13/78		100%	1.14[0.57,2.25]
Total (95% CI)	**74**	**78**		**100%**	**1.14[0.57,2.25]**
Total events: 14 (SSZ), 13 (Leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.36(P=0.72)					

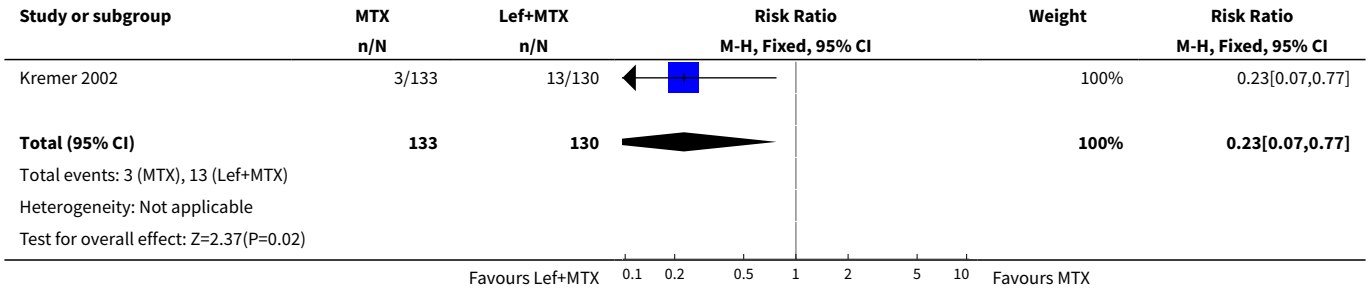


Analysis 3.6. Comparison 3 Treatment responder - ACR70, Outcome 6 leflunomide vs. sulfasalazine, at 24 months.

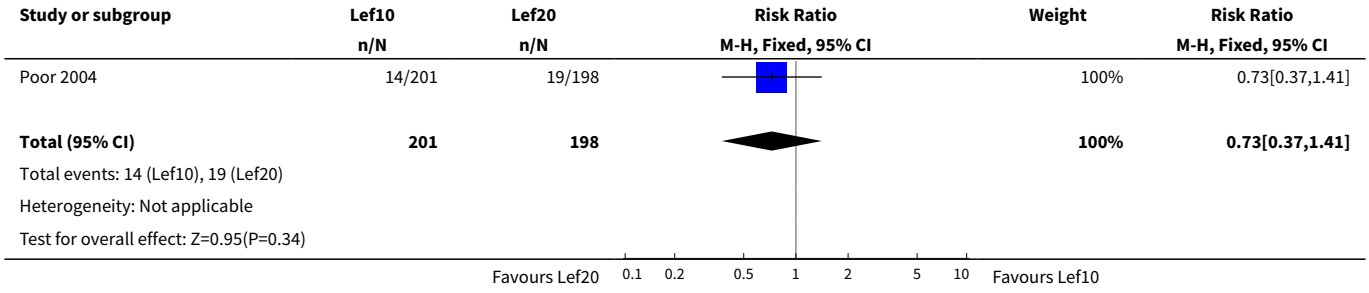
Study or subgroup	SSZ n/N	Leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	10/57	15/60		100%	0.7[0.34,1.43]
Total (95% CI)	**57**	**60**		**100%**	**0.7[0.34,1.43]**
Total events: 10 (SSZ), 15 (Leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					



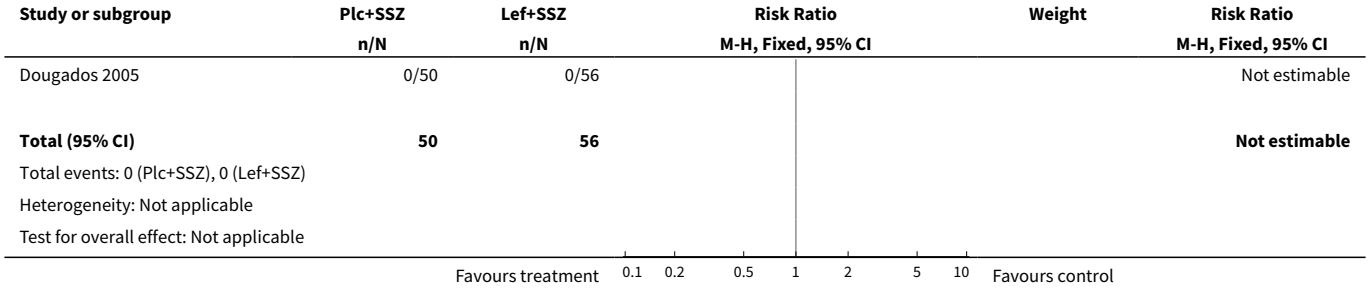
Analysis 3.7. Comparison 3 Treatment responder - ACR70, Outcome 7 leflunomide+MTX vs MTX, at 24 weeks.



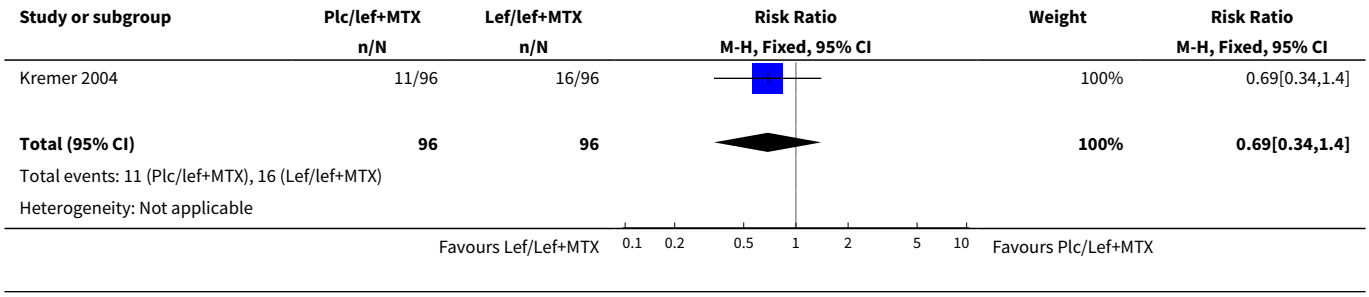
Analysis 3.8. Comparison 3 Treatment responder - ACR70, Outcome 8 leflunomide10mg vs leflunomide 20 mg, at 24 weeks.

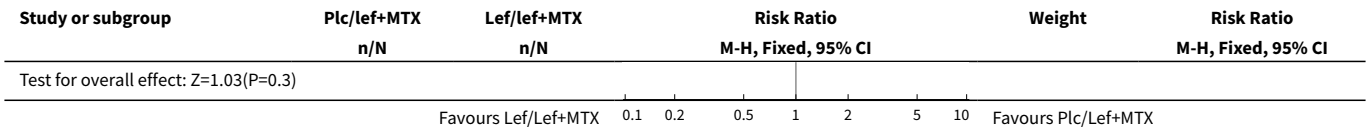


Analysis 3.9. Comparison 3 Treatment responder - ACR70, Outcome 9 leflunomide+SSZ vs. placebo+SSZ, at 24 weeks.

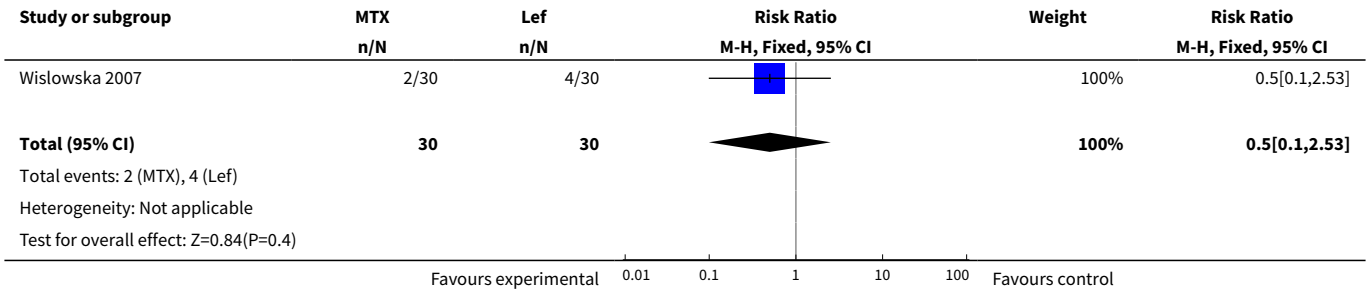


Analysis 3.10. Comparison 3 Treatment responder - ACR70, Outcome 10 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.

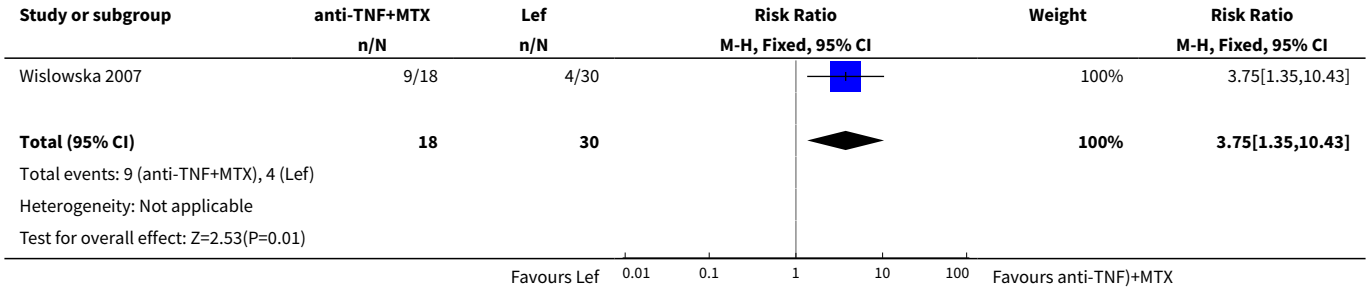




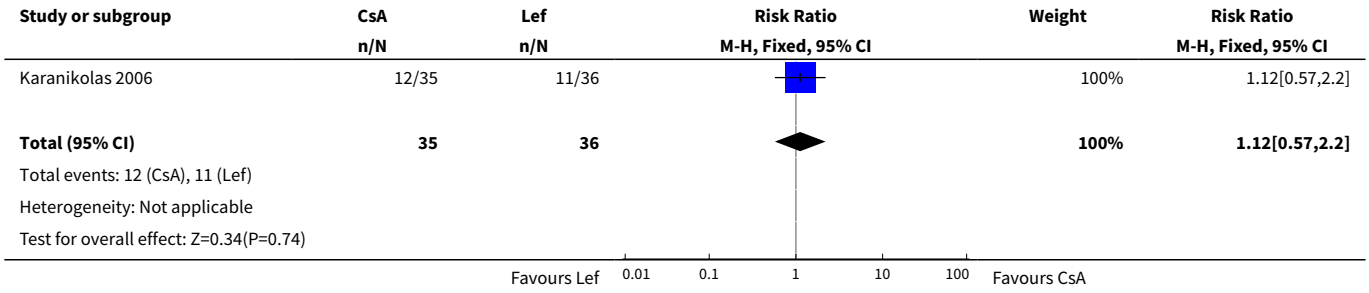
Analysis 3.11. Comparison 3 Treatment responder - ACR70, Outcome 11 leflunomide vs. methotrexate, at 24 weeks.



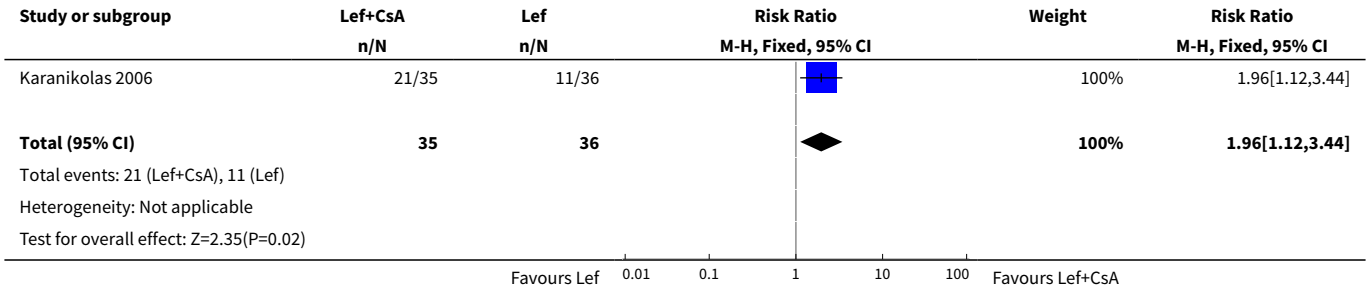
Analysis 3.12. Comparison 3 Treatment responder - ACR70, Outcome 12 leflunomide vs. anti-TNF+MTX, at 24 weeks.



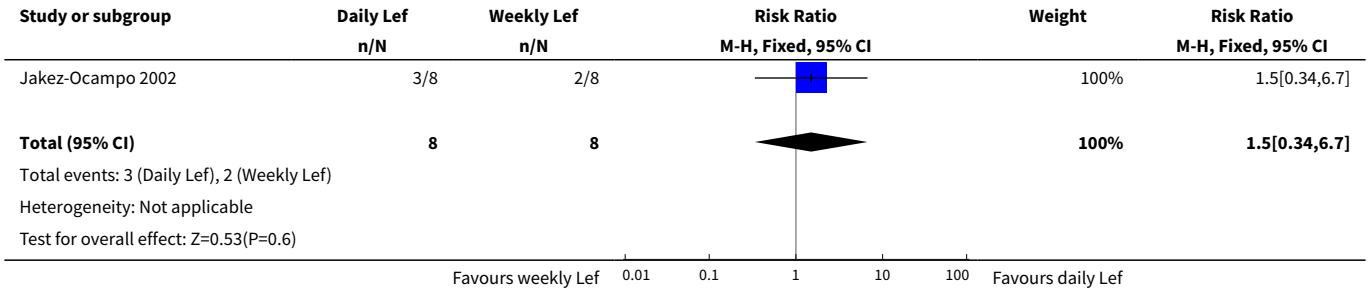
Analysis 3.13. Comparison 3 Treatment responder - ACR70, Outcome 13 Lef vs. CsA, at 12 months.



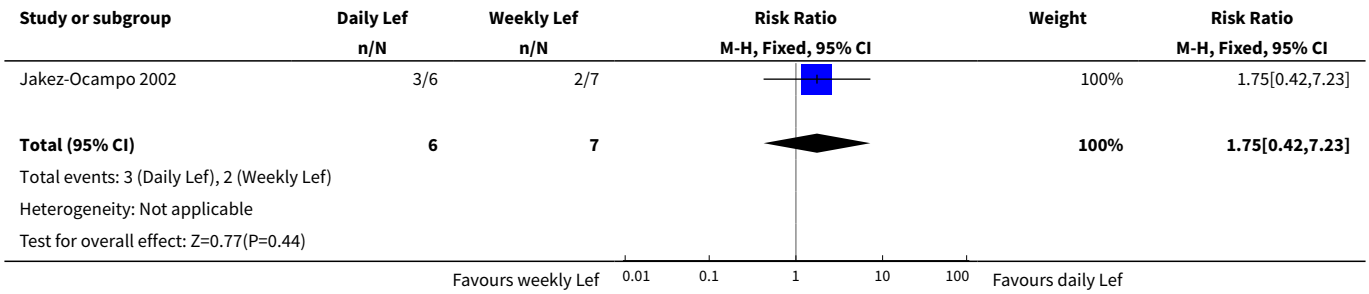
Analysis 3.14. Comparison 3 Treatment responder - ACR70, Outcome 14 Lef vs. Lef+CsA, at 12 months.



Analysis 3.15. Comparison 3 Treatment responder - ACR70, Outcome 15 Weekly Lef vs. daily Lef, at 6 months.



Analysis 3.16. Comparison 3 Treatment responder - ACR70, Outcome 16 Weekly Lef vs. daily Lef, at 12 months.



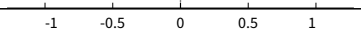
Comparison 4. Changes of tender joint count

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	3	724	Std. Mean Difference (IV, Fixed, 95% CI)	-0.57 [-0.72, -0.42]
2 leflunomide vs. placebo, at 12 months	1	300	Mean Difference (IV, Fixed, 95% CI)	-4.7 [-6.59, -2.81]

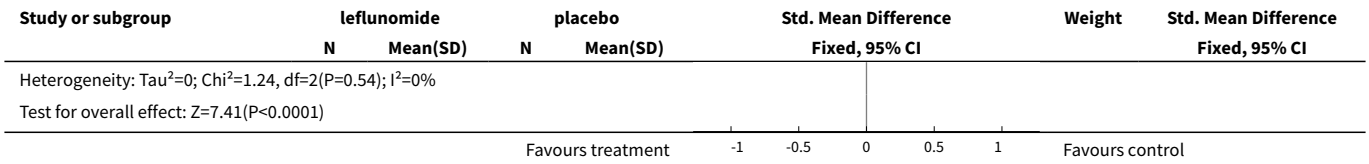
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 leflunomide vs. methotrexate, at 3 months	3	664	Mean Difference (IV, Fixed, 95% CI)	-0.51 [-1.29, 0.26]
4 leflunomide vs. methotrexate, at 4 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-8.98, 0.98]
5 leflunomide vs. methotrexate, at 6 months	5	763	Mean Difference (IV, Fixed, 95% CI)	-0.64 [-1.44, 0.15]
6 leflunomide vs. methotrexate, at 12 months	2	1346	Mean Difference (IV, Random, 95% CI)	0.23 [-2.21, 2.68]
7 leflunomide vs. methotrexate, at 2 years	2	770	Mean Difference (IV, Random, 95% CI)	-0.22 [-1.82, 1.39]
8 leflunomide vs. sulfasalazine, at 6 months	1	262	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-3.44, 0.24]
9 leflunomide vs. sulfasalazine, at 12 months	1	152	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-3.06, 1.26]
10 leflunomide vs. sulfasalazine, at 24 months	1	117	Mean Difference (IV, Fixed, 95% CI)	-3.33 [-5.83, -0.83]
11 leflunomide+MTX vs MTX, at 24 weeks	1	263	Mean Difference (IV, Fixed, 95% CI)	-7.60 [-10.59, -4.61]
12 Leflunomide 10 mg vs leflunomide 20 mg, at 24 weeks	1	397	Mean Difference (IV, Fixed, 95% CI)	1.32 [-0.25, 2.89]
13 leflunomide+SSZ vs. placebo+SSZ, at 24 months	1	106	Mean Difference (IV, Fixed, 95% CI)	-1.28 [-3.82, 1.26]
14 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	177	Mean Difference (IV, Fixed, 95% CI)	1.80 [-1.84, 5.44]
15 leflunomide vs. anti-TNF+MTX, at 24 weeks	1	48	Mean Difference (IV, Fixed, 95% CI)	3.30 [1.88, 4.72]
16 weekly Lef100 vs. weekly Lef200, at 6 months	1	47	Mean Difference (IV, Fixed, 95% CI)	-3.80 [-10.09, 2.49]

Analysis 4.1. Comparison 4 Changes of tender joint count, Outcome 1 leflunomide vs. placebo, at 6 months.

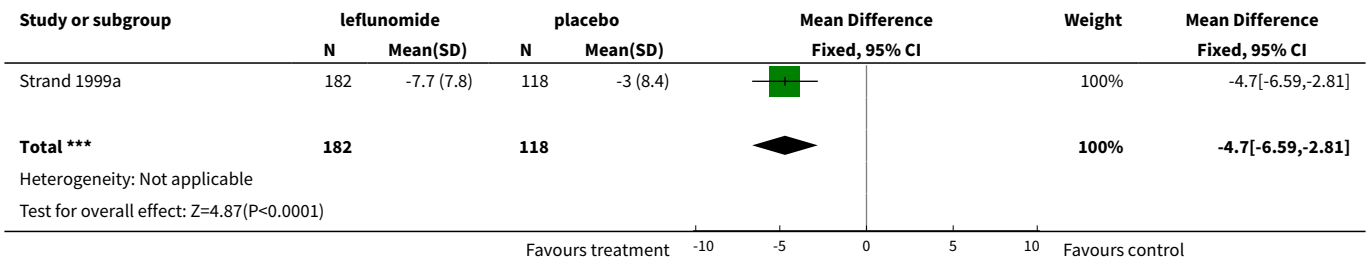
Study or subgroup	leflunomide		placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Mladenovic 1995	101	-16.5 (14.1)	102	-9.7 (12.6)		29.09%	-0.51[-0.79,-0.23]
Smolen 1999	130	-9.7 (7.8)	91	-4.3 (7.5)		29.88%	-0.7[-0.98,-0.43]
Strand 1999a	182	-7.5 (7.9)	118	-3.4 (8.2)		41.04%	-0.52[-0.75,-0.28]
Total ***	**413**		**311**			**100%**	**-0.57[-0.72,-0.42]**



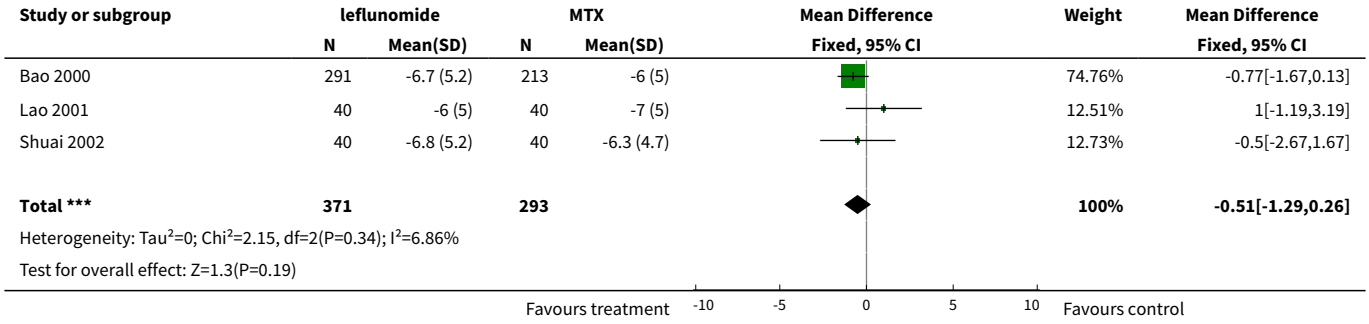
Favours treatment Favours control



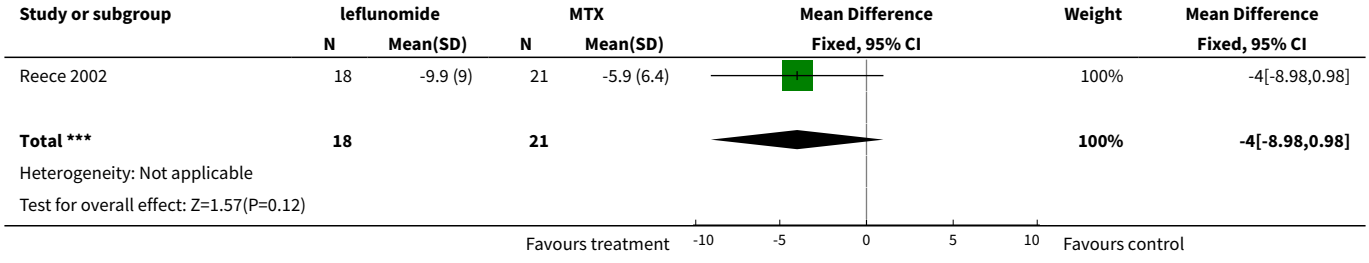
Analysis 4.2. Comparison 4 Changes of tender joint count, Outcome 2 leflunomide vs. placebo, at 12 months.



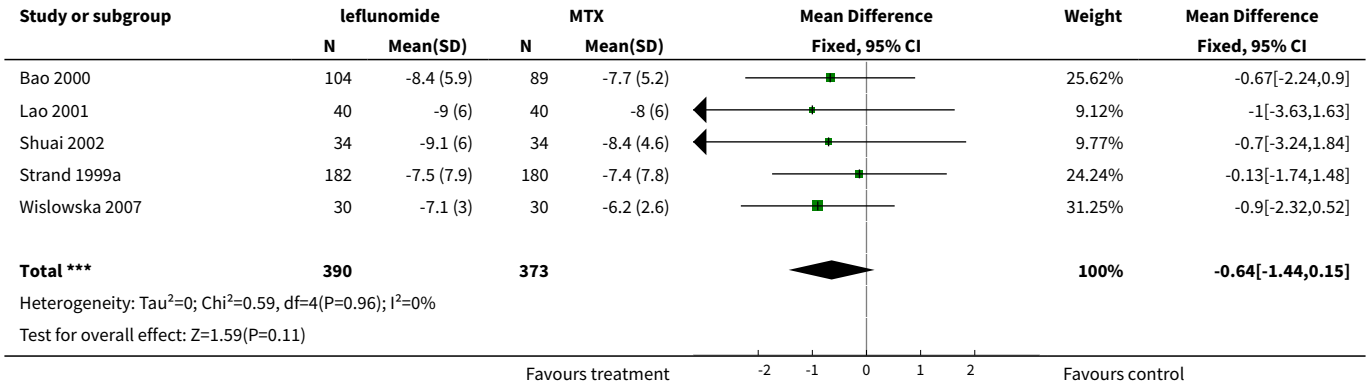
Analysis 4.3. Comparison 4 Changes of tender joint count, Outcome 3 leflunomide vs. methotrexate, at 3 months.



Analysis 4.4. Comparison 4 Changes of tender joint count, Outcome 4 leflunomide vs. methotrexate, at 4 months.



Analysis 4.5. Comparison 4 Changes of tender joint count, Outcome 5 leflunomide vs. methotrexate, at 6 months.

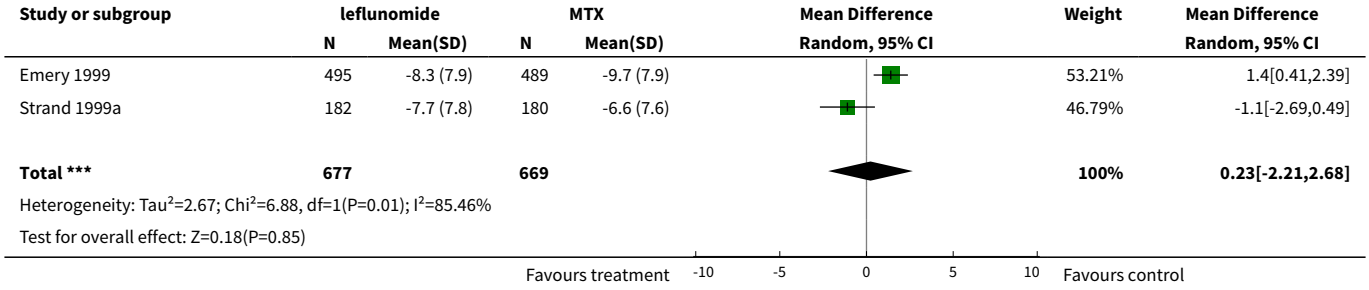


Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	104	-8.4 (5.9)	89	-7.7 (5.2)		25.62%	-0.67[-2.24,0.9]
Lao 2001	40	-9 (6)	40	-8 (6)		9.12%	-1[-3.63,1.63]
Shuai 2002	34	-9.1 (6)	34	-8.4 (4.6)		9.77%	-0.7[-3.24,1.84]
Strand 1999a	182	-7.5 (7.9)	180	-7.4 (7.8)		24.24%	-0.13[-1.74,1.48]
Wislowska 2007	30	-7.1 (3)	30	-6.2 (2.6)		31.25%	-0.9[-2.32,0.52]
Total ***	**390**		**373**			**100%**	**-0.64[-1.44,0.15]**

Heterogeneity: Tau²=0; Chi²=0.59, df=4(P=0.96); I²=0%

Test for overall effect: Z=1.59(P=0.11)

Analysis 4.6. Comparison 4 Changes of tender joint count, Outcome 6 leflunomide vs. methotrexate, at 12 months.

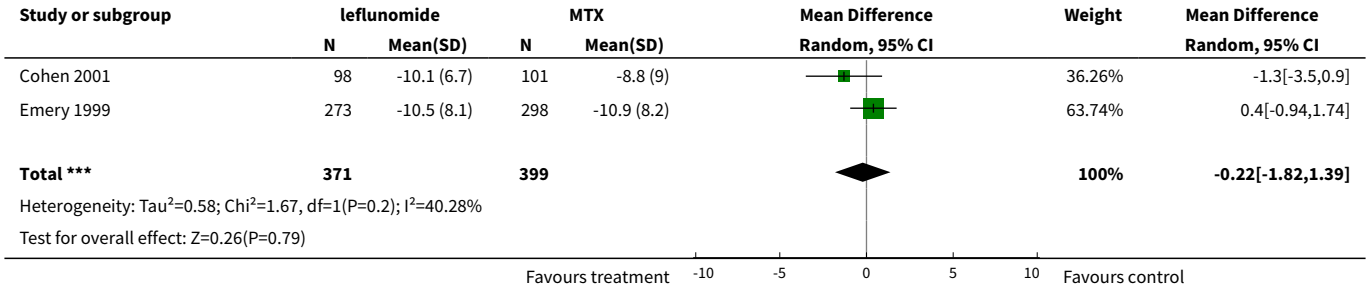


Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Emery 1999	495	-8.3 (7.9)	489	-9.7 (7.9)		53.21%	1.4[0.41,2.39]
Strand 1999a	182	-7.7 (7.8)	180	-6.6 (7.6)		46.79%	-1.1[-2.69,0.49]
Total ***	**677**		**669**			**100%**	**0.23[-2.21,2.68]**

Heterogeneity: Tau²=2.67; Chi²=6.88, df=1(P=0.01); I²=85.46%

Test for overall effect: Z=0.18(P=0.85)

Analysis 4.7. Comparison 4 Changes of tender joint count, Outcome 7 leflunomide vs. methotrexate, at 2 years.

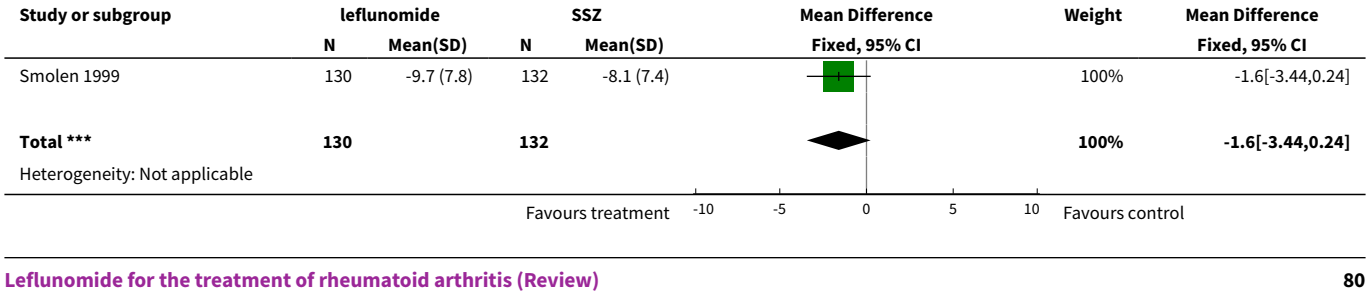


Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cohen 2001	98	-10.1 (6.7)	101	-8.8 (9)		36.26%	-1.3[-3.5,0.9]
Emery 1999	273	-10.5 (8.1)	298	-10.9 (8.2)		63.74%	0.4[-0.94,1.74]
Total ***	**371**		**399**			**100%**	**-0.22[-1.82,1.39]**

Heterogeneity: Tau²=0.58; Chi²=1.67, df=1(P=0.2); I²=40.28%

Test for overall effect: Z=0.26(P=0.79)

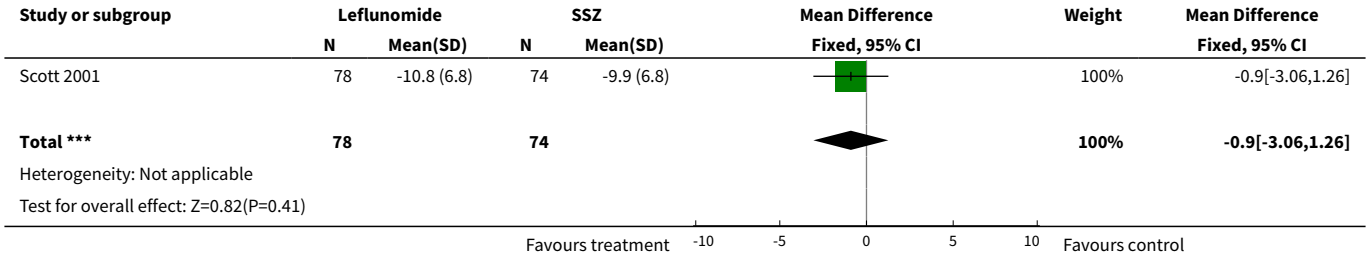
Analysis 4.8. Comparison 4 Changes of tender joint count, Outcome 8 leflunomide vs. sulfasalazine, at 6 months.



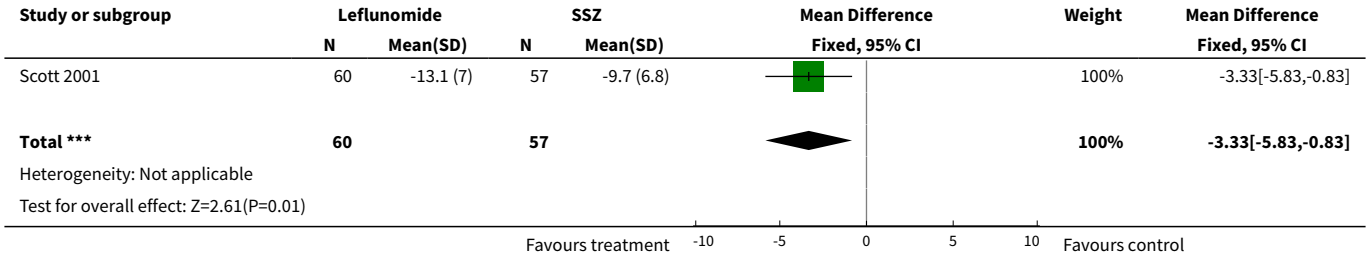
Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Smolen 1999	130	-9.7 (7.8)	132	-8.1 (7.4)		100%	-1.6[-3.44,0.24]
Total ***	**130**		**132**			**100%**	**-1.6[-3.44,0.24]**

Heterogeneity: Not applicable

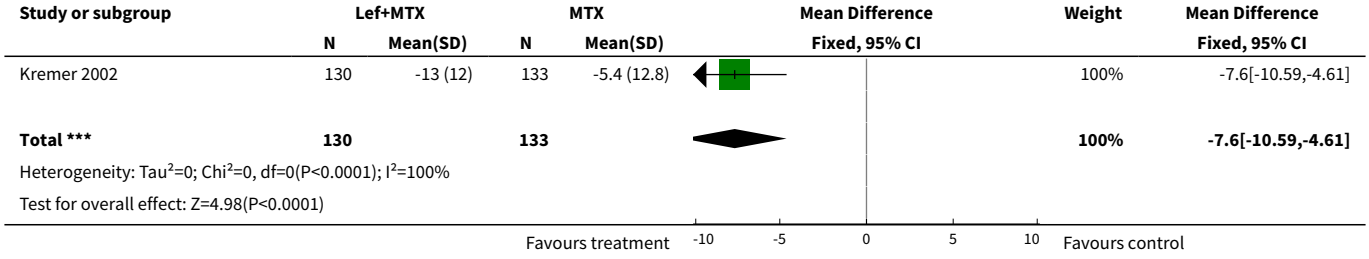
Analysis 4.9. Comparison 4 Changes of tender joint count, Outcome 9 leflunomide vs. sulfasalazine, at 12 months.



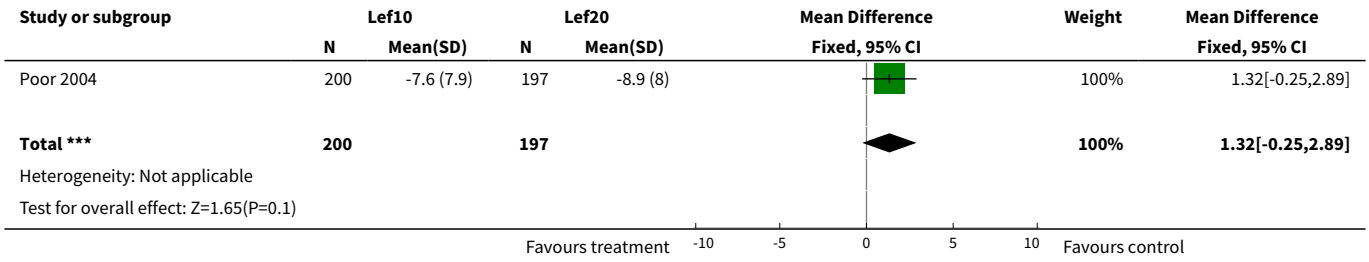
Analysis 4.10. Comparison 4 Changes of tender joint count, Outcome 10 leflunomide vs. sulfasalazine, at 24 months.



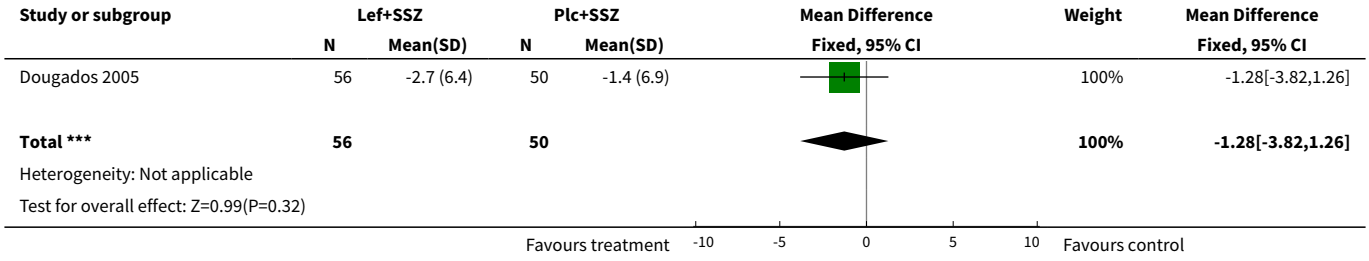
Analysis 4.11. Comparison 4 Changes of tender joint count, Outcome 11 leflunomide+MTX vs MTX, at 24 weeks.



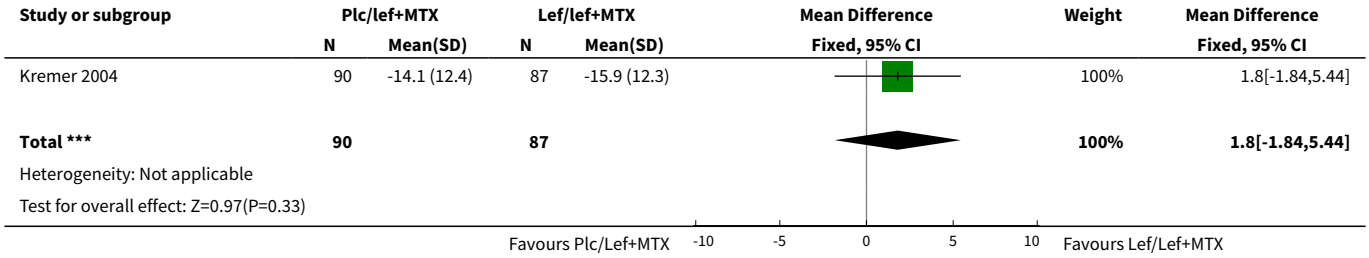
Analysis 4.12. Comparison 4 Changes of tender joint count, Outcome 12 Leflunomide 10 mg vs leflunomide 20 mg, at 24 weeks.



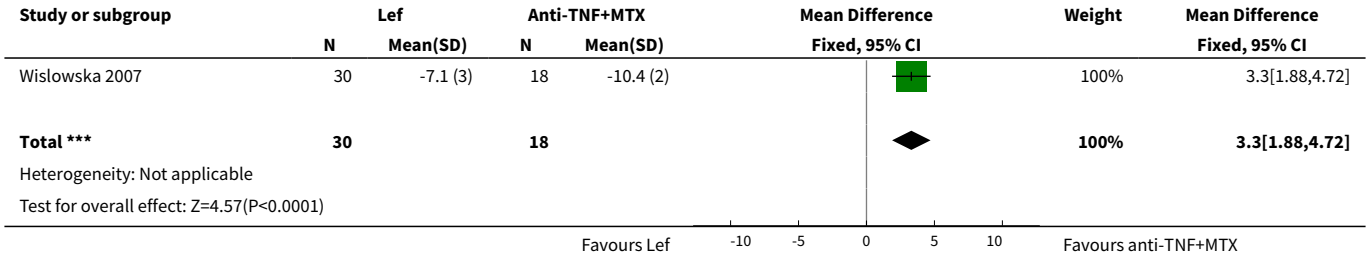
Analysis 4.13. Comparison 4 Changes of tender joint count, Outcome 13 leflunomide+SSZ vs. placebo+SSZ, at 24 months.



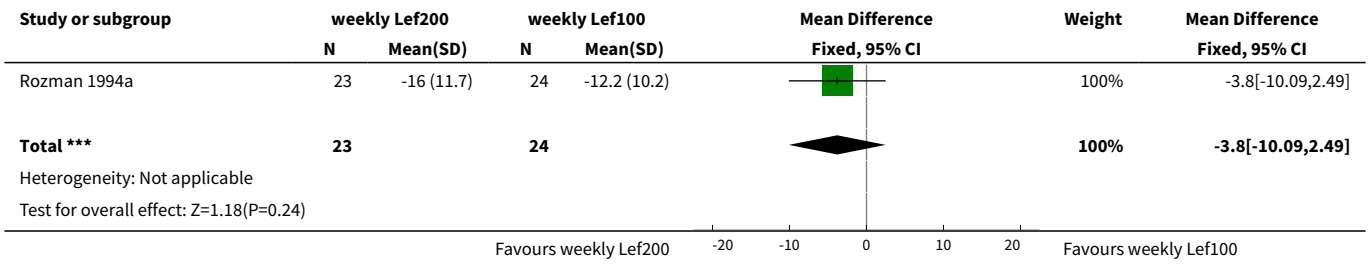
Analysis 4.14. Comparison 4 Changes of tender joint count, Outcome 14 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 4.15. Comparison 4 Changes of tender joint count, Outcome 15 leflunomide vs. anti-TNF+MTX, at 24 weeks.



Analysis 4.16. Comparison 4 Changes of tender joint count, Outcome 16 weekly Lef100 vs. weekly Lef200, at 6 months.

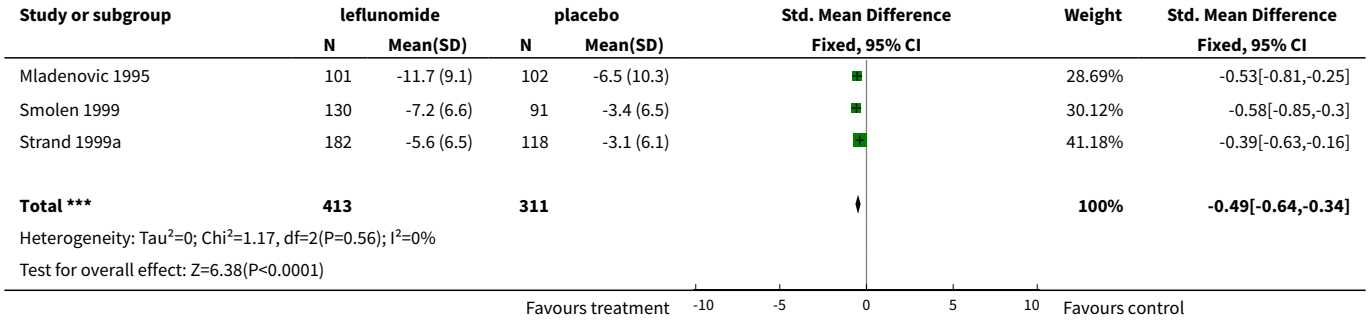


Comparison 5. Changes of swollen joint count

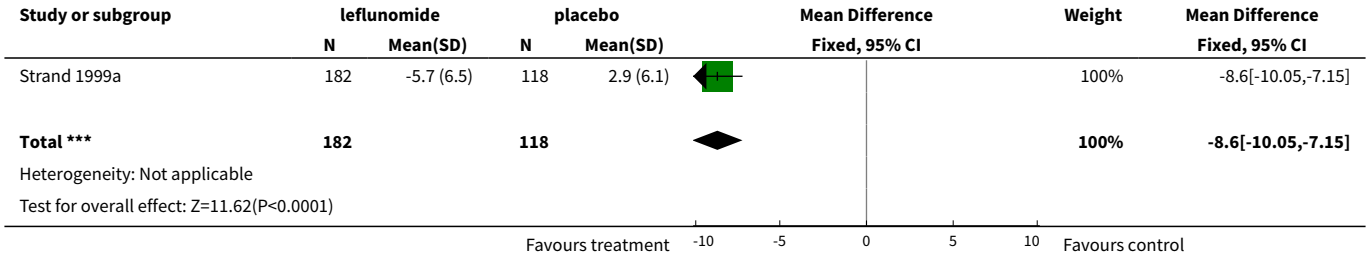
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	3	724	Std. Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.64, -0.34]
2 leflunomide vs. placebo, at 12 months	1	300	Mean Difference (IV, Fixed, 95% CI)	-8.6 [-10.05, -7.15]
3 leflunomide vs. methotrexate, at 3 months	3	664	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.82, 0.53]
4 leflunomide vs. methotrexate, at 4 months	1	39	Mean Difference (IV, Fixed, 95% CI)	0.0 [-4.44, 4.44]
5 leflunomide vs. methotrexate, at 6 months	5	763	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.47, 0.75]
6 leflunomide vs. methotrexate, at 12 months	2	1346	Mean Difference (IV, Random, 95% CI)	0.99 [-1.46, 3.44]
7 leflunomide vs. methotrexate, at 2 years	2	770	Mean Difference (IV, Random, 95% CI)	0.48 [-1.17, 2.12]
8 leflunomide vs. sulfasalazine, at 6 months	1	262	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.49, 0.49]
9 leflunomide vs. sulfasalazine, at 12 months	1	152	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-1.86, 1.62]
10 leflunomide vs. sulfasalazine, at 24 months	1	117	Mean Difference (IV, Fixed, 95% CI)	-2.62 [-4.67, -0.57]
11 leflunomide+MTX vs MTX, at 24 weeks	1	263	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-5.47, -1.73]
12 Leflunomide 10 mg vs leflunomide 20 mg, at 24 weeks	1	397	Mean Difference (IV, Fixed, 95% CI)	0.58 [-0.67, 1.83]
13 leflunomide+SSZ vs. placebo+SSZ, at 24 months	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-2.77, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	177	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-3.04, 1.24]
15 leflunomide vs. anti-TNF+MTX, at 24 weeks	1	48	Mean Difference (IV, Fixed, 95% CI)	1.40 [0.22, 2.58]
16 weekly Lef100 vs. weekly Lef200, at 6 months	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-6.09, 2.89]

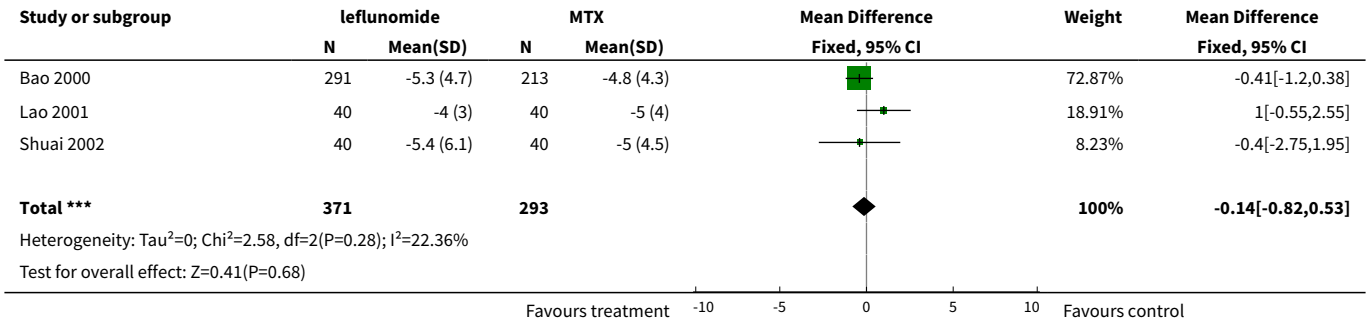
Analysis 5.1. Comparison 5 Changes of swollen joint count, Outcome 1 leflunomide vs. placebo, at 6 months.



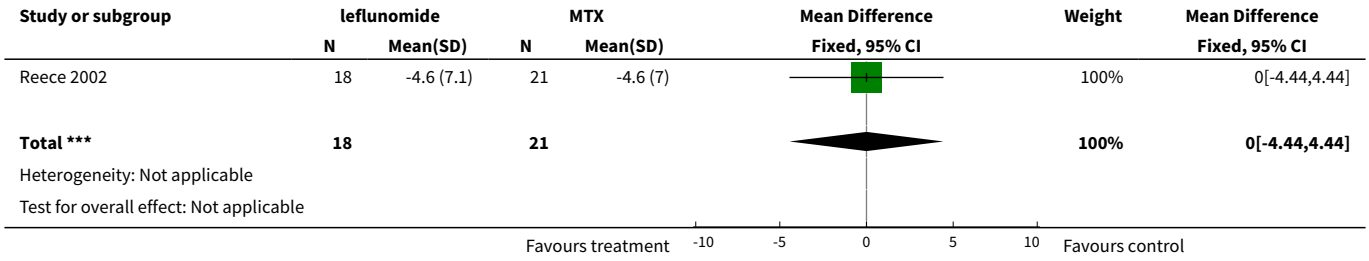
Analysis 5.2. Comparison 5 Changes of swollen joint count, Outcome 2 leflunomide vs. placebo, at 12 months.



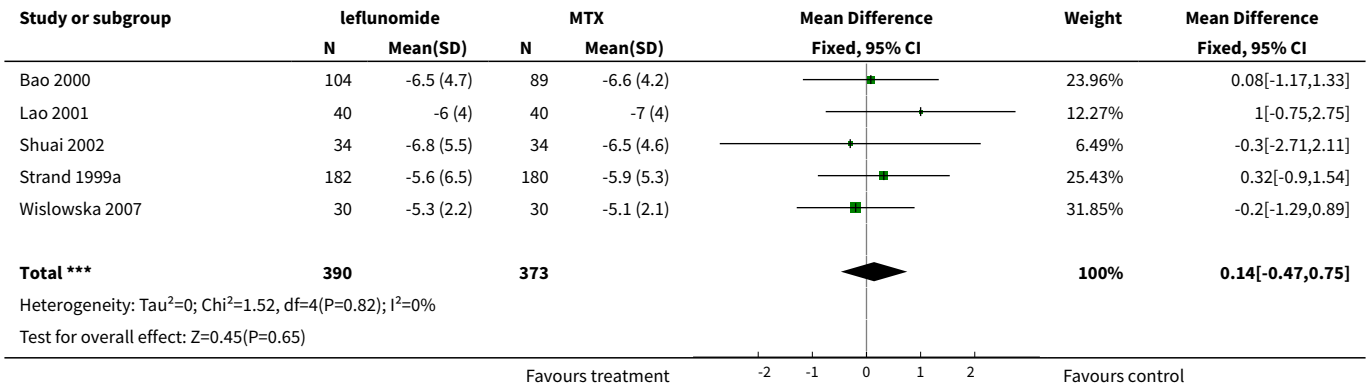
Analysis 5.3. Comparison 5 Changes of swollen joint count, Outcome 3 leflunomide vs. methotrexate, at 3 months.



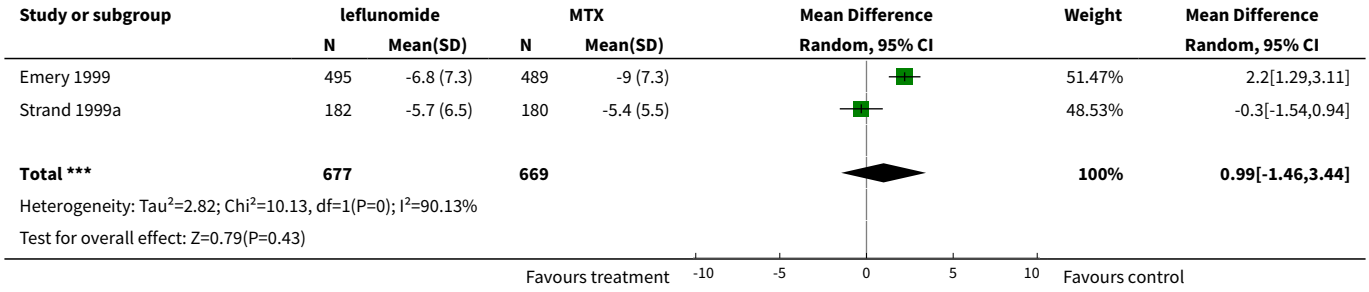
Analysis 5.4. Comparison 5 Changes of swollen joint count, Outcome 4 leflunomide vs. methotrexate, at 4 months.



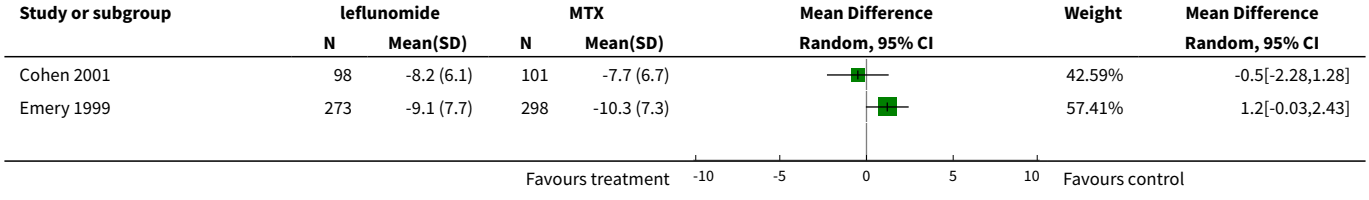
Analysis 5.5. Comparison 5 Changes of swollen joint count, Outcome 5 leflunomide vs. methotrexate, at 6 months.

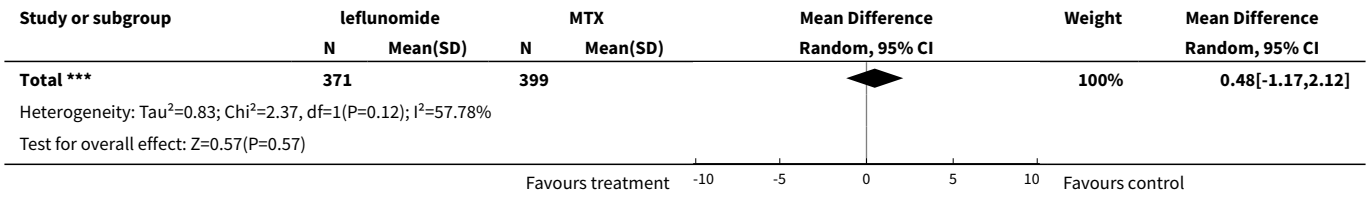


Analysis 5.6. Comparison 5 Changes of swollen joint count, Outcome 6 leflunomide vs. methotrexate, at 12 months.

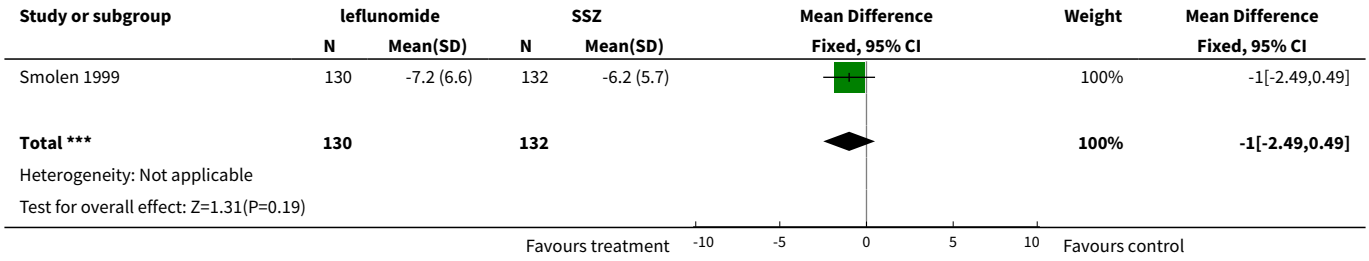


Analysis 5.7. Comparison 5 Changes of swollen joint count, Outcome 7 leflunomide vs. methotrexate, at 2 years.

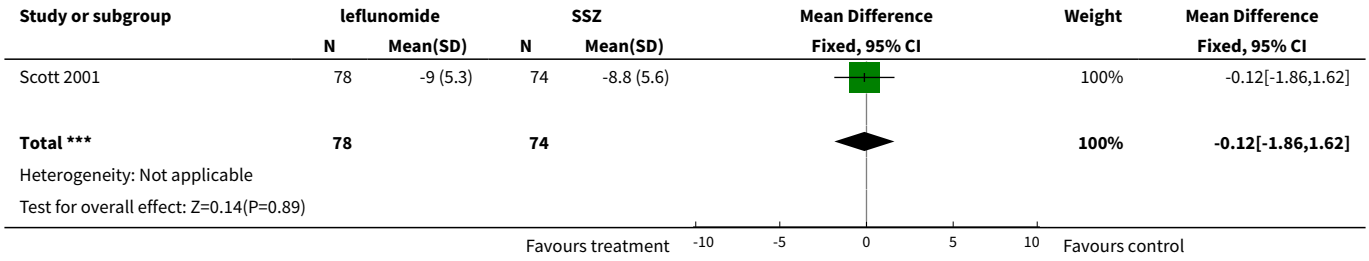




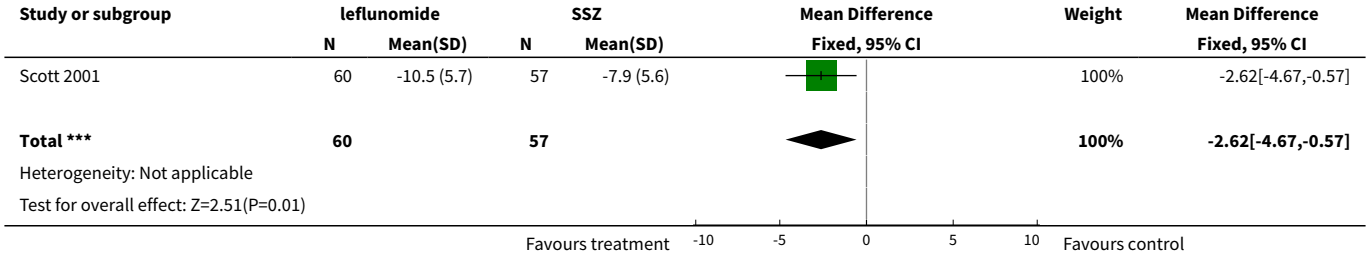
Analysis 5.8. Comparison 5 Changes of swollen joint count, Outcome 8 leflunomide vs. sulfasalazine, at 6 months.



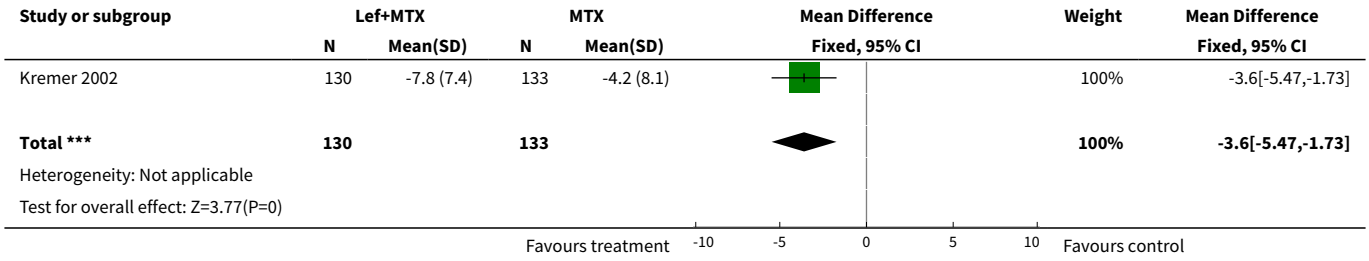
Analysis 5.9. Comparison 5 Changes of swollen joint count, Outcome 9 leflunomide vs. sulfasalazine, at 12 months.



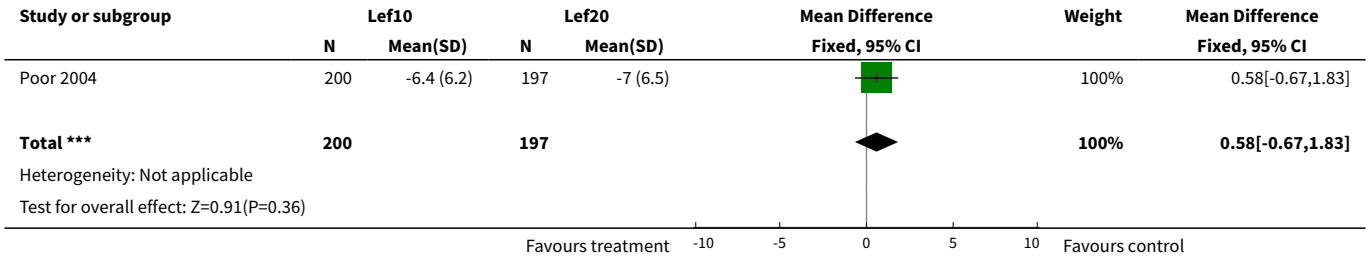
Analysis 5.10. Comparison 5 Changes of swollen joint count, Outcome 10 leflunomide vs. sulfasalazine, at 24 months.



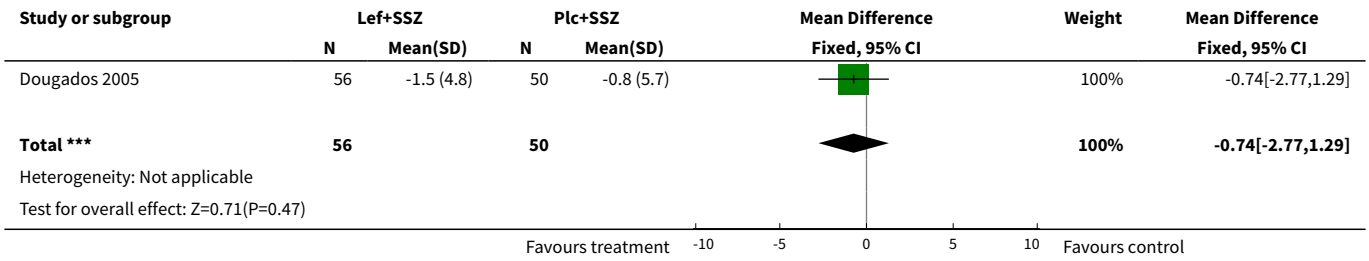
Analysis 5.11. Comparison 5 Changes of swollen joint count, Outcome 11 leflunomide+MTX vs MTX, at 24 weeks.



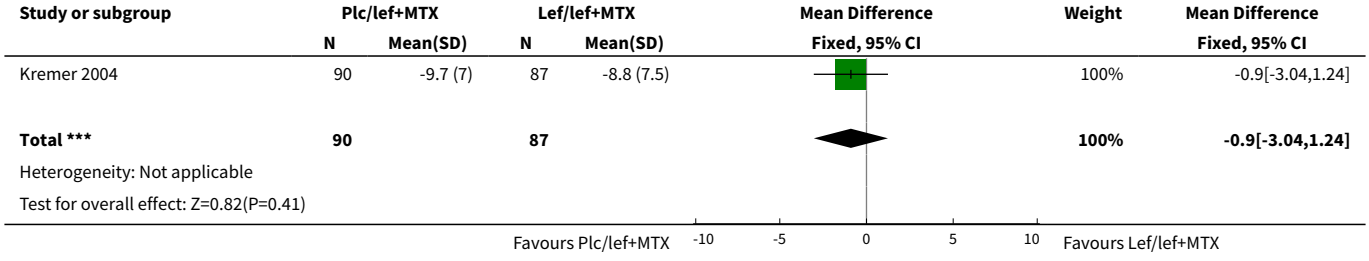
Analysis 5.12. Comparison 5 Changes of swollen joint count, Outcome 12 Leflunomide 10 mg vs leflunomide 20 mg, at 24 weeks.



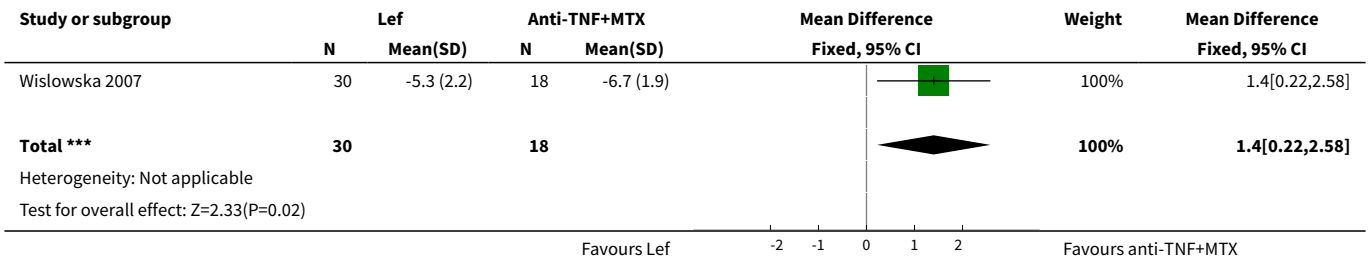
Analysis 5.13. Comparison 5 Changes of swollen joint count, Outcome 13 leflunomide+SSZ vs. placebo+SSZ, at 24 months.



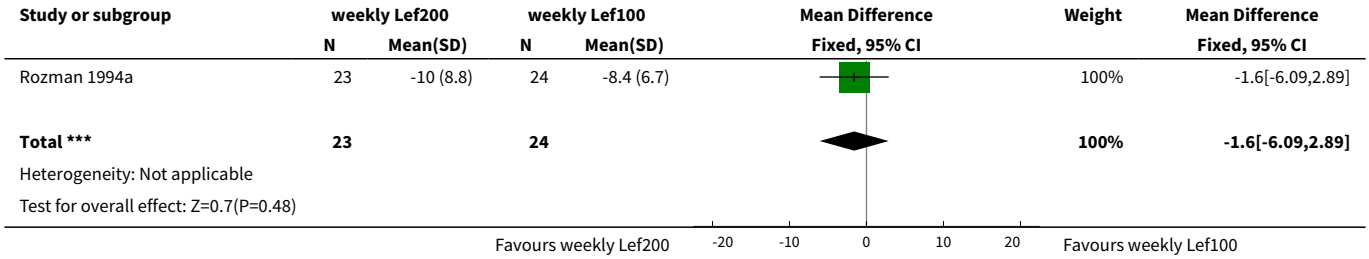
Analysis 5.14. Comparison 5 Changes of swollen joint count, Outcome 14 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 5.15. Comparison 5 Changes of swollen joint count, Outcome 15 leflunomide vs. anti-TNF+MTX, at 24 weeks.



Analysis 5.16. Comparison 5 Changes of swollen joint count, Outcome 16 weekly Lef100 vs. weekly Lef200, at 6 months.

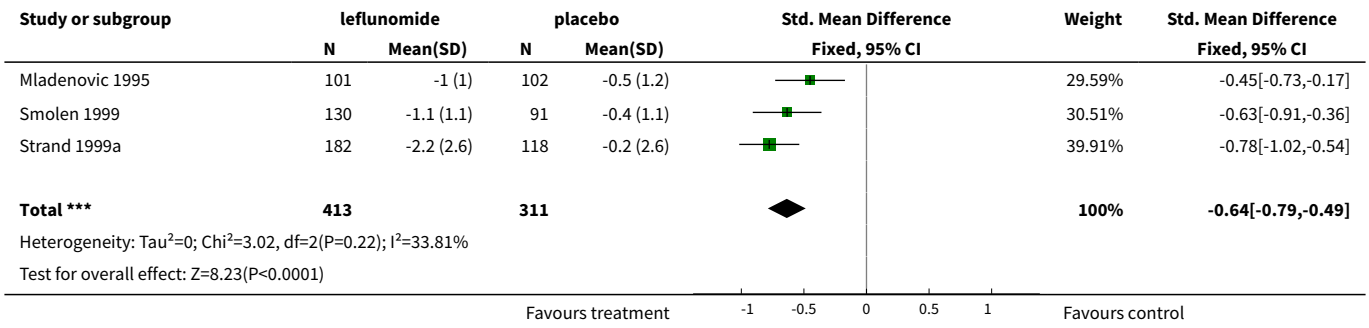


Comparison 6. Changes of patient global assessment

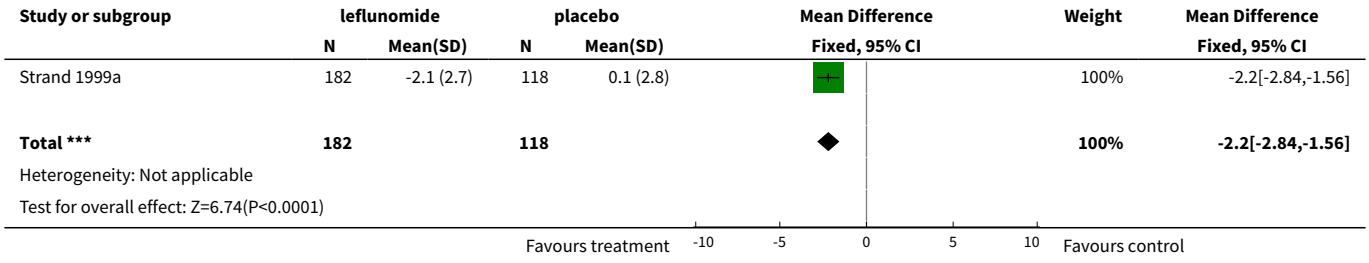
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	3	724	Std. Mean Difference (IV, Fixed, 95% CI)	-0.64 [-0.79, -0.49]
2 leflunomide vs. placebo, at 12 months	1	300	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-2.84, -1.56]
3 leflunomide vs. methotrexate, at 3 months	3	664	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.52, 0.05]
4 leflunomide vs. methotrexate, at 4 months	1	39	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.53, 0.73]
5 leflunomide vs. methotrexate, at 6 months	4	703	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-0.95, -0.26]
6 leflunomide vs. methotrexate, at 12 months	2	1346	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.98, 0.77]
7 leflunomide vs. methotrexate, at 2 years	2	770	Mean Difference (IV, Random, 95% CI)	-0.33 [-1.30, 0.64]
8 leflunomide vs. sulfasalazine, at 6 months	1	262	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.25, 0.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 leflunomide vs. sulfasalazine, at 12 months	1	152	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.55, 0.61]
10 leflunomide vs. sulfasalazine, at 24 months	1	117	Mean Difference (IV, Fixed, 95% CI)	-0.68 [-1.35, -0.01]
11 leflunomide+MTX vs MTX, at 24 weeks	1	263	Mean Difference (IV, Fixed, 95% CI)	-15.5 [-21.86, -9.14]
12 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	175	Mean Difference (IV, Fixed, 95% CI)	1.10 [-6.80, 9.00]
13 weekly Lef100 vs. weekly Lef200, at 6 months	1	47	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.09, 0.89]

Analysis 6.1. Comparison 6 Changes of patient global assessment, Outcome 1 leflunomide vs. placebo, at 6 months.

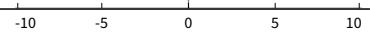


Analysis 6.2. Comparison 6 Changes of patient global assessment, Outcome 2 leflunomide vs. placebo, at 12 months.



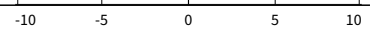
Analysis 6.3. Comparison 6 Changes of patient global assessment, Outcome 3 leflunomide vs. methotrexate, at 3 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	291	-3.6 (2)	213	-3.2 (2)		65.65%	-0.42[-0.78,-0.06]
Lao 2001	40	-2.5 (1.4)	40	-2.9 (1.4)		22.29%	0.4[-0.21,1.01]
Shuai 2002	40	-4.1 (2)	40	-3.7 (1.8)		12.07%	-0.4[-1.23,0.43]
Total ***	**371**		**293**			**100%**	**-0.23[-0.52,0.05]**
Heterogeneity: Tau^2=0; Chi^2=5.29, df=2(P=0.07); I^2=62.22%							
Test for overall effect: Z=1.59(P=0.11)							



Analysis 6.4. Comparison 6 Changes of patient global assessment, Outcome 4 leflunomide vs. methotrexate, at 4 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Reece 2002	18	-0.9 (0.9)	21	-1 (1.1)		100%	0.1[-0.53,0.73]
Total ***	**18**		**21**			**100%**	**0.1[-0.53,0.73]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.31(P=0.75)							

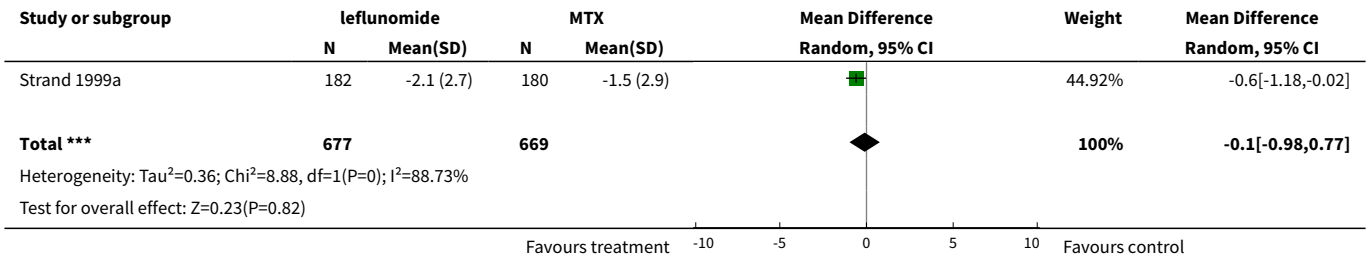


Analysis 6.5. Comparison 6 Changes of patient global assessment, Outcome 5 leflunomide vs. methotrexate, at 6 months.

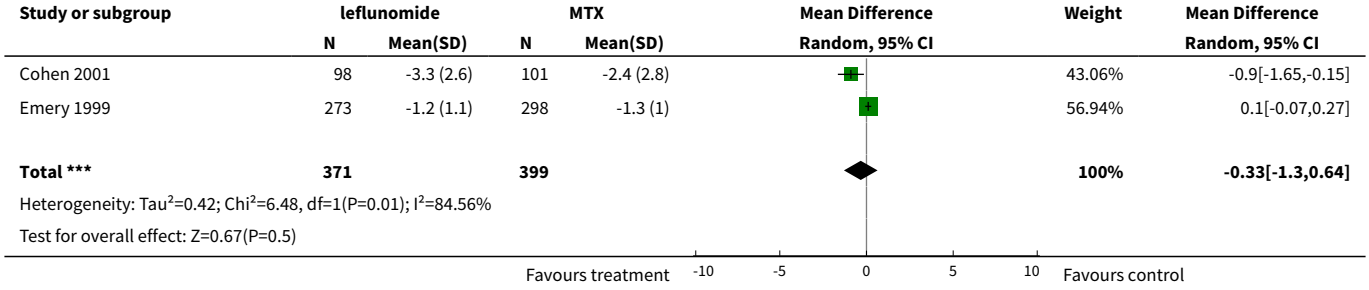
Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	104	-4.1 (2)	89	-3.5 (2.2)		33.29%	-0.52[-1.12,0.08]
Lao 2001	40	-4 (1.9)	40	-3.7 (2.1)		15.79%	-0.3[-1.18,0.58]
Shuai 2002	34	-4.8 (2.1)	34	-4 (2)		12.8%	-0.8[-1.77,0.17]
Strand 1999a	182	-2.2 (2.6)	180	-1.5 (2.9)		38.12%	-0.74[-1.3,-0.18]
Total ***	**360**		**343**			**100%**	**-0.6[-0.95,-0.26]**
Heterogeneity: Tau^2=0; Chi^2=0.91, df=3(P=0.82); I^2=0%							
Test for overall effect: Z=3.4(P=0)							

Analysis 6.6. Comparison 6 Changes of patient global assessment, Outcome 6 leflunomide vs. methotrexate, at 12 months.

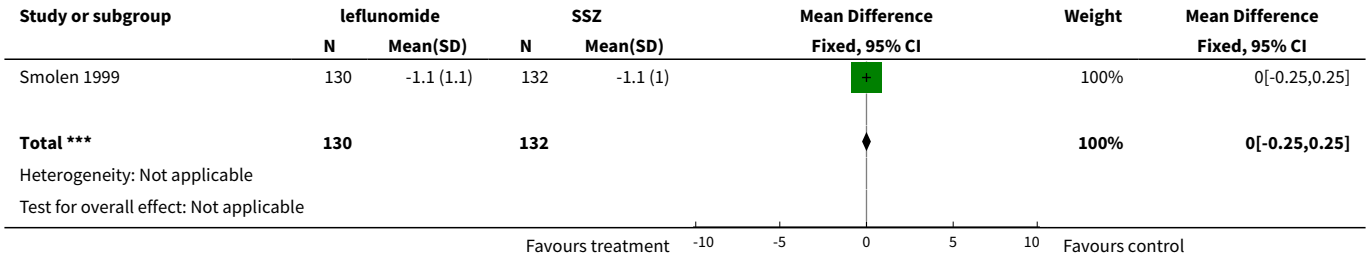
Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Emery 1999	495	-0.9 (1.1)	489	-1.2 (1)		55.08%	0.3[0.17,0.43]



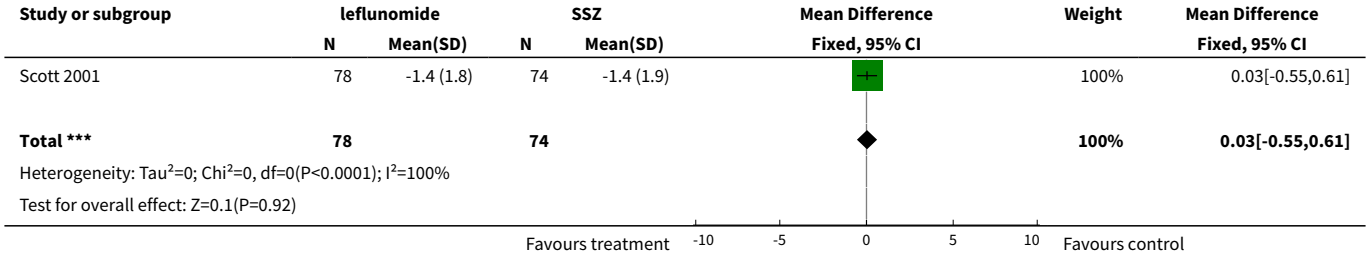
Analysis 6.7. Comparison 6 Changes of patient global assessment, Outcome 7 leflunomide vs. methotrexate, at 2 years.



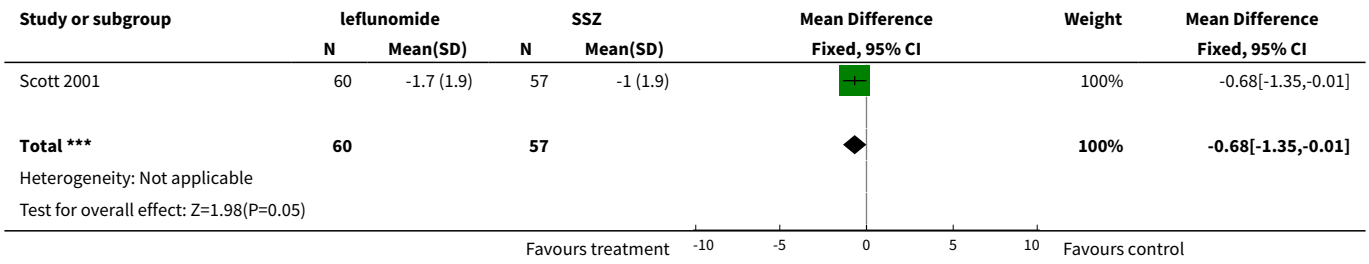
Analysis 6.8. Comparison 6 Changes of patient global assessment, Outcome 8 leflunomide vs. sulfasalazine, at 6 months.



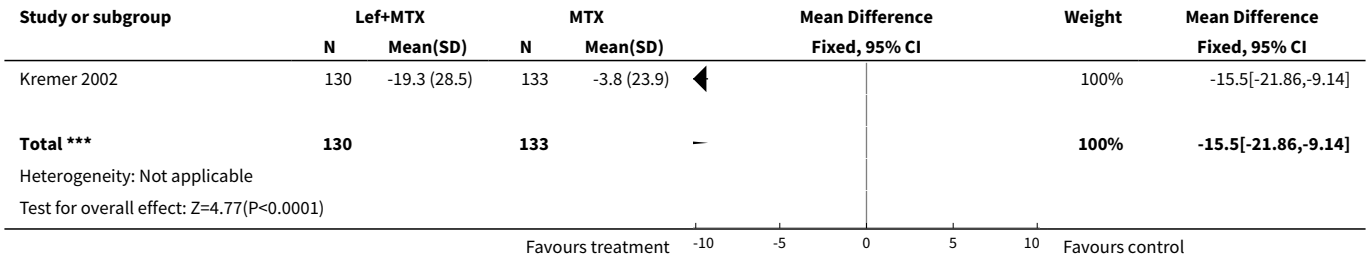
Analysis 6.9. Comparison 6 Changes of patient global assessment, Outcome 9 leflunomide vs. sulfasalazine, at 12 months.



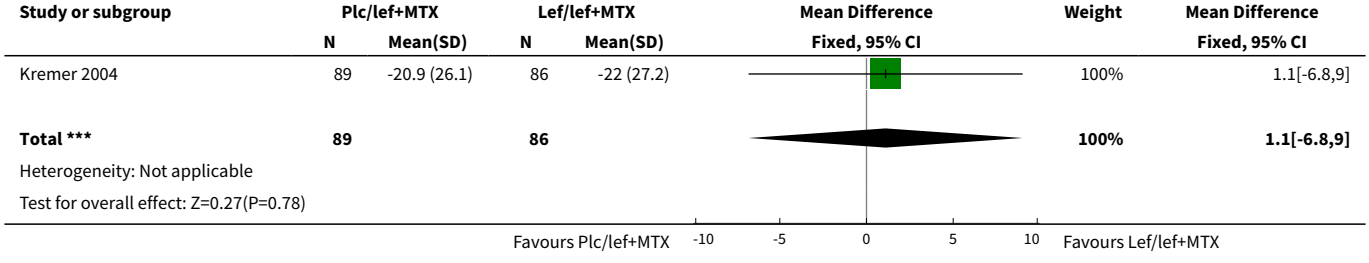
Analysis 6.10. Comparison 6 Changes of patient global assessment, Outcome 10 leflunomide vs. sulfasalazine, at 24 months.



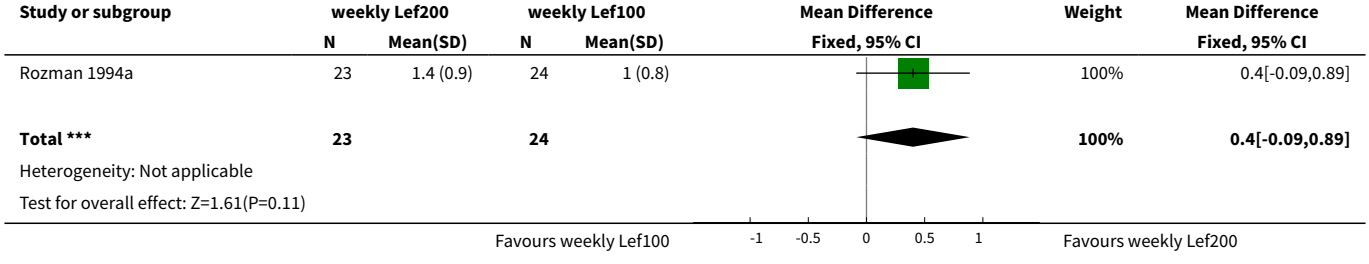
Analysis 6.11. Comparison 6 Changes of patient global assessment, Outcome 11 leflunomide+MTX vs MTX, at 24 weeks.



Analysis 6.12. Comparison 6 Changes of patient global assessment, Outcome 12 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 6.13. Comparison 6 Changes of patient global assessment, Outcome 13 weekly Lef100 vs. weekly Lef200, at 6 months.

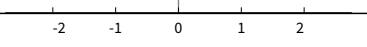


Comparison 7. Changes of physician global assessment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	3	724	Std. Mean Difference (IV, Fixed, 95% CI)	-0.67 [-0.82, -0.52]
2 leflunomide vs. placebo, at 12 months	1	300	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-2.41, -1.19]
3 leflunomide vs. methotrexate, at 3 months	3	664	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.56, 0.02]
4 leflunomide vs. methotrexate, at 4 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.67, 0.47]
5 leflunomide vs. methotrexate, at 6 months	4	703	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.82, -0.15]
6 leflunomide vs. methotrexate, at 12 months	2	1346	Mean Difference (IV, Random, 95% CI)	0.01 [-0.67, 0.68]
7 leflunomide vs. methotrexate, at 2 years	2	770	Mean Difference (IV, Random, 95% CI)	-0.14 [-1.11, 0.83]
8 leflunomide vs. sulfasalazine, at 6 months	1	262	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.32, 0.12]
9 leflunomide vs. sulfasalazine, at 12 months	1	152	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.70, 0.48]
10 leflunomide vs. sulfasalazine, at 24 months	1	117	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-1.37, -0.03]
11 leflunomide+MTX vs MTX, at 24 weeks	1	263	Mean Difference (IV, Fixed, 95% CI)	-17.10 [-22.71, -11.49]
12 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	175	Mean Difference (IV, Fixed, 95% CI)	4.40 [-2.11, 10.91]
13 weekly Lef100 vs. weekly Lef200, at 6 months	1	47	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.11, 0.91]

Analysis 7.1. Comparison 7 Changes of physician global assessment, Outcome 1 leflunomide vs. placebo, at 6 months.

Study or subgroup	leflunomide		placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Mladenovic 1995	101	-1.1 (1)	102	-0.6 (1)		29.56%	-0.5[-0.78,-0.22]
Smolen 1999	130	-1.1 (1)	91	-0.3 (1)		29.82%	-0.8[-1.08,-0.52]
Strand 1999a	182	-3 (2.5)	118	-1.2 (2.4)		40.62%	-0.7[-0.94,-0.46]



Favours treatment | Favours control

Study or subgroup	leflunomide N	leflunomide Mean(SD)	placebo N	placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Total ***	**413**		**311**			**100%**	**-0.67[-0.82,-0.52]**
Heterogeneity: Tau^2=0; Chi^2=2.31, df=2(P=0.32); I^2=13.39%							
Test for overall effect: Z=8.62(P<0.0001)							

Favours treatment -2 -1 0 1 2 Favours control

Analysis 7.2. Comparison 7 Changes of physician global assessment, Outcome 2 leflunomide vs. placebo, at 12 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Strand 1999a	182	-2.8 (2.8)	118	-1 (2.5)		100%	-1.8[-2.41,-1.19]
Total ***	**182**		**118**			**100%**	**-1.8[-2.41,-1.19]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=5.81(P<0.0001)							

Favours treatment -10 -5 0 5 10 Favours control

Analysis 7.3. Comparison 7 Changes of physician global assessment, Outcome 3 leflunomide vs. methotrexate, at 3 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	291	-3.6 (2)	213	-3.1 (2)		67.16%	-0.46[-0.82,-0.1]
Lao 2001	40	-2.4 (1.5)	40	-2.7 (1.4)		21.14%	0.3[-0.34,0.94]
Shuai 2002	40	-3.8 (1.9)	40	-3.6 (2)		11.7%	-0.2[-1.05,0.65]
Total ***	**371**		**293**			**100%**	**-0.27[-0.56,0.02]**
Heterogeneity: Tau^2=0; Chi^2=4.2, df=2(P=0.12); I^2=52.41%							
Test for overall effect: Z=1.8(P=0.07)							

Favours treatment -10 -5 0 5 10 Favours control

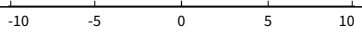
Analysis 7.4. Comparison 7 Changes of physician global assessment, Outcome 4 leflunomide vs. methotrexate, at 4 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Reece 2002	18	-0.9 (0.8)	21	-0.8 (1)		100%	-0.1[-0.67,0.47]
Total ***	**18**		**21**			**100%**	**-0.1[-0.67,0.47]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.35(P=0.73)							

Favours treatment -10 -5 0 5 10 Favours control

Analysis 7.5. Comparison 7 Changes of physician global assessment, Outcome 5 leflunomide vs. methotrexate, at 6 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	104	-4 (2)	89	-3.5 (2.2)		31.8%	-0.59[-1.19,0.01]
Lao 2001	40	-3.7 (1.9)	40	-3.5 (2)		15.42%	-0.2[-1.05,0.65]
Shuai 2002	34	-4.5 (2.1)	34	-3.9 (1.9)		12.44%	-0.6[-1.55,0.35]
Strand 1999a	182	-3 (2.5)	180	-2.5 (2.6)		40.34%	-0.47[-1,0.06]
Total ***	**360**		**343**			**100%**	**-0.48[-0.82,-0.15]**
Heterogeneity: Tau^2=0; Chi^2=0.61, df=3(P=0.9); I^2=0%							
Test for overall effect: Z=2.82(P=0)							



Analysis 7.6. Comparison 7 Changes of physician global assessment, Outcome 6 leflunomide vs. methotrexate, at 12 months.

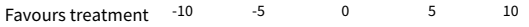
Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Emery 1999	495	-0.9 (1)	489	-1.2 (1)		58.11%	0.3[0.18,0.42]
Strand 1999a	182	-2.8 (2.8)	180	-2.4 (2.7)		41.89%	-0.4[-0.97,0.17]
Total ***	**677**		**669**			**100%**	**0.01[-0.67,0.68]**
Heterogeneity: Tau^2=0.2; Chi^2=5.59, df=1(P=0.02); I^2=82.11%							
Test for overall effect: Z=0.02(P=0.98)							

Analysis 7.7. Comparison 7 Changes of physician global assessment, Outcome 7 leflunomide vs. methotrexate, at 2 years.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cohen 2001	98	-4.1 (2.4)	101	-3.4 (2.7)		43.84%	-0.7[-1.41,0.01]
Emery 1999	273	-1.1 (1.1)	298	-1.4 (1)		56.16%	0.3[0.13,0.47]
Total ***	**371**		**399**			**100%**	**-0.14[-1.11,0.83]**
Heterogeneity: Tau^2=0.43; Chi^2=7.21, df=1(P=0.01); I^2=86.13%							
Test for overall effect: Z=0.28(P=0.78)							

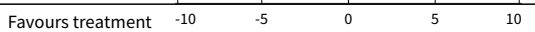
Analysis 7.8. Comparison 7 Changes of physician global assessment, Outcome 8 leflunomide vs. sulfasalazine, at 6 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Smolen 1999	130	-1.1 (1)	132	-1 (0.8)		100%	-0.1[-0.32,0.12]
Total ***	**130**		**132**			**100%**	**-0.1[-0.32,0.12]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.89(P=0.37)							



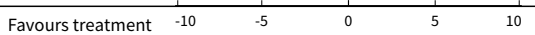
Analysis 7.9. Comparison 7 Changes of physician global assessment, Outcome 9 leflunomide vs. sulfasalazine, at 12 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Scott 2001	78	-1.4 (1.9)	74	-1.3 (1.9)		100%	-0.11[-0.7,0.48]
Total ***	**78**		**74**			**100%**	**-0.11[-0.7,0.48]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.37(P=0.71)							



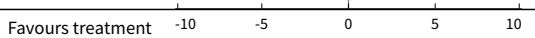
Analysis 7.10. Comparison 7 Changes of physician global assessment, Outcome 10 leflunomide vs. sulfasalazine, at 24 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Scott 2001	60	-1.8 (1.8)	57	-1.1 (1.9)		100%	-0.7[-1.37,-0.03]
Total ***	**60**		**57**			**100%**	**-0.7[-1.37,-0.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.05(P=0.04)							

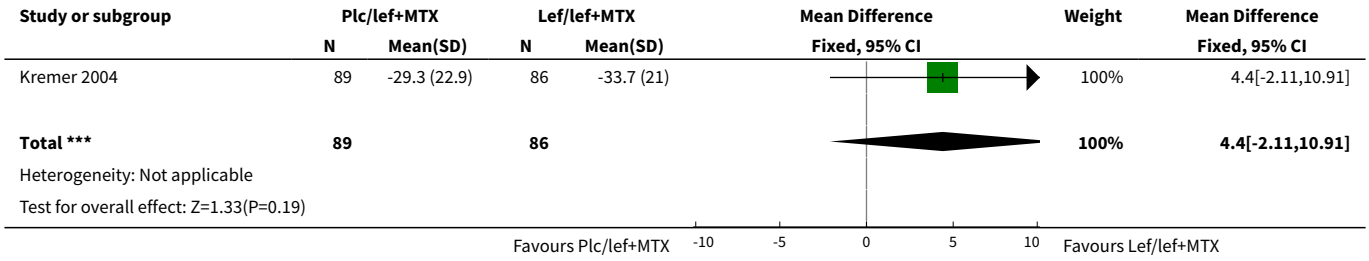


Analysis 7.11. Comparison 7 Changes of physician global assessment, Outcome 11 leflunomide+MTX vs MTX, at 24 weeks.

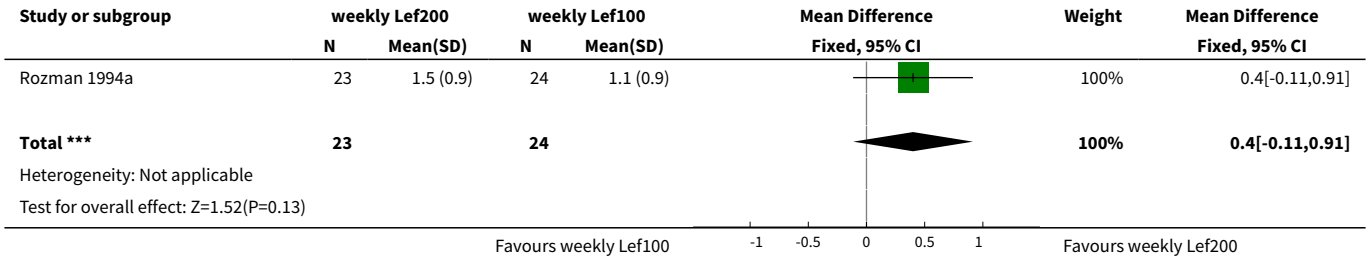
Study or subgroup	Lef+MTX N	Lef+MTX Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kremer 2002	130	-27.9 (23.1)	133	-10.8 (23.3)		100%	-17.1[-22.71,-11.49]
Total ***	**130**		**133**			**100%**	**-17.1[-22.71,-11.49]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.97(P<0.0001)							



Analysis 7.12. Comparison 7 Changes of physician global assessment, Outcome 12 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 7.13. Comparison 7 Changes of physician global assessment, Outcome 13 weekly Lef100 vs. weekly Lef200, at 6 months.



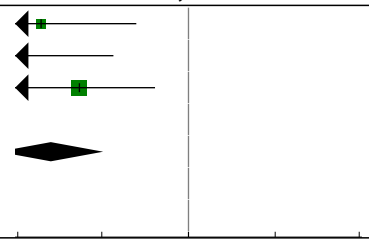
Comparison 8. Changes of ESR (mm/hr)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	3	724	Mean Difference (IV, Fixed, 95% CI)	-7.94 [-10.96, -4.92]
2 leflunomide vs. placebo, at 12 months	1	300	Mean Difference (IV, Fixed, 95% CI)	-8.9 [-13.68, -4.12]
3 leflunomide vs. methotrexate, at 3 months	3	664	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-3.24, 2.71]
4 leflunomide vs. methotrexate, at 4 months	1	39	Mean Difference (IV, Fixed, 95% CI)	8.3 [-4.38, 20.98]
5 leflunomide vs. methotrexate, at 6 months	5	763	Mean Difference (IV, Fixed, 95% CI)	1.54 [-1.41, 4.48]
6 leflunomide vs. methotrexate, at 12 months	2	910	Mean Difference (IV, Random, 95% CI)	7.05 [-6.28, 20.37]
7 leflunomide vs. methotrexate, at 2 years	2	747	Mean Difference (IV, Random, 95% CI)	7.51 [-3.74, 18.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 leflunomide vs. sulfasalazine, at 6 months	1	261	Mean Difference (IV, Fixed, 95% CI)	9.20 [3.47, 14.93]
9 leflunomide vs. sulfasalazine, at 12 months	1	150	Mean Difference (IV, Fixed, 95% CI)	8.1 [-0.13, 16.33]
10 leflunomide vs. sulfasalazine, at 24 months	1	114	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-11.03, 8.83]
11 leflunomide+MTX vs MTX, at 24 weeks	1	263	Mean Difference (IV, Fixed, 95% CI)	0.80 [-4.31, 5.91]
12 leflunomide+SSZ vs. placebo+SSZ, at 24 months	1	106	Mean Difference (IV, Fixed, 95% CI)	0.54 [-8.44, 9.52]
13 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	178	Mean Difference (IV, Fixed, 95% CI)	-2.4 [-9.29, 4.49]
14 leflunomide vs. anti-TNF+MTX, at 24 weeks	1	48	Mean Difference (IV, Fixed, 95% CI)	13.0 [-2.19, 28.19]

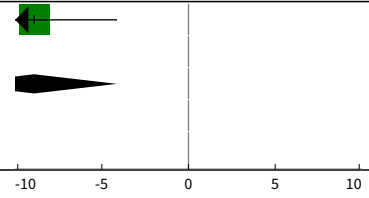
Analysis 8.1. Comparison 8 Changes of ESR (mm/hr), Outcome 1 leflunomide vs. placebo, at 6 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Mladenovic 1995	101	-5.4 (19.3)	102	3.1 (20.6)		30.25%	-8.5[-13.99,-3.01]
Smolen 1999	130	-7.4 (23.2)	91	3.4 (24.8)		21.78%	-10.8[-17.27,-4.33]
Strand 1999a	182	-5.3 (20.1)	118	1 (18)		47.97%	-6.29[-10.65,-1.93]
Total ***	**413**		**311**			**100%**	**-7.94[-10.96,-4.92]**
Heterogeneity: Tau²=0; Chi²=1.34, df=2(P=0.51); I²=0%							
Test for overall effect: Z=5.15(P<0.0001)							



Analysis 8.2. Comparison 8 Changes of ESR (mm/hr), Outcome 2 leflunomide vs. placebo, at 12 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Strand 1999a	182	-6.3 (22.9)	118	2.6 (19)		100%	-8.9[-13.68,-4.12]
Total ***	**182**		**118**			**100%**	**-8.9[-13.68,-4.12]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.65(P=0)							



Analysis 8.3. Comparison 8 Changes of ESR (mm/hr), Outcome 3 leflunomide vs. methotrexate, at 3 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	291	-20.1 (19.9)	213	-19.2 (19.9)		71.69%	-0.9[-4.42,2.62]
Lao 2001	40	-19.7 (16.4)	40	-21 (19)		14.65%	1.3[-6.48,9.08]
Shuai 2002	40	-20.3 (19.4)	40	-21.7 (17.3)		13.66%	1.4[-6.66,9.46]
Total ***	**371**		**293**			**100%**	**-0.26[-3.24,2.71]**
Heterogeneity: Tau²=0; Chi²=0.44, df=2(P=0.8); I²=0%							
Test for overall effect: Z=0.17(P=0.86)							

Favours treatment Favours control

Analysis 8.4. Comparison 8 Changes of ESR (mm/hr), Outcome 4 leflunomide vs. methotrexate, at 4 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Reece 2002	18	-3.3 (18.3)	21	-11.6 (22.1)		100%	8.3[-4.38,20.98]
Total ***	**18**		**21**			**100%**	**8.3[-4.38,20.98]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.28(P=0.2)							

Favours treatment Favours control

Analysis 8.5. Comparison 8 Changes of ESR (mm/hr), Outcome 5 leflunomide vs. methotrexate, at 6 months.

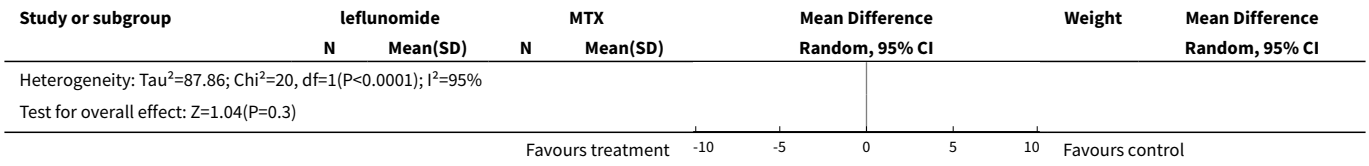
Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	104	-18.6 (20.4)	89	-22 (21.1)		25.09%	3.4[-2.48,9.28]
Lao 2001	40	-24 (19.6)	40	-30 (21)		10.93%	6[-2.9,14.9]
Shuai 2002	34	-25.9 (22.7)	34	-26.7 (20.2)		8.3%	0.8[-9.41,11.01]
Strand 1999a	182	-5.3 (20.1)	180	-5.4 (20.4)		49.85%	0.04[-4.13,4.21]
Wislowska 2007	30	-41 (26)	30	-40 (22)		5.83%	-1[-13.19,11.19]
Total ***	**390**		**373**			**100%**	**1.54[-1.41,4.48]**
Heterogeneity: Tau²=0; Chi²=2.03, df=4(P=0.73); I²=0%							
Test for overall effect: Z=1.02(P=0.31)							

Favours treatment Favours control

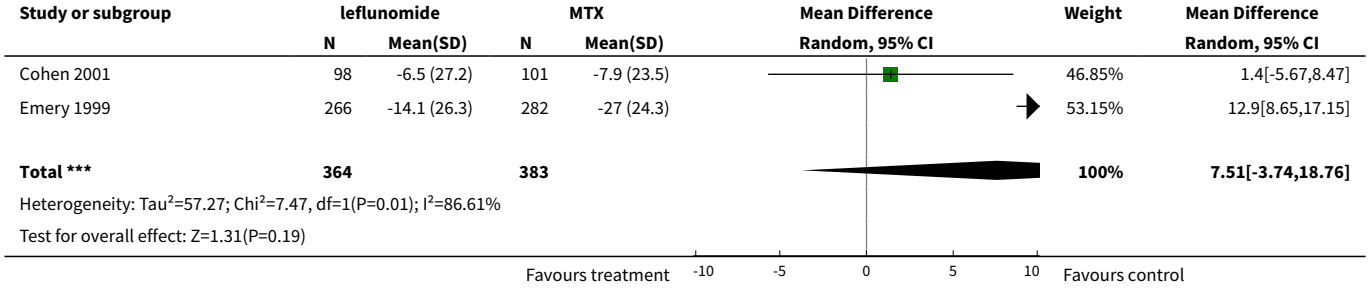
Analysis 8.6. Comparison 8 Changes of ESR (mm/hr), Outcome 6 leflunomide vs. methotrexate, at 12 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Emery 1999	266	-14.4 (24.1)	282	-28.2 (22.7)		50.33%	13.8[9.87,17.73]
Strand 1999a	182	-6.3 (22.9)	180	-6.5 (20.6)		49.67%	0.2[-4.29,4.69]
Total ***	**448**		**462**			**100%**	**7.05[-6.28,20.37]**

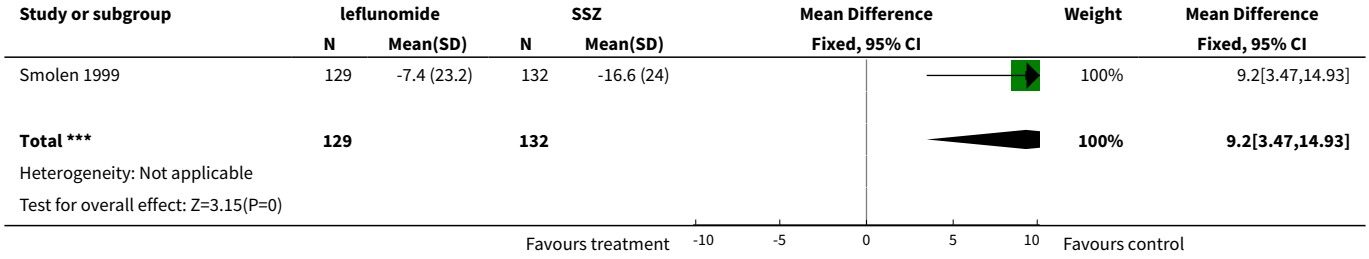
Favours treatment Favours control



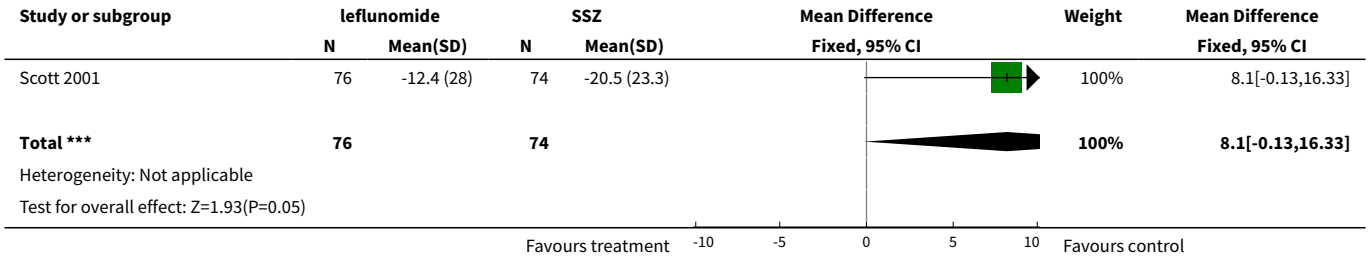
Analysis 8.7. Comparison 8 Changes of ESR (mm/hr), Outcome 7 leflunomide vs. methotrexate, at 2 years.



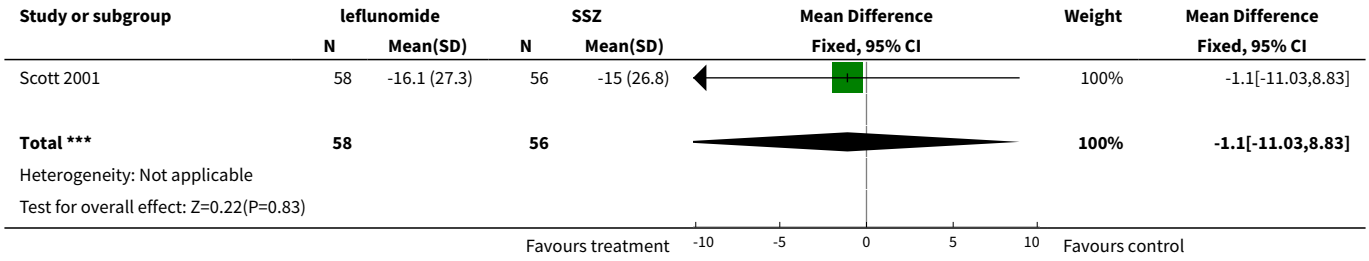
Analysis 8.8. Comparison 8 Changes of ESR (mm/hr), Outcome 8 leflunomide vs. sulfasalazine, at 6 months.



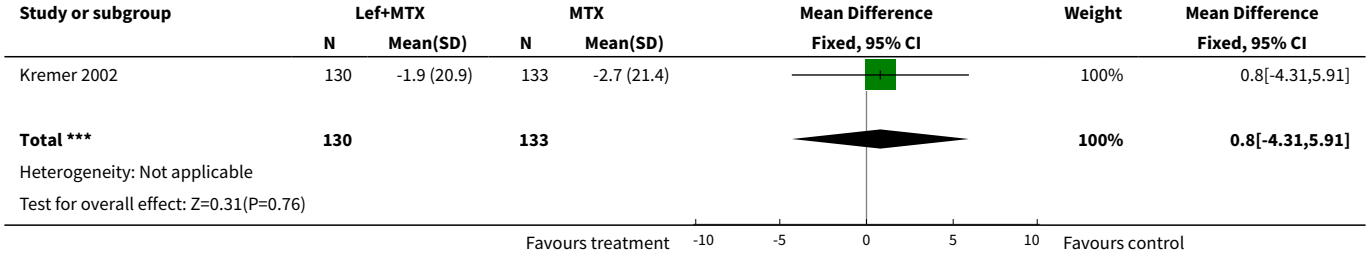
Analysis 8.9. Comparison 8 Changes of ESR (mm/hr), Outcome 9 leflunomide vs. sulfasalazine, at 12 months.



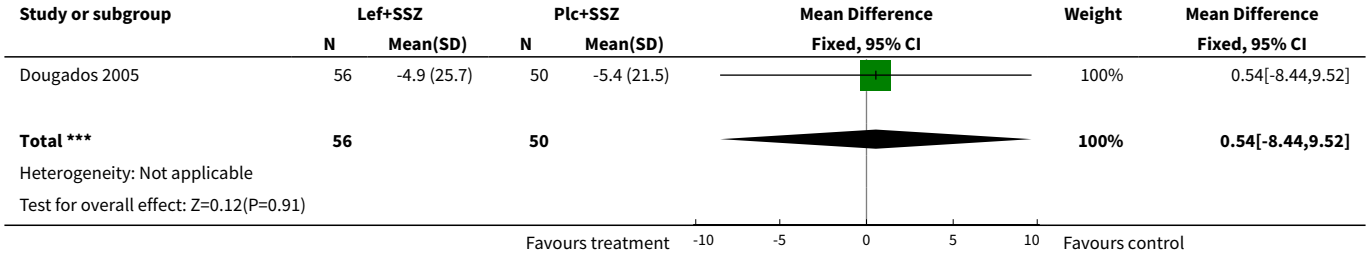
Analysis 8.10. Comparison 8 Changes of ESR (mm/hr), Outcome 10 leflunomide vs. sulfasalazine, at 24 months.



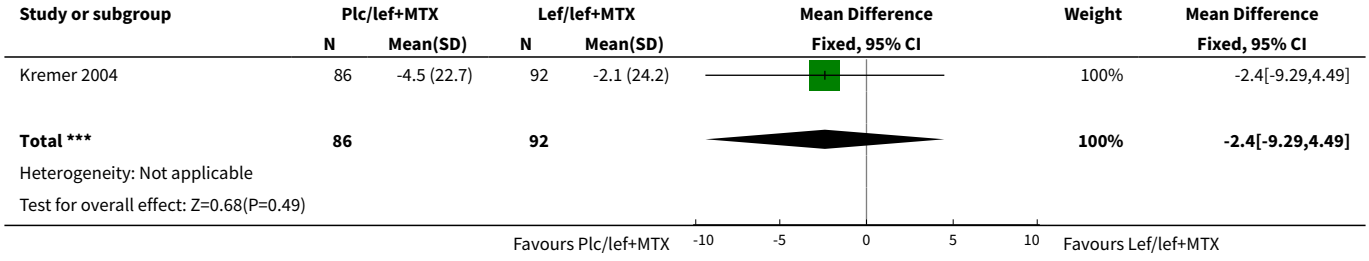
Analysis 8.11. Comparison 8 Changes of ESR (mm/hr), Outcome 11 leflunomide+MTX vs MTX, at 24 weeks.



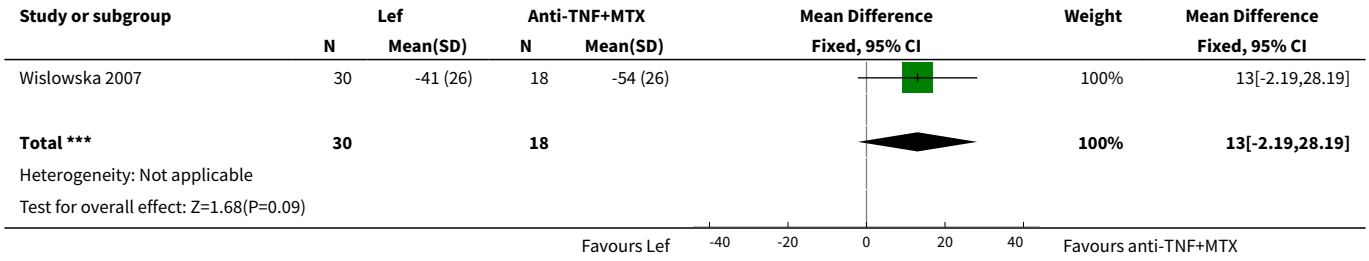
Analysis 8.12. Comparison 8 Changes of ESR (mm/hr), Outcome 12 leflunomide+SSZ vs. placebo+SSZ, at 24 months.



Analysis 8.13. Comparison 8 Changes of ESR (mm/hr), Outcome 13 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



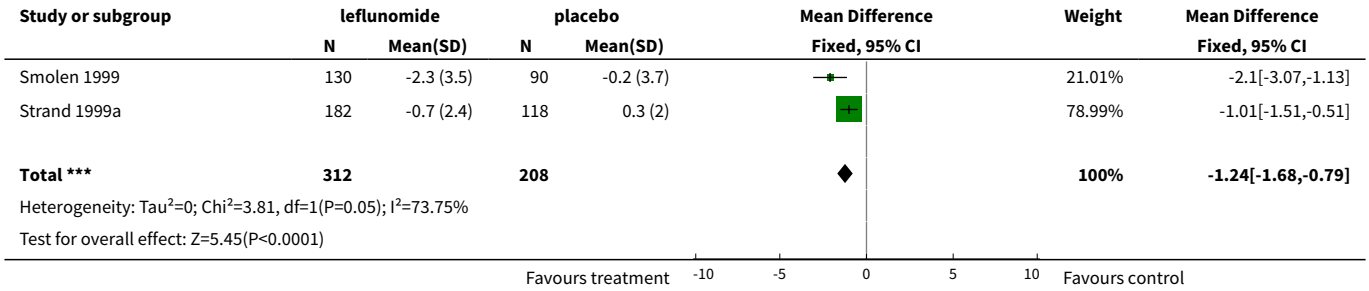
Analysis 8.14. Comparison 8 Changes of ESR (mm/hr), Outcome 14 leflunomide vs. anti-TNF+MTX, at 24 weeks.



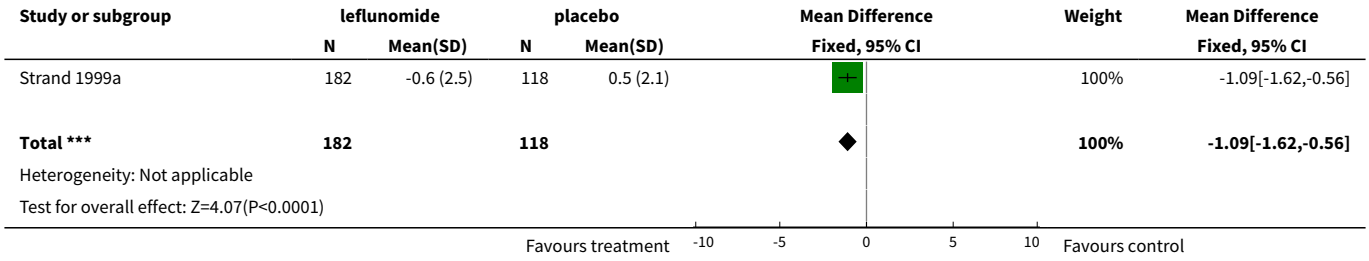
Comparison 9. Changes of CRP (mg/dl)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	2	520	Mean Difference (IV, Fixed, 95% CI)	-1.24 [-1.68, -0.79]
2 leflunomide vs. placebo, at 12 months	1	300	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-1.62, -0.56]
3 leflunomide vs. methotrexate, at 3 months	3	664	Mean Difference (IV, Fixed, 95% CI)	-3.02 [-5.94, -0.09]
4 leflunomide vs. methotrexate, at 4 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-3.00 [-22.42, 16.42]
5 leflunomide vs. methotrexate, at 6 months	4	703	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.60, 0.25]
6 leflunomide vs. methotrexate, at 12 months	2	907	Mean Difference (IV, Random, 95% CI)	0.62 [-0.30, 1.54]
7 leflunomide vs. methotrexate, at 2 years	2	744	Mean Difference (IV, Random, 95% CI)	-0.48 [-3.67, 2.72]
8 leflunomide vs. sulfasalazine, at 6 months	1	260	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.98, -0.42]
9 leflunomide vs. sulfasalazine, at 12 months	1	150	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-2.17, -0.03]
10 leflunomide vs. sulfasalazine, at 24 months	1	111	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.77, -0.03]
11 leflunomide+MTX vs MTX, at 24 weeks	1	263	Mean Difference (IV, Fixed, 95% CI)	-12.1 [-19.84, -4.36]
12 leflunomide+SSZ vs. placebo+SSZ, at 24 months	1	106	Mean Difference (IV, Fixed, 95% CI)	-8.15 [-18.64, 2.34]
13 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	179	Mean Difference (IV, Fixed, 95% CI)	5.0 [-3.52, 13.52]

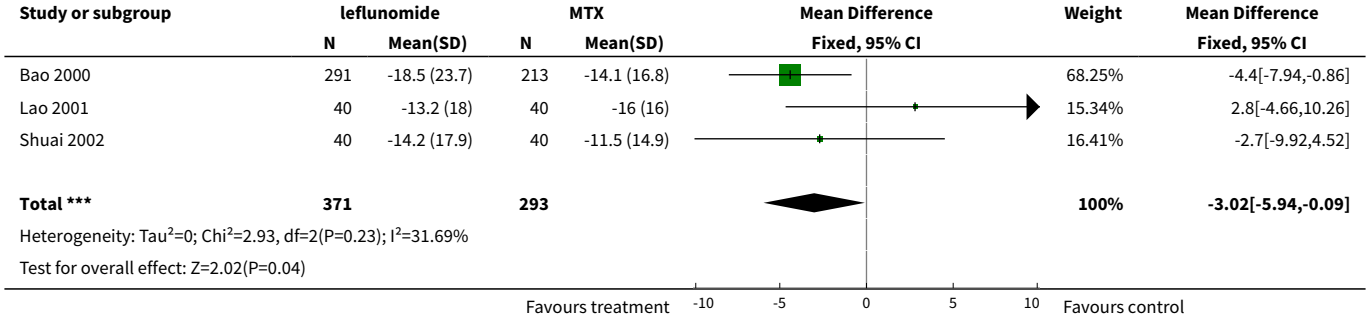
Analysis 9.1. Comparison 9 Changes of CRP (mg/dl), Outcome 1 leflunomide vs. placebo, at 6 months.



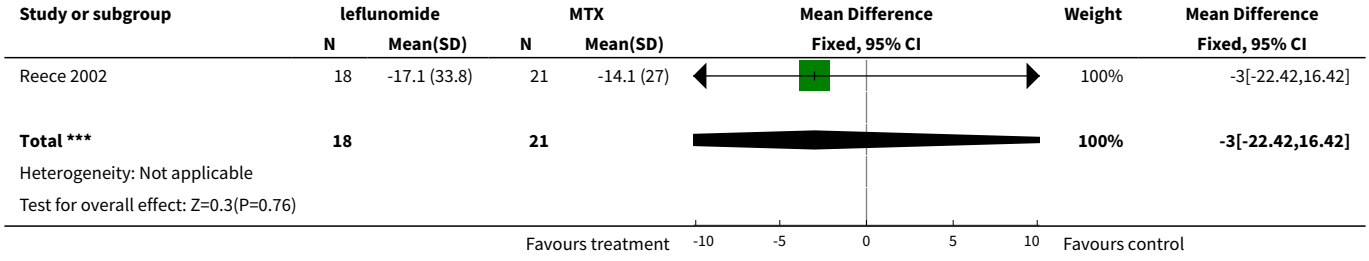
Analysis 9.2. Comparison 9 Changes of CRP (mg/dl), Outcome 2 leflunomide vs. placebo, at 12 months.



Analysis 9.3. Comparison 9 Changes of CRP (mg/dl), Outcome 3 leflunomide vs. methotrexate, at 3 months.

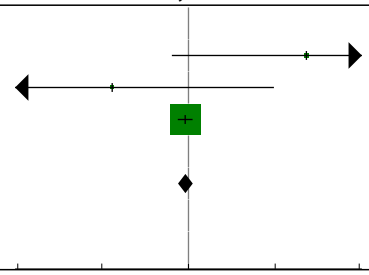


Analysis 9.4. Comparison 9 Changes of CRP (mg/dl), Outcome 4 leflunomide vs. methotrexate, at 4 months.



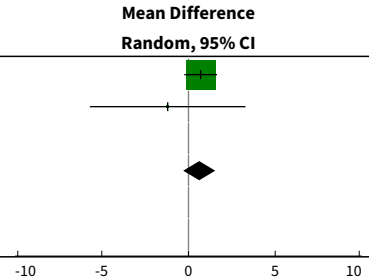
Analysis 9.5. Comparison 9 Changes of CRP (mg/dl), Outcome 5 leflunomide vs. methotrexate, at 6 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	104	-14.6 (21)	89	0 (0)			Not estimable
Lao 2001	40	-13.2 (17.4)	40	-20 (18)		0.3%	6.8[-0.96,14.56]
Shuai 2002	34	-19.8 (21.2)	34	-15.4 (17.9)		0.21%	-4.4[-13.73,4.93]
Strand 1999a	182	-0.7 (2.4)	180	-0.5 (1.7)		99.49%	-0.19[-0.62,0.24]
Total ***	**360**		**343**			**100%**	**-0.18[-0.6,0.25]**
Heterogeneity: Tau^2=0; Chi^2=3.9, df=2(P=0.14); I^2=48.69%							
Test for overall effect: Z=0.82(P=0.41)							



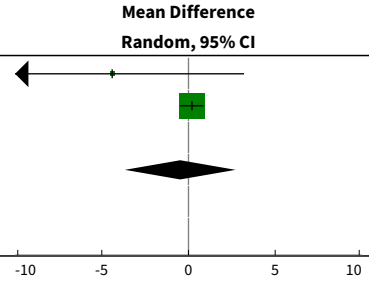
Analysis 9.6. Comparison 9 Changes of CRP (mg/dl), Outcome 6 leflunomide vs. methotrexate, at 12 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Emery 1999	260	-2.2 (6.9)	285	-2.9 (3.7)		95.78%	0.7[-0.24,1.64]
Strand 1999a	182	-6.2 (24.5)	180	-5 (18.7)		4.22%	-1.2[-5.69,3.29]
Total ***	**442**		**465**			**100%**	**0.62[-0.3,1.54]**
Heterogeneity: Tau^2=0; Chi^2=0.66, df=1(P=0.42); I^2=0%							
Test for overall effect: Z=1.32(P=0.19)							



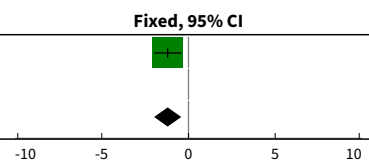
Analysis 9.7. Comparison 9 Changes of CRP (mg/dl), Outcome 7 leflunomide vs. methotrexate, at 2 years.

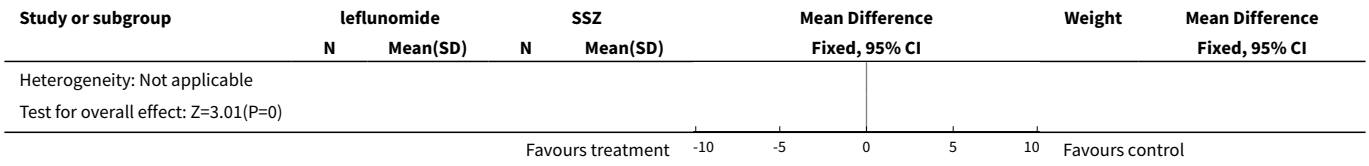
Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cohen 2001	98	-9.8 (27.9)	101	-5.4 (26.8)		14.71%	-4.4[-12,3.2]
Emery 1999	260	-2.6 (4.2)	285	-2.8 (3.8)		85.29%	0.2[-0.47,0.87]
Total ***	**358**		**386**			**100%**	**-0.48[-3.67,2.72]**
Heterogeneity: Tau^2=2.99; Chi^2=1.39, df=1(P=0.24); I^2=28.3%							
Test for overall effect: Z=0.29(P=0.77)							



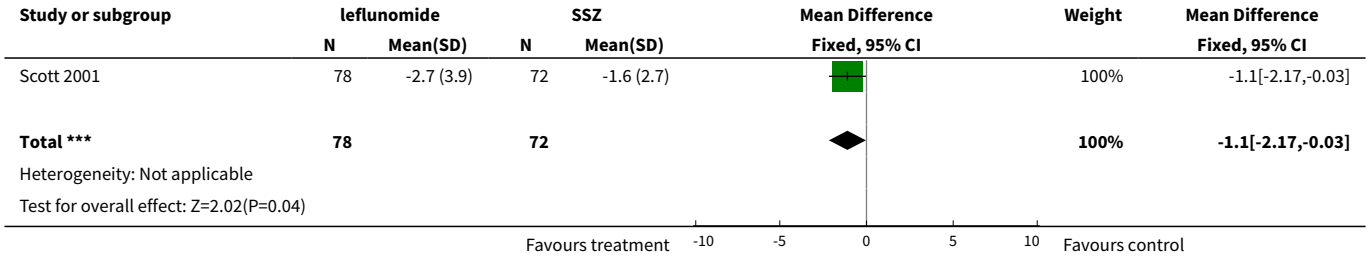
Analysis 9.8. Comparison 9 Changes of CRP (mg/dl), Outcome 8 leflunomide vs. sulfasalazine, at 6 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Smolen 1999	130	-2.3 (3.5)	130	-1.1 (2.9)		100%	-1.2[-1.98,-0.42]
Total ***	**130**		**130**			**100%**	**-1.2[-1.98,-0.42]**

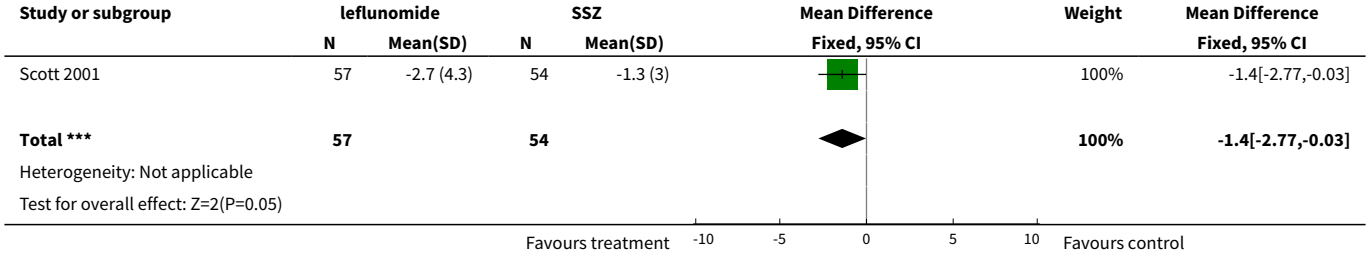




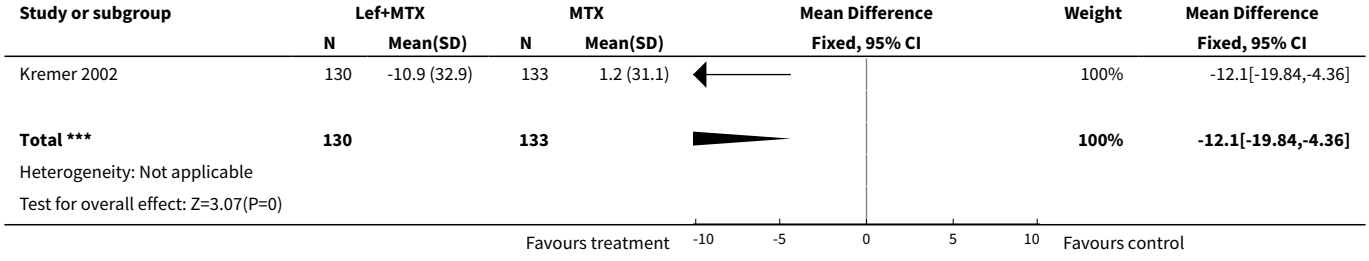
Analysis 9.9. Comparison 9 Changes of CRP (mg/dl), Outcome 9 leflunomide vs. sulfasalazine, at 12 months.



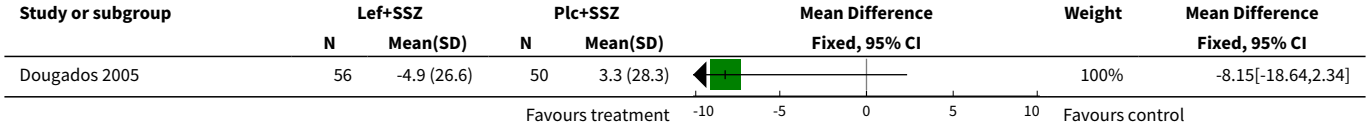
Analysis 9.10. Comparison 9 Changes of CRP (mg/dl), Outcome 10 leflunomide vs. sulfasalazine, at 24 months.

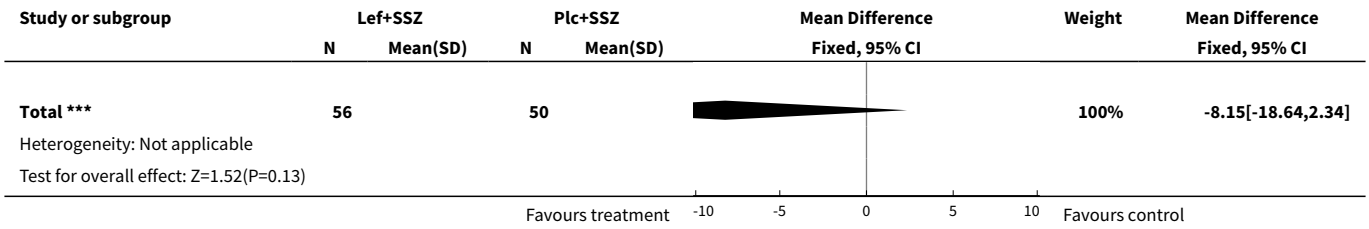


Analysis 9.11. Comparison 9 Changes of CRP (mg/dl), Outcome 11 leflunomide+MTX vs MTX, at 24 weeks.

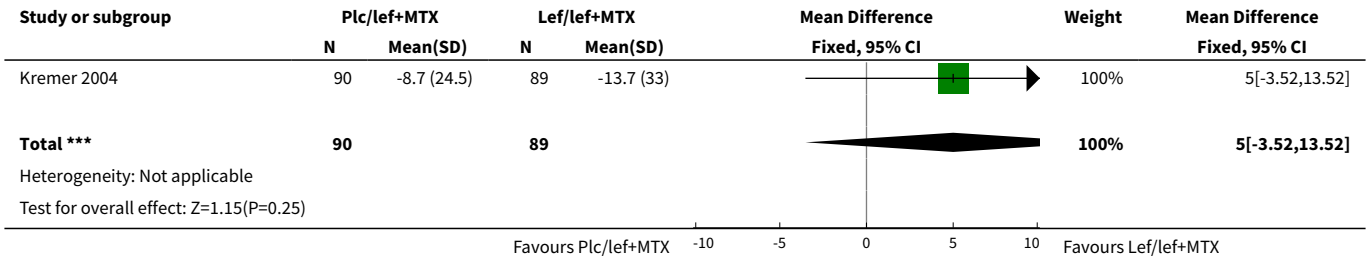


Analysis 9.12. Comparison 9 Changes of CRP (mg/dl), Outcome 12 leflunomide+SSZ vs. placebo+SSZ, at 24 months.





Analysis 9.13. Comparison 9 Changes of CRP (mg/dl), Outcome 13 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Comparison 10. Changes of pain (VAS, mm)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	3	724	Mean Difference (IV, Fixed, 95% CI)	-13.81 [-15.91, -11.71]
2 leflunomide vs. placebo, at 12 months	1	300	Mean Difference (IV, Fixed, 95% CI)	-18.0 [-24.04, -11.96]
3 leflunomide vs. methotrexate, at 3 months	3	664	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.44, 0.17]
4 leflunomide vs. methotrexate, at 4 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-6.1 [-20.22, 8.02]
5 leflunomide vs. methotrexate, at 6 months	5	763	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.78, 0.15]
6 leflunomide vs. methotrexate, at 12 months	2	932	Mean Difference (IV, Random, 95% CI)	5.31 [-6.44, 17.07]
7 leflunomide vs. methotrexate, at 2 years	2	769	Mean Difference (IV, Random, 95% CI)	-1.80 [-15.21, 11.61]
8 leflunomide vs. sulfasalazine, at 6 months	1	262	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-14.21, -0.79]
9 leflunomide vs. sulfasalazine, at 12 months	1	151	Mean Difference (IV, Fixed, 95% CI)	-11.40 [-20.35, -2.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 leflunomide vs. sulfasalazine, at 24 months	1	117	Mean Difference (IV, Fixed, 95% CI)	-15.10 [-25.16, -5.04]
11 leflunomide+MTX vs MTX, at 24 weeks	1	263	Mean Difference (IV, Fixed, 95% CI)	-16.9 [-23.70, -10.10]
12 leflunomide+SSZ vs. placebo+SSZ, at 24 months	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.89 [-9.77, 7.99]
13 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	175	Mean Difference (IV, Fixed, 95% CI)	0.30 [-7.63, 8.23]
14 leflunomide vs. anti-TNF+MTX, at 24 weeks	1	48	Mean Difference (IV, Fixed, 95% CI)	11.0 [1.29, 20.71]

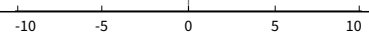
Analysis 10.1. Comparison 10 Changes of pain (VAS, mm), Outcome 1 leflunomide vs. placebo, at 6 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Mladenovic 1995	101	-10 (8.1)	102	3 (9)		79.53%	-13[-15.35,-10.65]
Smolen 1999	130	-27.3 (29.7)	91	-8.8 (29.9)		6.91%	-18.5[-26.49,-10.51]
Strand 1999a	182	-23 (26)	118	-6.8 (23.7)		13.56%	-16.2[-21.9,-10.5]
Total ***	**413**		**311**			**100%**	**-13.81[-15.91,-11.71]**
Heterogeneity: Tau^2=0; Chi^2=2.45, df=2(P=0.29); I^2=18.48%							
Test for overall effect: Z=12.89(P<0.0001)							

Favours treatment — Favours control

Analysis 10.2. Comparison 10 Changes of pain (VAS, mm), Outcome 2 leflunomide vs. placebo, at 12 months.

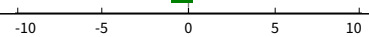
Study or subgroup	leflunomide N	leflunomide Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Strand 1999a	182	-22 (29)	118	-4 (24)		100%	-18[-24.04,-11.96]
Total ***	**182**		**118**			**100%**	**-18[-24.04,-11.96]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.84(P<0.0001)							



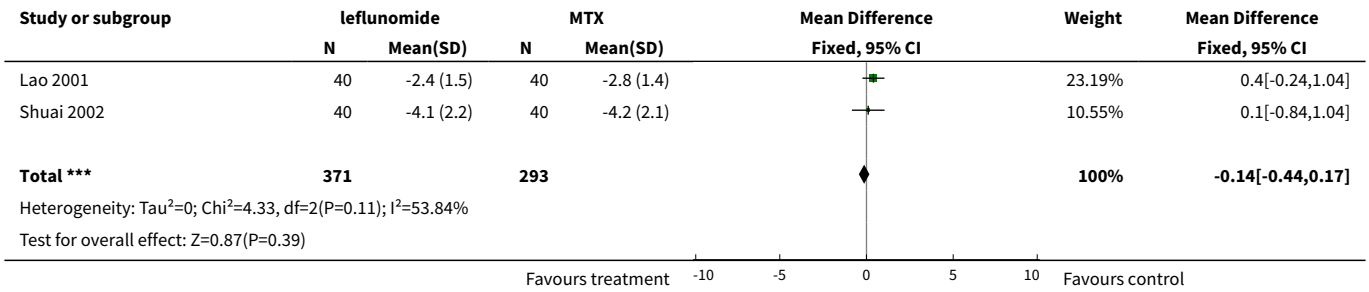
Favours treatment — Favours control

Analysis 10.3. Comparison 10 Changes of pain (VAS, mm), Outcome 3 leflunomide vs. methotrexate, at 3 months.

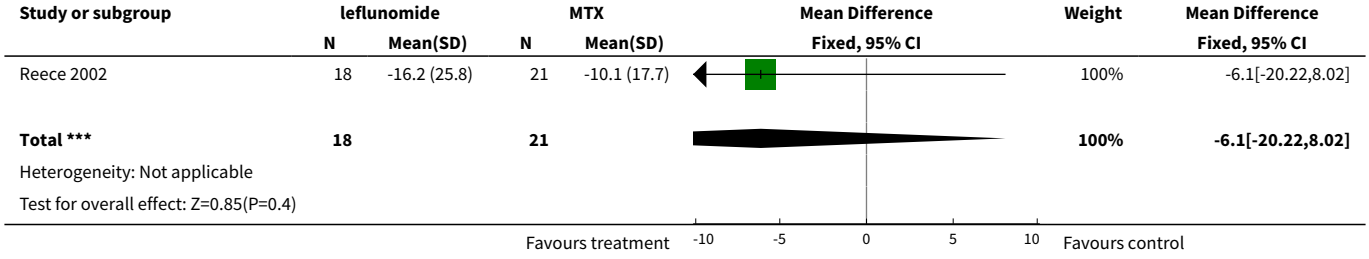
Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bao 2000	291	-3.7 (2.1)	213	-3.4 (2.1)		66.26%	-0.36[-0.74,0.02]



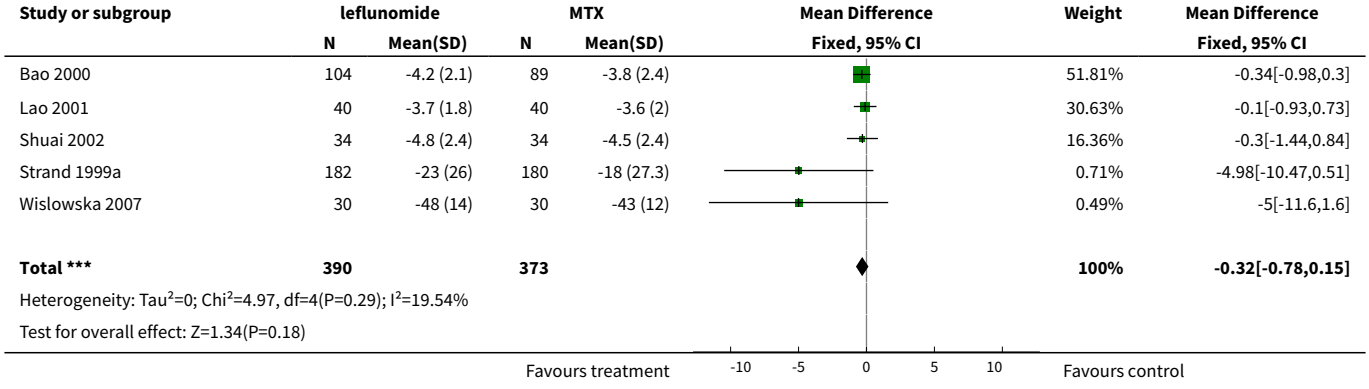
Favours treatment — Favours control



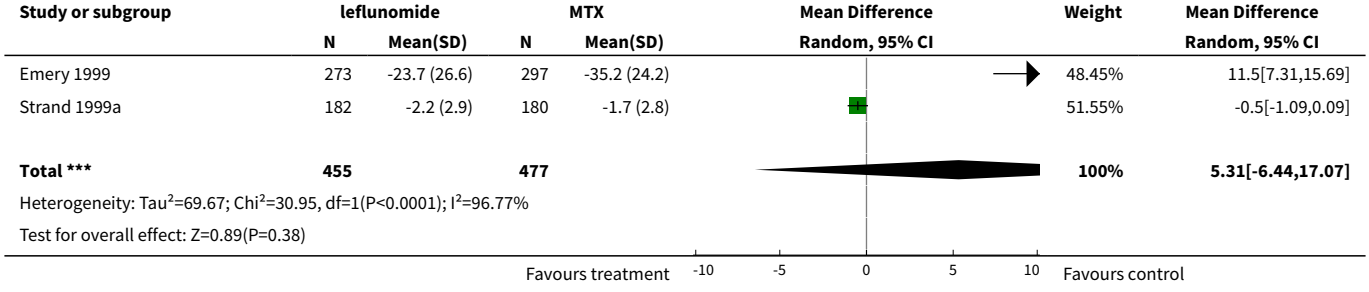
Analysis 10.4. Comparison 10 Changes of pain (VAS, mm), Outcome 4 leflunomide vs. methotrexate, at 4 months.



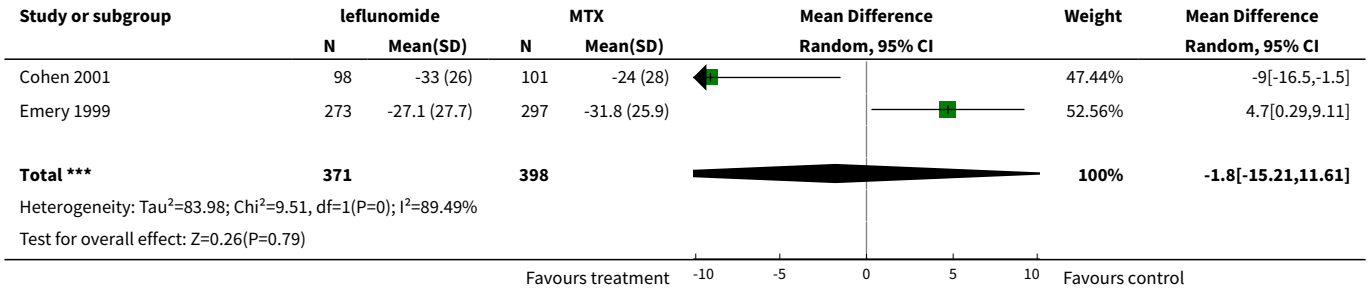
Analysis 10.5. Comparison 10 Changes of pain (VAS, mm), Outcome 5 leflunomide vs. methotrexate, at 6 months.



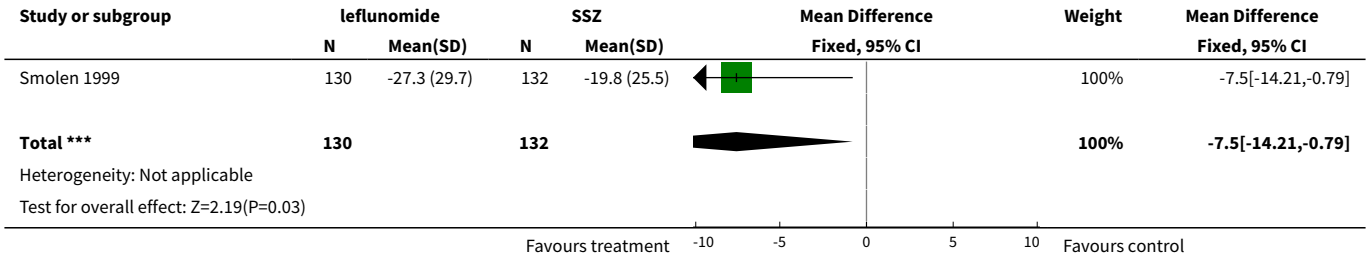
Analysis 10.6. Comparison 10 Changes of pain (VAS, mm), Outcome 6 leflunomide vs. methotrexate, at 12 months.



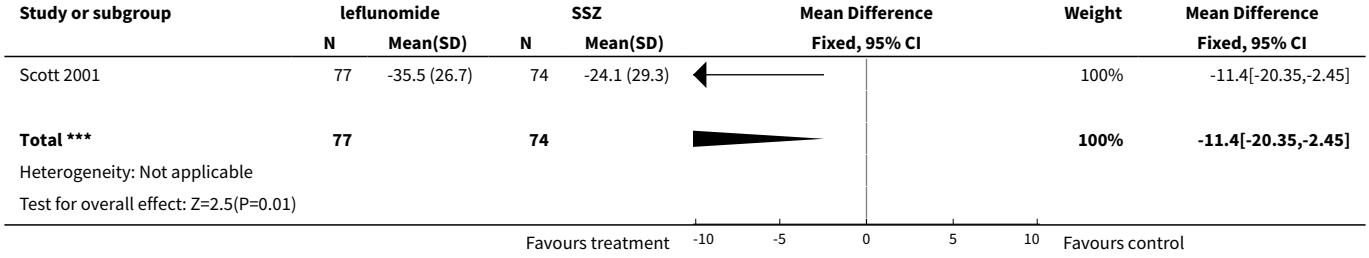
Analysis 10.7. Comparison 10 Changes of pain (VAS, mm), Outcome 7 leflunomide vs. methotrexate, at 2 years.



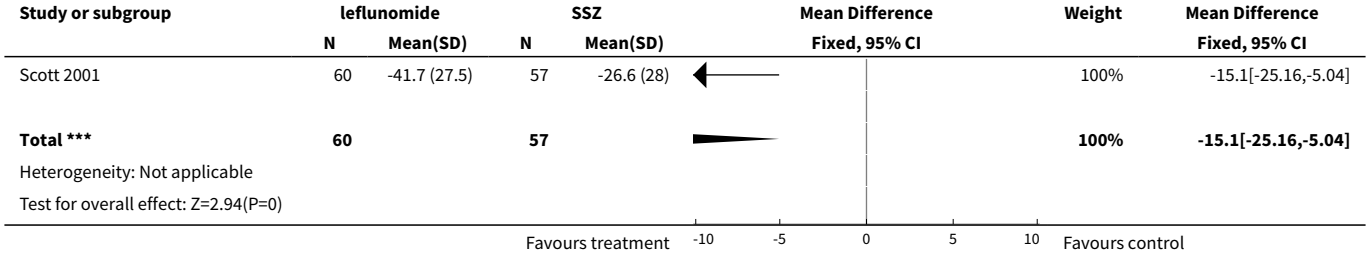
Analysis 10.8. Comparison 10 Changes of pain (VAS, mm), Outcome 8 leflunomide vs. sulfasalazine, at 6 months.



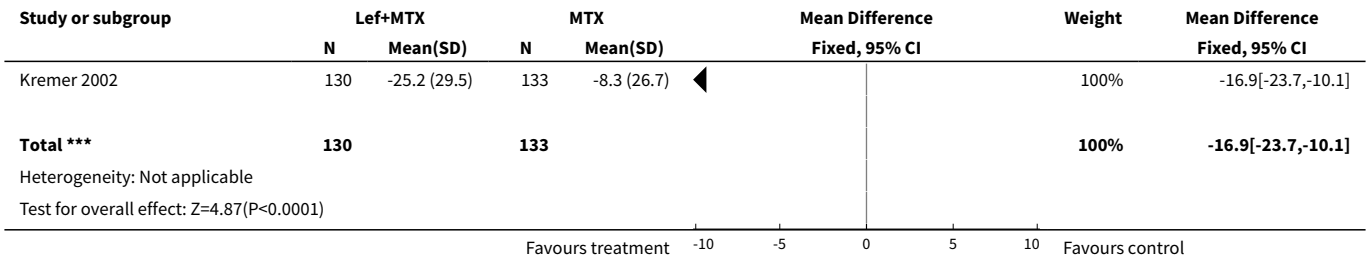
Analysis 10.9. Comparison 10 Changes of pain (VAS, mm), Outcome 9 leflunomide vs. sulfasalazine, at 12 months.



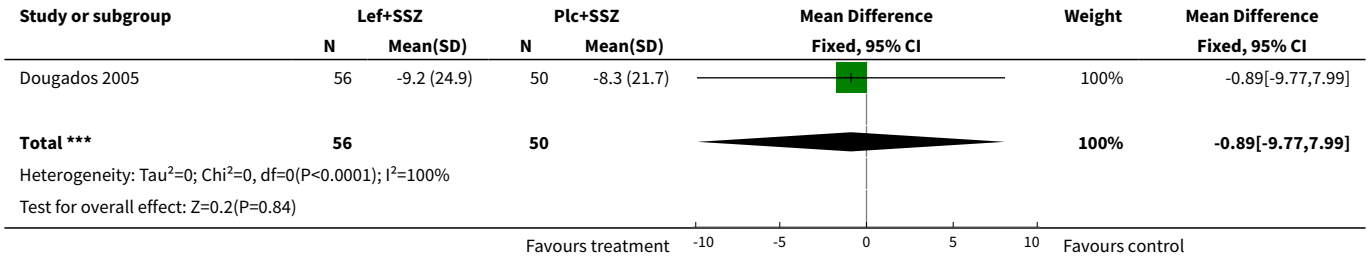
Analysis 10.10. Comparison 10 Changes of pain (VAS, mm), Outcome 10 leflunomide vs. sulfasalazine, at 24 months.



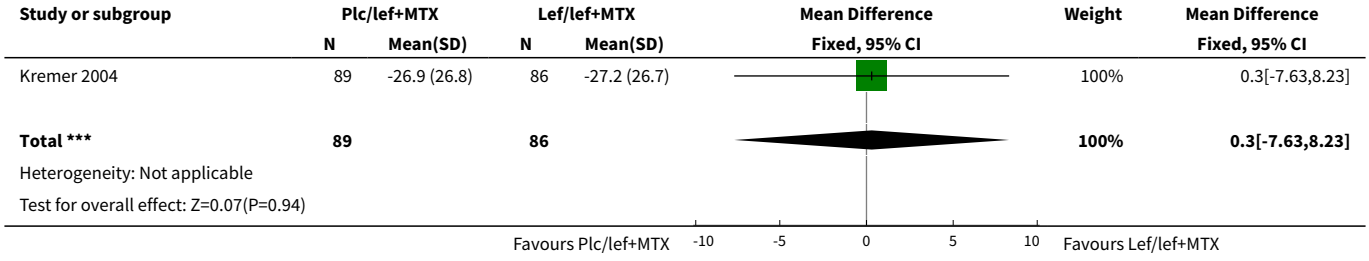
Analysis 10.11. Comparison 10 Changes of pain (VAS, mm), Outcome 11 leflunomide+MTX vs MTX, at 24 weeks.



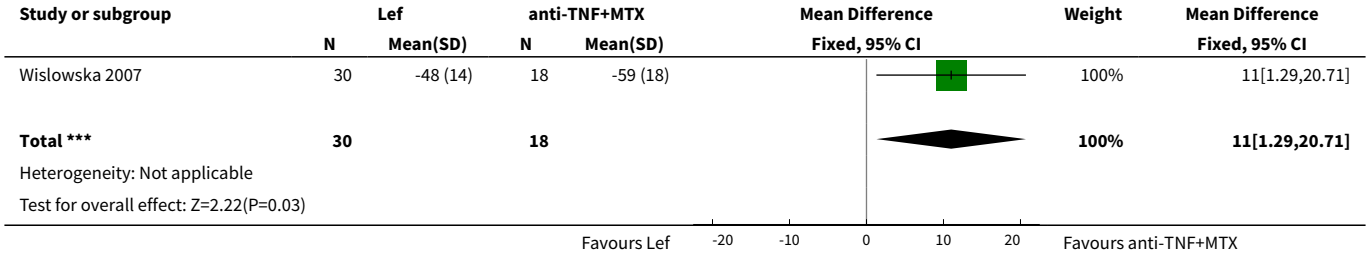
Analysis 10.12. Comparison 10 Changes of pain (VAS, mm), Outcome 12 leflunomide+SSZ vs. placebo+SSZ, at 24 months.



Analysis 10.13. Comparison 10 Changes of pain (VAS, mm), Outcome 13 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 10.14. Comparison 10 Changes of pain (VAS, mm), Outcome 14 leflunomide vs. anti-TNF+MTX, at 24 weeks.



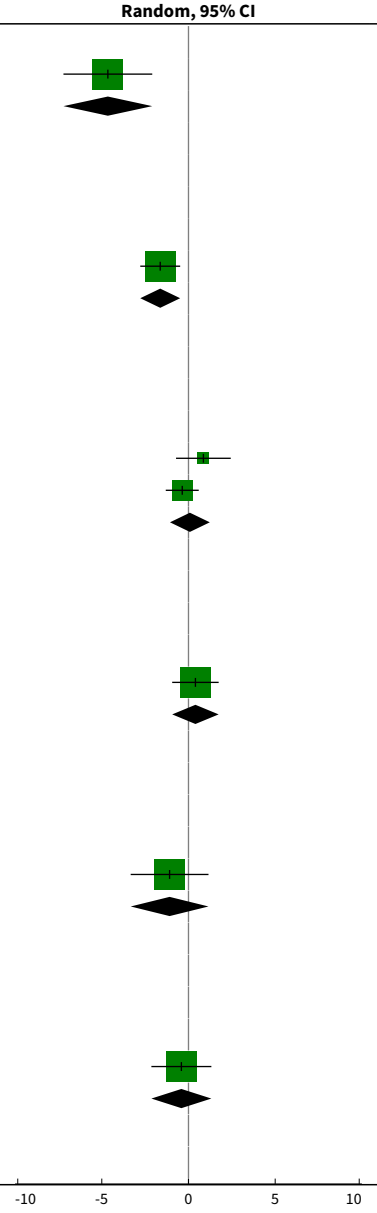
Comparison 11. Changes in hand joint radiographs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Sharp score	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 leflunomide vs. placebo, at 6 months	1	149	Mean Difference (IV, Random, 95% CI)	-4.65 [-7.21, -2.09]
1.2 leflunomide vs. placebo, at 12 months	1	214	Mean Difference (IV, Random, 95% CI)	-1.63 [-2.78, -0.48]
1.3 leflunomide vs. methotrexate, at 12 months	2	893	Mean Difference (IV, Random, 95% CI)	0.08 [-1.07, 1.23]
1.4 leflunomide vs. methotrexate, at 24 months	1	137	Mean Difference (IV, Random, 95% CI)	0.40 [-0.94, 1.74]
1.5 leflunomide vs. sulfasalazine, at 6 months	1	171	Mean Difference (IV, Random, 95% CI)	-1.09 [-3.33, 1.15]
1.6 leflunomide vs. sulfasalazine, at 12 months	1	113	Mean Difference (IV, Random, 95% CI)	-0.41 [-2.14, 1.32]
2 Total Larsen score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 leflunomide vs. placebo, at 6 months	1	151	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.06, -0.02]
2.2 leflunomide vs. sulfasalazine, at 6 months	1	168	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.01, 0.01]
2.3 leflunomide vs. sulfasalazine, at 12 months	1	113	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.01, 0.01]
2.4 leflunomide vs. sulfasalazine, at 24 months	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.19, 0.11]
3 Larsen erosion score, hands and feet	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 leflunomide vs. placebo, hands, at 6 months	1	151	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.06, -0.02]
3.2 leflunomide vs. sulfasalazine, hands, at 6 months	1	168	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.01, 0.01]
3.3 leflunomide vs. sulfasalazine, hands, at 12 months	1	113	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.02, 0.02]
3.4 leflunomide vs. sulfasalazine, hands, at 24 months	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.20, 0.08]
3.5 leflunomide vs. placebo, feet, at 6 months	1	151	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.08, -0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6 leflunomide vs. sulfasalazine, feet, at 6 months	1	168	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.04, 0.02]
3.7 leflunomide vs. sulfasalazine, feet, at 12 months	1	113	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.04, 0.02]
3.8 leflunomide vs. sulfasalazine, feet, at 24 months	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.28, 0.24]

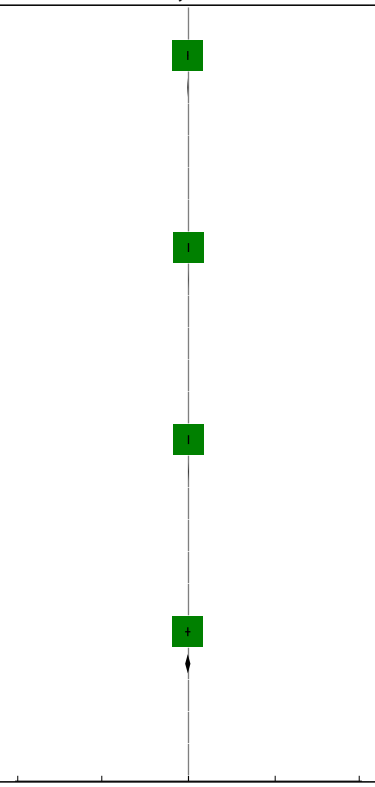
Analysis 11.1. Comparison 11 Changes in hand joint radiographs, Outcome 1 Total Sharp score.

Study or subgroup	Leflunomide N	Leflunomide Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
11.1.1 leflunomide vs. placebo, at 6 months							
Sharp 2000	87	1.2 (2.9)	62	5.9 (10)		100%	-4.65[-7.21,-2.09]
Subtotal ***	**87**		**62**			**100%**	**-4.65[-7.21,-2.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.56(P=0)							
11.1.2 leflunomide vs. placebo, at 12 months							
Sharp 2000	131	0.5 (4.5)	83	2.2 (4)		100%	-1.63[-2.78,-0.48]
Subtotal ***	**131**		**83**			**100%**	**-1.63[-2.78,-0.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.78(P=0.01)							
11.1.3 leflunomide vs. methotrexate, at 12 months							
Emery 1999	302	2.5 (5.4)	324	1.6 (13.4)		36.15%	0.86[-0.72,2.44]
Strand 1999a	131	0.5 (4.5)	136	0.9 (3.3)		63.85%	-0.36[-1.31,0.59]
Subtotal ***	**433**		**460**			**100%**	**0.08[-1.07,1.23]**
Heterogeneity: Tau^2=0.3; Chi^2=1.69, df=1(P=0.19); I^2=40.68%							
Test for overall effect: Z=0.14(P=0.89)							
11.1.4 leflunomide vs. methotrexate, at 24 months							
Cohen 2001	71	1.6 (4.2)	66	1.2 (3.8)		100%	0.4[-0.94,1.74]
Subtotal ***	**71**		**66**			**100%**	**0.4[-0.94,1.74]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.59(P=0.56)							
11.1.5 leflunomide vs. sulfasalazine, at 6 months							
Sharp 2000	87	1.2 (2.9)	84	2.3 (10.1)		100%	-1.09[-3.33,1.15]
Subtotal ***	**87**		**84**			**100%**	**-1.09[-3.33,1.15]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.95(P=0.34)							
11.1.6 leflunomide vs. sulfasalazine, at 12 months							
Sharp 2000	60	1 (6.1)	53	1.4 (2.9)		100%	-0.41[-2.14,1.32]
Subtotal ***	**60**		**53**			**100%**	**-0.41[-2.14,1.32]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.46(P=0.64)							



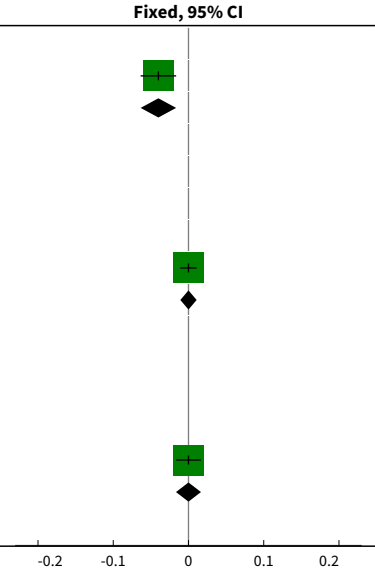
Analysis 11.2. Comparison 11 Changes in hand joint radiographs, Outcome 2 Total Larsen score.

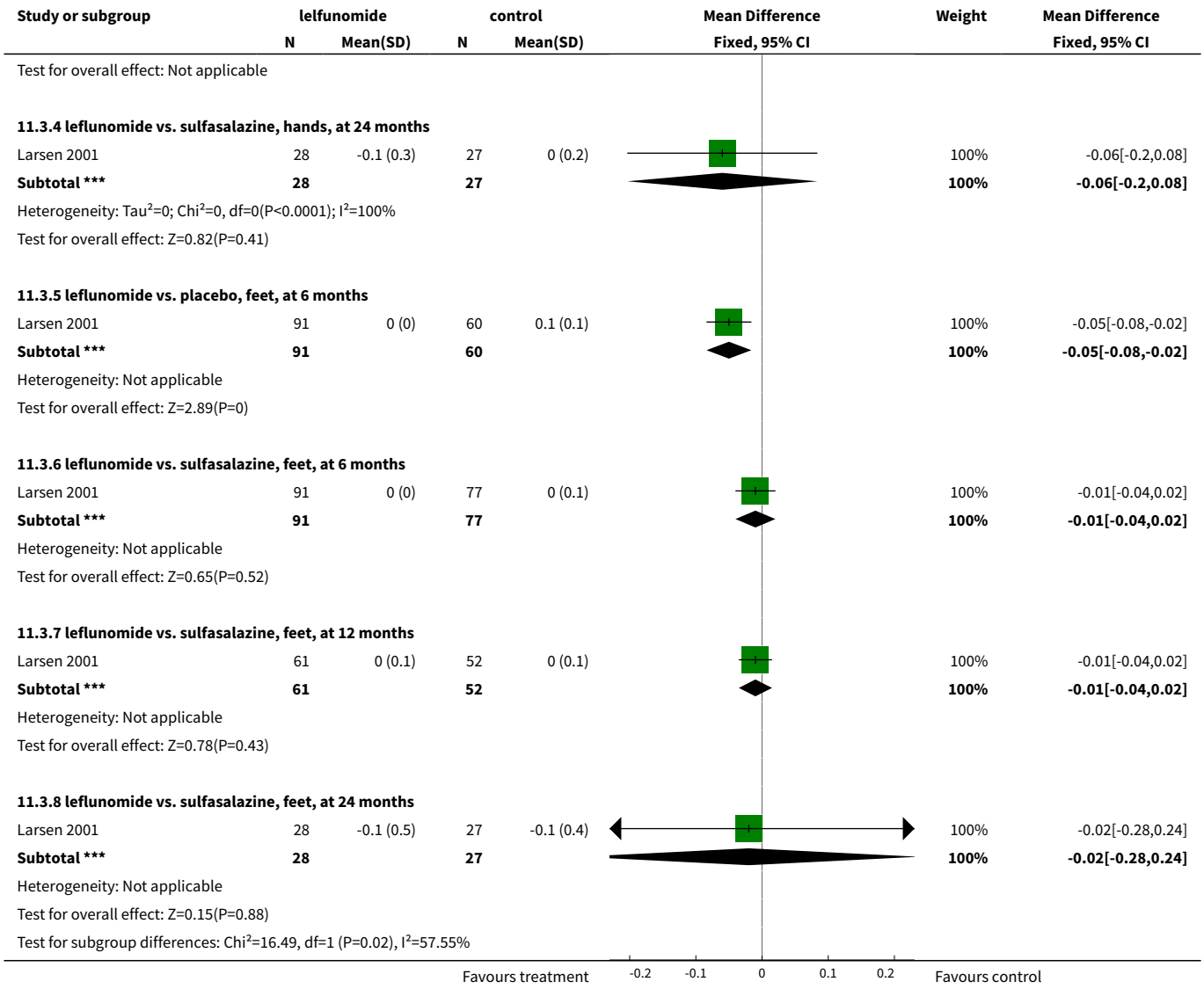
Study or subgroup	lelfunomide N	lelfunomide Mean(SD)	control N	control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.2.1 leflunomide vs. placebo, at 6 months							
Scott 2001	91	0 (0)	60	0.1 (0.1)		100%	-0.04[-0.06,-0.02]
Subtotal ***	**91**		**60**			**100%**	**-0.04[-0.06,-0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.32(P=0)							
11.2.2 leflunomide vs. sulfasalazine, at 6 months							
Scott 2001	91	0 (0)	77	0 (0)		100%	0[-0.01,0.01]
Subtotal ***	**91**		**77**			**100%**	**0[-0.01,0.01]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
11.2.3 leflunomide vs. sulfasalazine, at 12 months							
Scott 2001	61	0 (0)	52	0 (0)		100%	0[-0.01,0.01]
Subtotal ***	**61**		**52**			**100%**	**0[-0.01,0.01]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
11.2.4 leflunomide vs. sulfasalazine, at 24 months							
Scott 2001	28	-0.1 (0.3)	27	-0 (0.2)		100%	-0.04[-0.19,0.11]
Subtotal ***	**28**		**27**			**100%**	**-0.04[-0.19,0.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.52(P=0.61)							
Test for subgroup differences: Chi^2=10.18, df=1 (P=0.02), I^2=70.54%							



Analysis 11.3. Comparison 11 Changes in hand joint radiographs, Outcome 3 Larsen erosion score, hands and feet.

Study or subgroup	lelfunomide N	lelfunomide Mean(SD)	control N	control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.3.1 leflunomide vs. placebo, hands, at 6 months							
Larsen 2001	91	0 (0)	60	0.1 (0.1)		100%	-0.04[-0.06,-0.02]
Subtotal ***	**91**		**60**			**100%**	**-0.04[-0.06,-0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.32(P=0)							
11.3.2 leflunomide vs. sulfasalazine, hands, at 6 months							
Larsen 2001	91	0 (0)	77	0 (0)		100%	0[-0.01,0.01]
Subtotal ***	**91**		**77**			**100%**	**0[-0.01,0.01]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
11.3.3 leflunomide vs. sulfasalazine, hands, at 12 months							
Larsen 2001	61	0 (0.1)	52	0 (0)		100%	0[-0.02,0.02]
Subtotal ***	**61**		**52**			**100%**	**0[-0.02,0.02]**
Heterogeneity: Not applicable							





Comparison 12. Changes in function and health-related quality of life

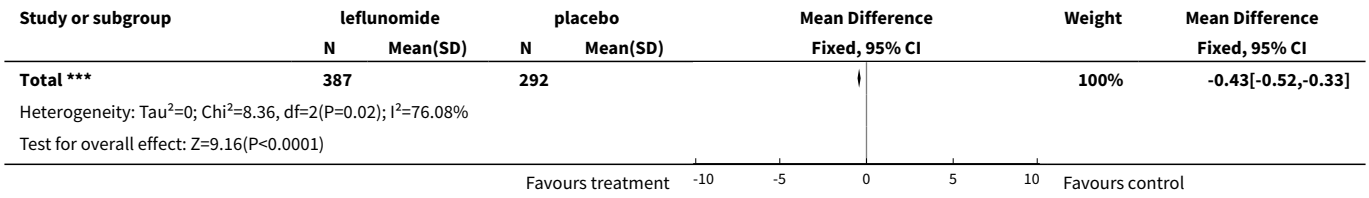
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes of HAQ scores in leflunomide vs. placebo, at 6 months	3	679	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.52, -0.33]
2 Changes of HAQ scores in leflunomide vs. placebo, at 12 months	1	264	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.60, -0.36]
3 Changes of HAQ scores in leflunomide vs. MTX, at 3 months	2	160	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.12, 0.14]
4 Changes of HAQ scores in leflunomide vs. MTX, at 6 months	3	208	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.11, 0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Changes of HAQ scores in leflunomide vs. MTX, at 12 months	2	861	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.09, 0.05]
6 Changes of HAQ scores in leflunomide vs. MTX, at 2 years	1	530	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.04, 0.14]
7 Changes of HAQ scores in leflunomide vs. SSZ, at 6 months	1	229	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.42, -0.08]
8 Changes of HAQ scores in leflunomide vs. SSZ, at 12 months	1	128	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.33, 0.05]
9 Changes of HAQ scores in leflunomide vs. SSZ, at 24 months	1	96	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.57, -0.01]
10 Changes of MHAQ scores in leflunomide vs. placebo, at 6 months	1	300	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.46, -0.24]
11 Changes of MHAQ scores in leflunomide vs. placebo, at 12 months	1	296	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.48, -0.24]
12 Changes of MHAQ scores in leflunomide vs. MTX, at 6 months	1	362	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.22, -0.02]
13 Changes of MHAQ scores in leflunomide vs. MTX, at 12 months	1	357	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.25, -0.03]
14 Changes of MHAQ scores in leflunomide vs. MTX, at 24 months	1	199	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.29, -0.01]
15 Changes of PET top 5 scores in leflunomide vs. placebo, at 12 months	1	266	Mean Difference (IV, Fixed, 95% CI)	-6.24 [-8.46, -4.02]
16 Changes of PET top 5 scores in leflunomide vs. MTX, at 12 months	1	333	Mean Difference (IV, Fixed, 95% CI)	-3.50 [-5.62, -1.38]
17 Changes of SF-36 physical component scores in leflunomide vs. placebo, at 12 months	1	251	Mean Difference (IV, Fixed, 95% CI)	-6.60 [-8.91, -4.29]
18 Changes of SF-36 physical component scores in leflunomide vs. MTX, at 12 months	1	316	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-5.41, -0.59]
19 Changes of SF-36 mental component scores in leflunomide vs. placebo, at 12 months	1	251	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-3.53, 2.13]
20 Changes of SF-36 mental component scores in leflunomide vs. MTX, at 12 months	1	316	Mean Difference (IV, Fixed, 95% CI)	-0.6 [-3.01, 1.81]
21 Changes of work productivity scores in leflunomide vs. placebo, at 12 months	1	198	Mean Difference (IV, Fixed, 95% CI)	-9.5 [-14.25, -4.75]

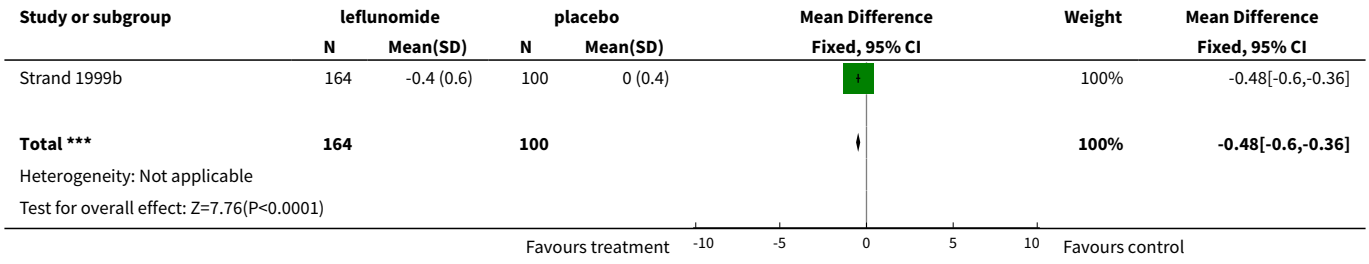
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Changes of work productivity scores in leflunomide vs. MTX, at 12 months	1	252	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-6.37, 1.77]
23 Changes of HAQ scores in leflunomide+MTX vs. MTX, at 24 weeks	1	263	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.42, -0.18]
24 Changes of HAQ scores in leflunomide10mg vs. leflunomide20mg, at 24 months	1	291	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.03, 0.27]
25 Changes of HAQ-DI in leflunomide+SSZ vs. placebo+SSZ, at 24 months	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.23, 0.07]
26 Changes of mean HAQ scores in leflunomide+SSZ vs. placebo+SSZ, at 24 months	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.20, 0.06]
27 Changes of MHAQ scores in leflunomide vs. MTX, at 4 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-2.34 [-7.64, 2.96]
28 Changes of Chinese disability scores in leflunomide vs. MTX	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
28.1 At 3 months	1	504	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.18, -0.00]
28.2 At 6 months	1	193	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.20, 0.10]
29 Change of HAQ-DI in Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	182	Mean Difference (IV, Fixed, 95% CI)	0.21 [0.05, 0.37]
30 Change of SF-36 physical component scores in Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	161	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-5.14, 1.34]
31 Change of SF-36 mental component scores in Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	161	Mean Difference (IV, Fixed, 95% CI)	-2.7 [-5.63, 0.23]
32 Changes of HAQ score, leflunomide vs. anti-TNF, at 24 weeks	1	48	Mean Difference (IV, Fixed, 95% CI)	0.49 [0.34, 0.64]

Analysis 12.1. Comparison 12 Changes in function and health-related quality of life, Outcome 1 Changes of HAQ scores in leflunomide vs. placebo, at 6 months.

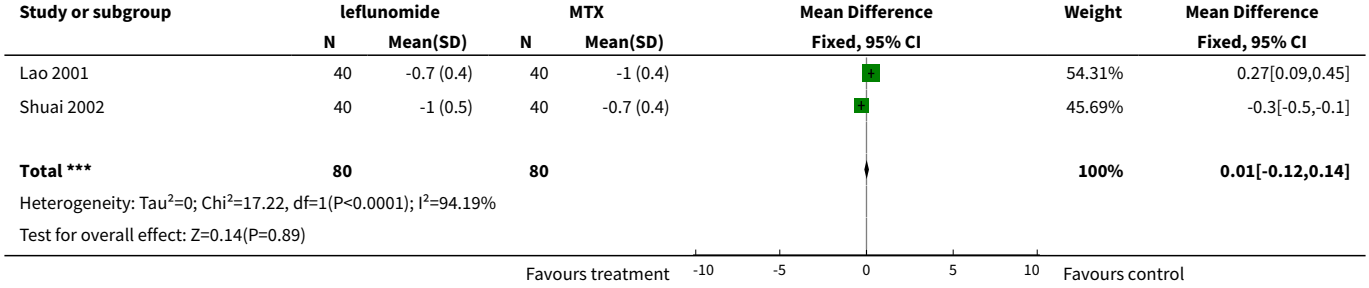
Study or subgroup	leflunomide		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Mladenovic 1995	101	-13.6 (12.9)	102	-8.1 (13)		0.07%	-5.5[-9.06,-1.94]
Smolen 1999	130	-0.5 (0.5)	91	-0 (0.5)		46.25%	-0.46[-0.59,-0.33]
Strand 1999b	156	-0.5 (0.6)	99	-0.1 (0.4)		53.68%	-0.39[-0.51,-0.27]



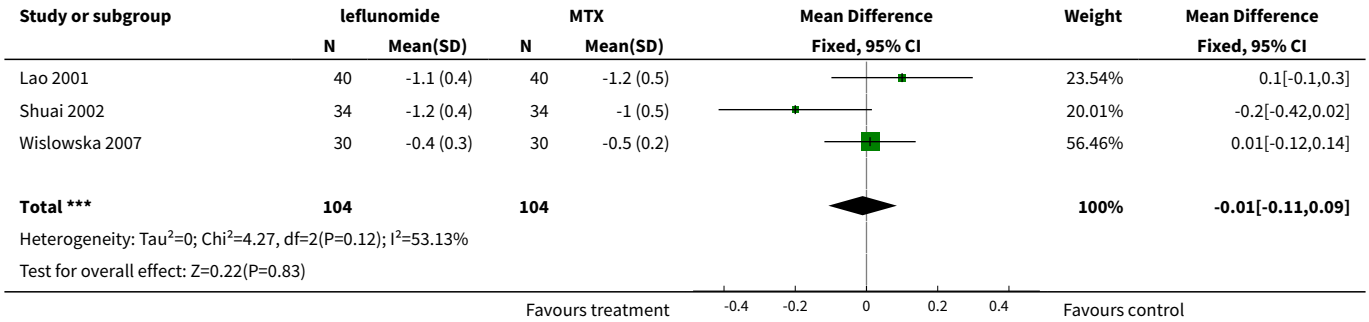
Analysis 12.2. Comparison 12 Changes in function and health-related quality of life, Outcome 2 Changes of HAQ scores in leflunomide vs. placebo, at 12 months.



Analysis 12.3. Comparison 12 Changes in function and health-related quality of life, Outcome 3 Changes of HAQ scores in leflunomide vs. MTX, at 3 months.

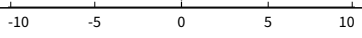


Analysis 12.4. Comparison 12 Changes in function and health-related quality of life, Outcome 4 Changes of HAQ scores in leflunomide vs. MTX, at 6 months.



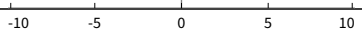
Analysis 12.5. Comparison 12 Changes in function and health-related quality of life, Outcome 5 Changes of HAQ scores in leflunomide vs. MTX, at 12 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Emery 1999	252	-0.5 (0.5)	278	-0.5 (0.5)		69.47%	0.06[-0.02,0.14]
Strand 1999b	164	-0.4 (0.6)	167	-0.3 (0.6)		30.53%	-0.19[-0.31,-0.07]
Total ***	**416**		**445**			**100%**	**-0.02[-0.09,0.05]**
Heterogeneity: Tau^2=0; Chi^2=10.68, df=1(P=0); I^2=90.64%							
Test for overall effect: Z=0.46(P=0.64)							



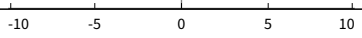
Analysis 12.6. Comparison 12 Changes in function and health-related quality of life, Outcome 6 Changes of HAQ scores in leflunomide vs. MTX, at 2 years.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	MTX N	MTX Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Emery 1999	252	-0.4 (0.6)	278	-0.5 (0.6)		100%	0.05[-0.04,0.14]
Total ***	**252**		**278**			**100%**	**0.05[-0.04,0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.04(P=0.3)							



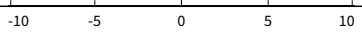
Analysis 12.7. Comparison 12 Changes in function and health-related quality of life, Outcome 7 Changes of HAQ scores in leflunomide vs. SSZ, at 6 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Scott 2001	116	-0.7 (0.7)	113	-0.4 (0.7)		100%	-0.25[-0.42,-0.08]
Total ***	**116**		**113**			**100%**	**-0.25[-0.42,-0.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.82(P=0)							



Analysis 12.8. Comparison 12 Changes in function and health-related quality of life, Outcome 8 Changes of HAQ scores in leflunomide vs. SSZ, at 12 months.

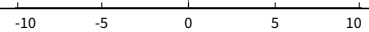
Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Scott 2001	66	-0.7 (0.6)	62	-0.5 (0.5)		100%	-0.14[-0.33,0.05]
Total ***	**66**		**62**			**100%**	**-0.14[-0.33,0.05]**
Heterogeneity: Not applicable							



Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=1.45(P=0.15)							

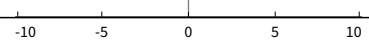
Analysis 12.9. Comparison 12 Changes in function and health-related quality of life, Outcome 9 Changes of HAQ scores in leflunomide vs. SSZ, at 24 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	SSZ N	SSZ Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Scott 2001	51	-0.9 (0.7)	45	-0.6 (0.7)		100%	-0.29[-0.57,-0.01]
Total ***	**51**		**45**			**100%**	**-0.29[-0.57,-0.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.03(P=0.04)							



Analysis 12.10. Comparison 12 Changes in function and health-related quality of life, Outcome 10 Changes of MHAQ scores in leflunomide vs. placebo, at 6 months.

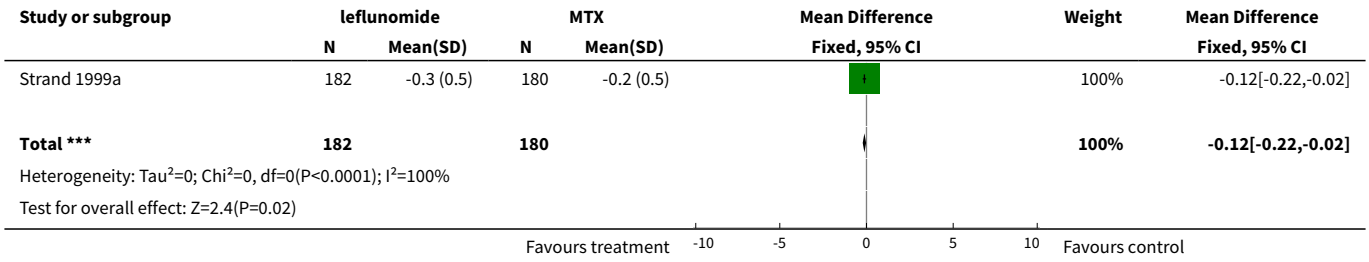
Study or subgroup	leflunomide N	leflunomide Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Strand 1999a	182	-0.3 (0.5)	118	0 (0.5)		100%	-0.35[-0.46,-0.24]
Total ***	**182**		**118**			**100%**	**-0.35[-0.46,-0.24]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.99(P<0.0001)							



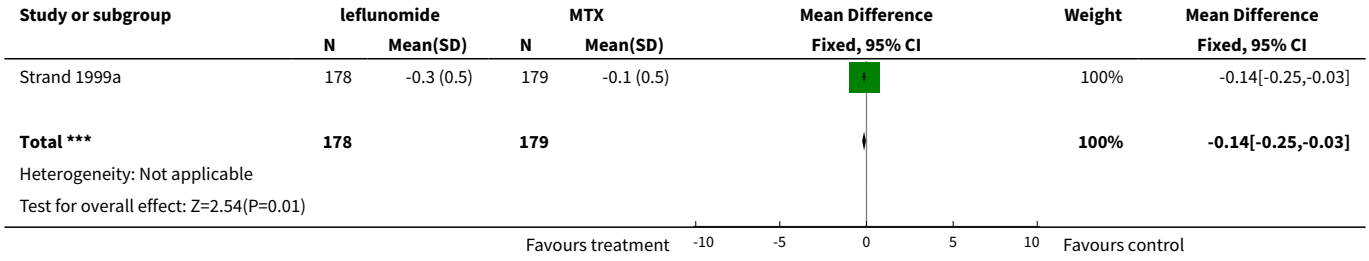
Analysis 12.11. Comparison 12 Changes in function and health-related quality of life, Outcome 11 Changes of MHAQ scores in leflunomide vs. placebo, at 12 months.

Study or subgroup	leflunomide N	leflunomide Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Strand 1999a	178	-0.3 (0.5)	118	0.1 (0.5)		100%	-0.36[-0.48,-0.24]
Total ***	**178**		**118**			**100%**	**-0.36[-0.48,-0.24]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.87(P<0.0001)							

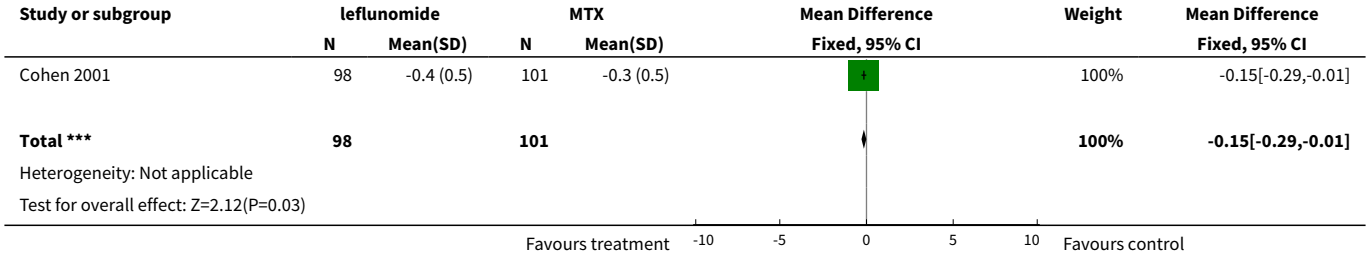
Analysis 12.12. Comparison 12 Changes in function and health-related quality of life, Outcome 12 Changes of MHAQ scores in leflunomide vs. MTX, at 6 months.



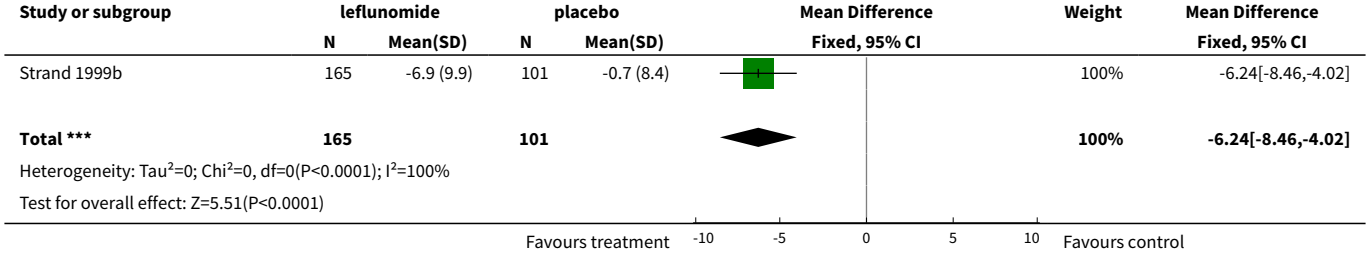
Analysis 12.13. Comparison 12 Changes in function and health-related quality of life, Outcome 13 Changes of MHAQ scores in leflunomide vs. MTX, at 12 months.



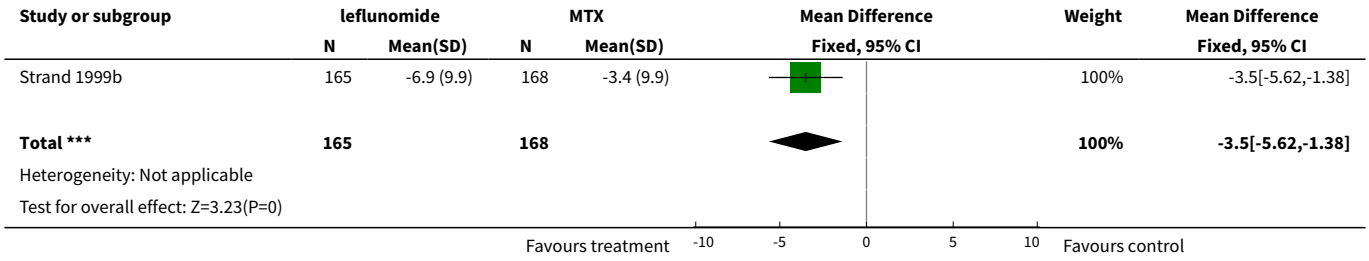
Analysis 12.14. Comparison 12 Changes in function and health-related quality of life, Outcome 14 Changes of MHAQ scores in leflunomide vs. MTX, at 24 months.



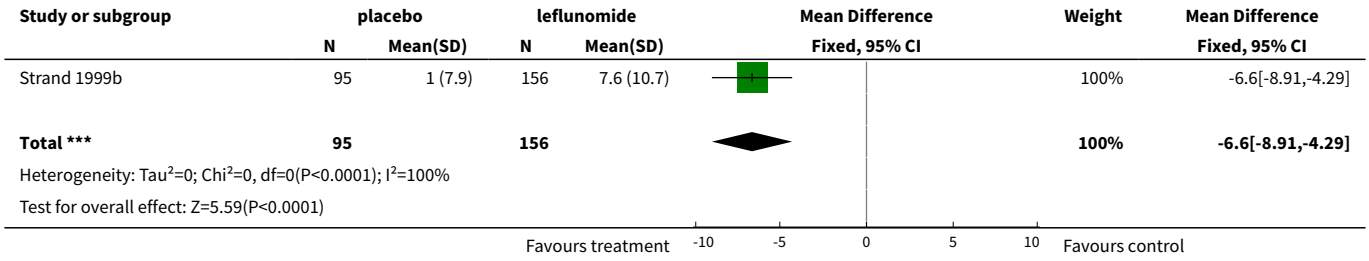
Analysis 12.15. Comparison 12 Changes in function and health-related quality of life, Outcome 15 Changes of PET top 5 scores in leflunomide vs. placebo, at 12 months.



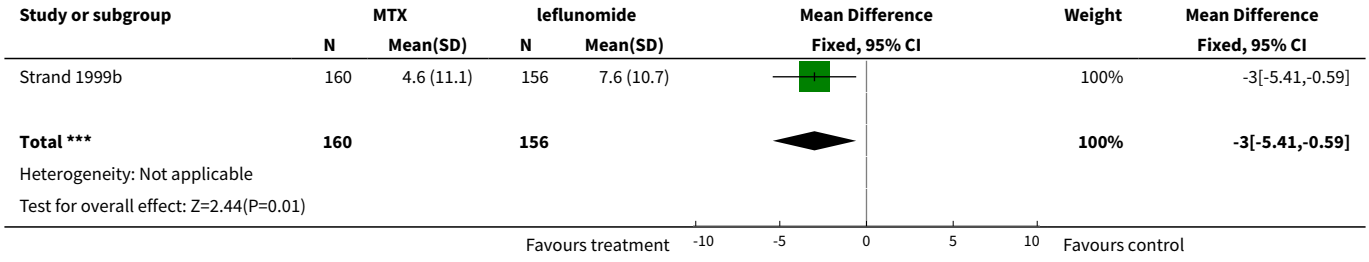
Analysis 12.16. Comparison 12 Changes in function and health-related quality of life, Outcome 16 Changes of PET top 5 scores in leflunomide vs. MTX, at 12 months.



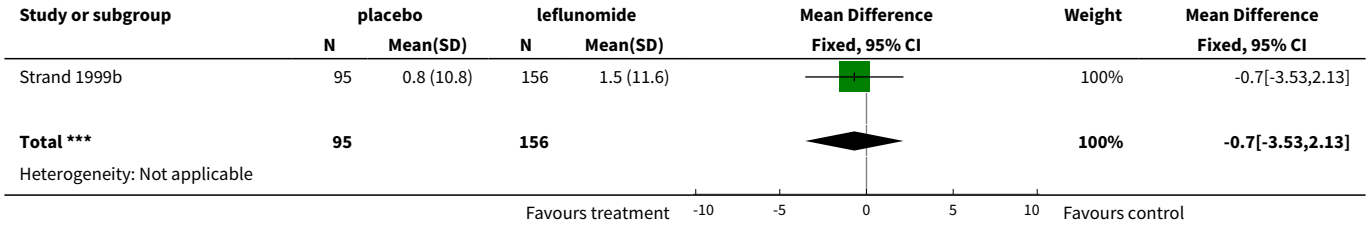
Analysis 12.17. Comparison 12 Changes in function and health-related quality of life, Outcome 17 Changes of SF-36 physical component scores in leflunomide vs. placebo, at 12 months.

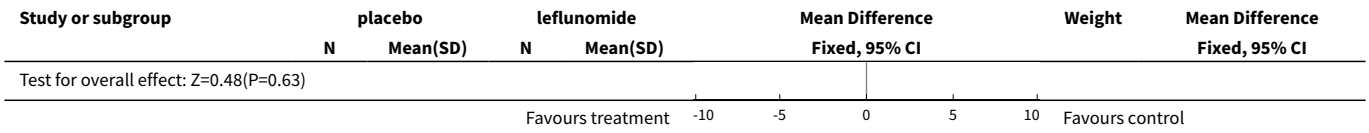


Analysis 12.18. Comparison 12 Changes in function and health-related quality of life, Outcome 18 Changes of SF-36 physical component scores in leflunomide vs. MTX, at 12 months.

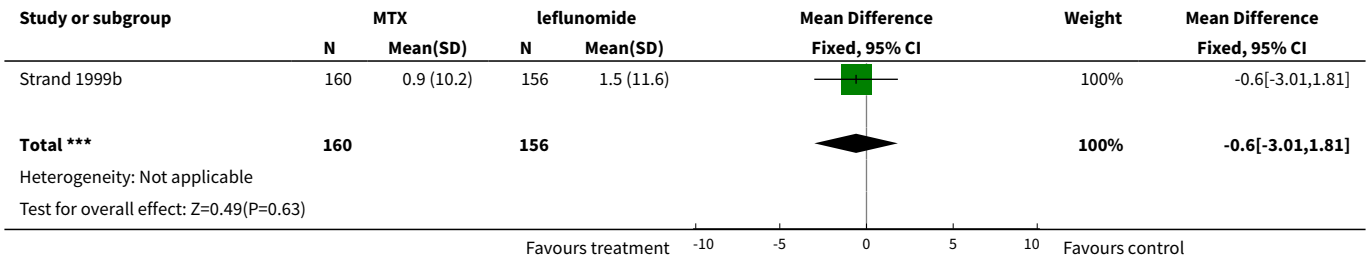


Analysis 12.19. Comparison 12 Changes in function and health-related quality of life, Outcome 19 Changes of SF-36 mental component scores in leflunomide vs. placebo, at 12 months.

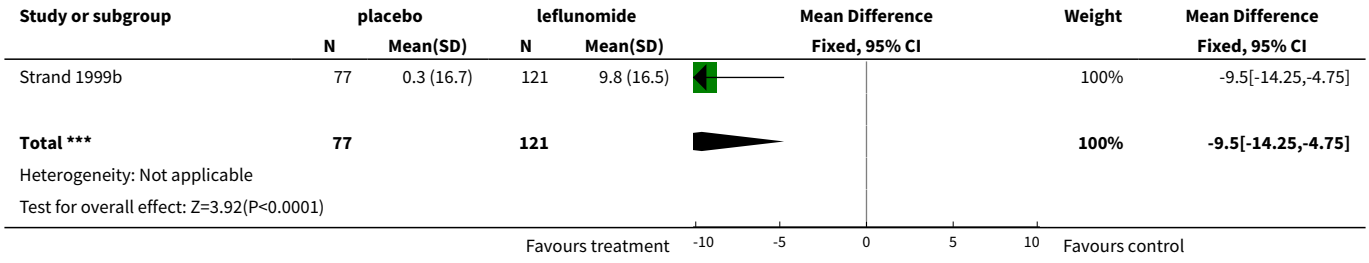




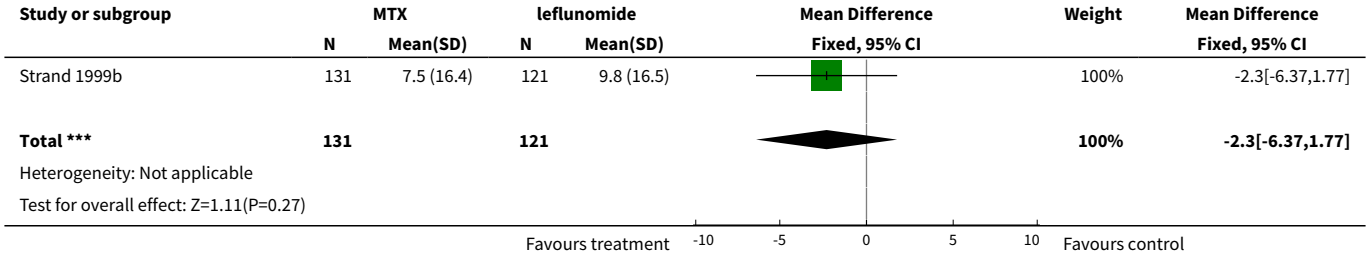
Analysis 12.20. Comparison 12 Changes in function and health-related quality of life, Outcome 20 Changes of SF-36 mental component scores in leflunomide vs. MTX, at 12 months.



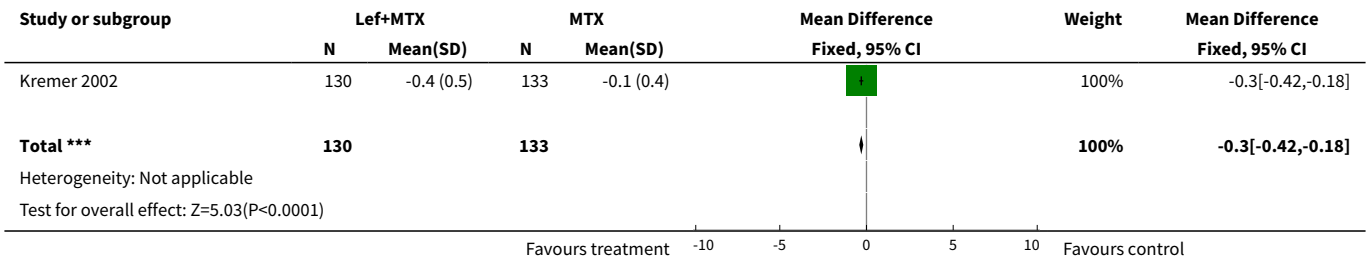
Analysis 12.21. Comparison 12 Changes in function and health-related quality of life, Outcome 21 Changes of work productivity scores in leflunomide vs. placebo, at 12 months.



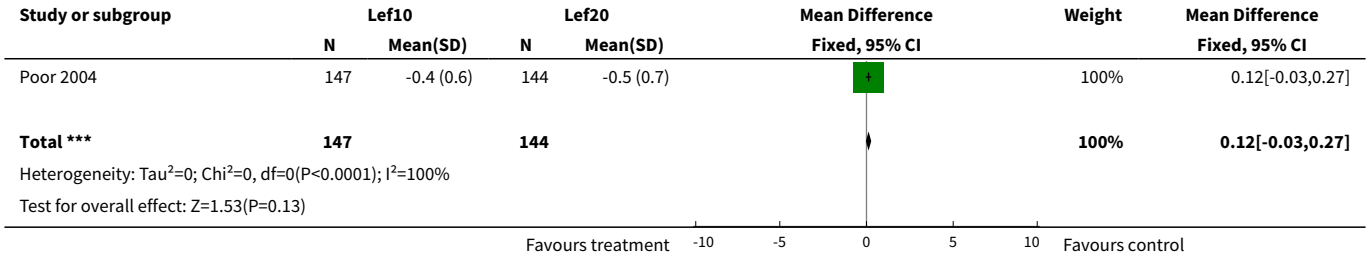
Analysis 12.22. Comparison 12 Changes in function and health-related quality of life, Outcome 22 Changes of work productivity scores in leflunomide vs. MTX, at 12 months.



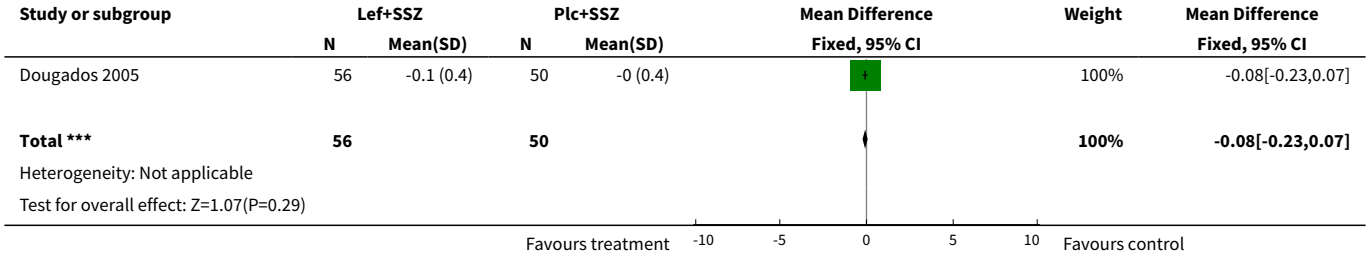
Analysis 12.23. Comparison 12 Changes in function and health-related quality of life, Outcome 23 Changes of HAQ scores in leflunomide+MTX vs. MTX, at 24 weeks.



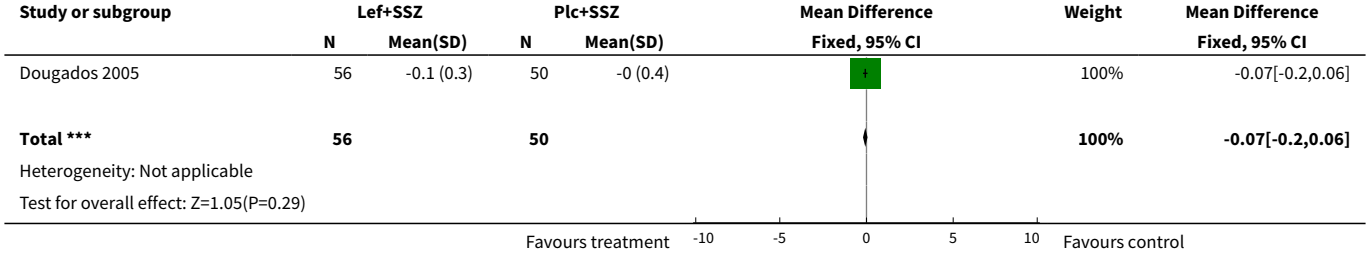
Analysis 12.24. Comparison 12 Changes in function and health-related quality of life, Outcome 24 Changes of HAQ scores in leflunomide10mg vs. leflunomide20mg, at 24 months.



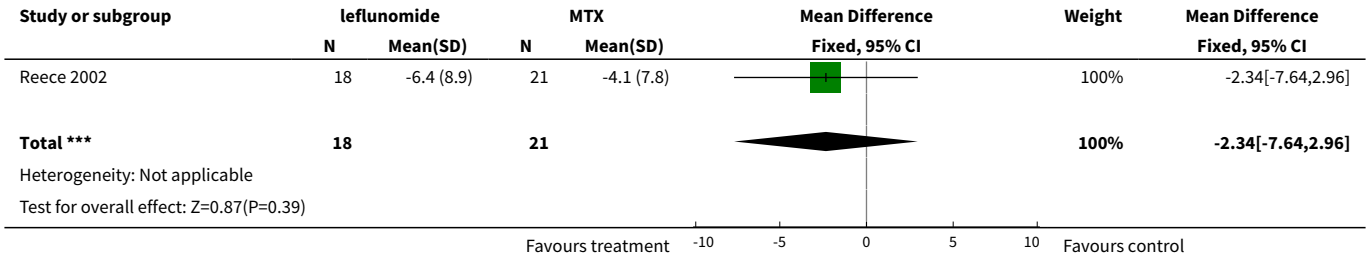
Analysis 12.25. Comparison 12 Changes in function and health-related quality of life, Outcome 25 Changes of HAQ-DI in leflunomide+SSZ vs. placebo+SSZ, at 24 months.



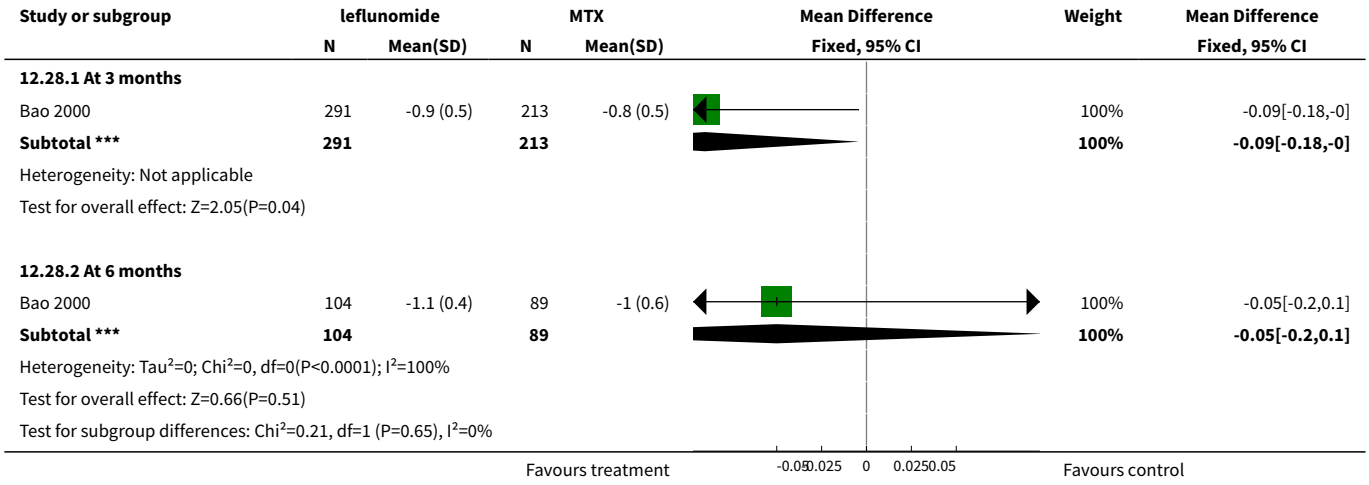
Analysis 12.26. Comparison 12 Changes in function and health-related quality of life, Outcome 26 Changes of mean HAQ scores in leflunomide+SSZ vs. placebo+SSZ, at 24 months.



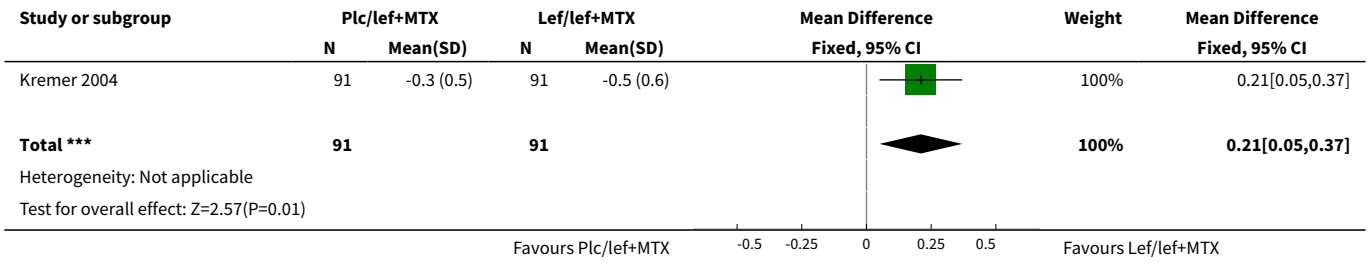
Analysis 12.27. Comparison 12 Changes in function and health-related quality of life, Outcome 27 Changes of MHAQ scores in leflunomide vs. MTX, at 4 months.



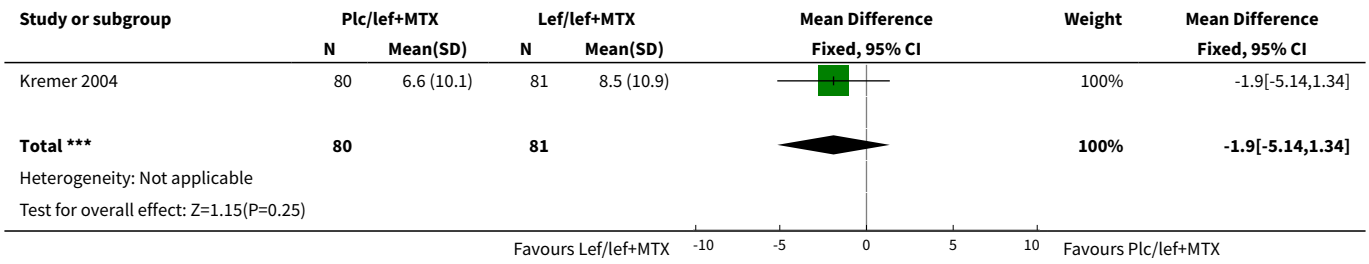
Analysis 12.28. Comparison 12 Changes in function and health-related quality of life, Outcome 28 Changes of Chinese disability scores in leflunomide vs. MTX.



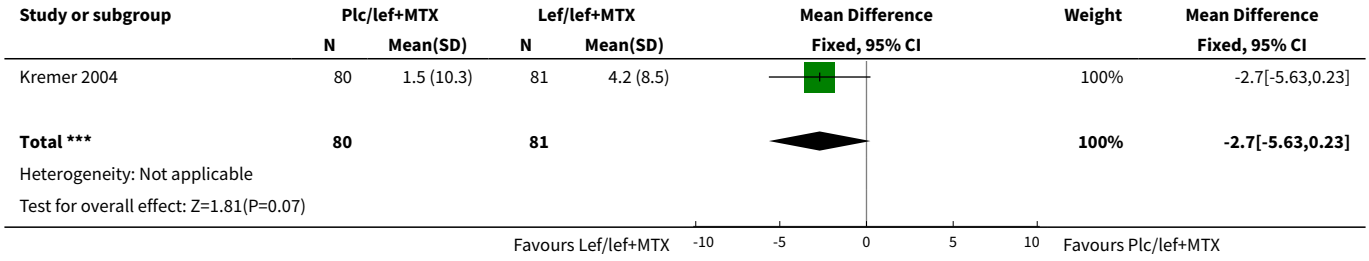
Analysis 12.29. Comparison 12 Changes in function and health-related quality of life, Outcome 29 Change of HAQ-DI in Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



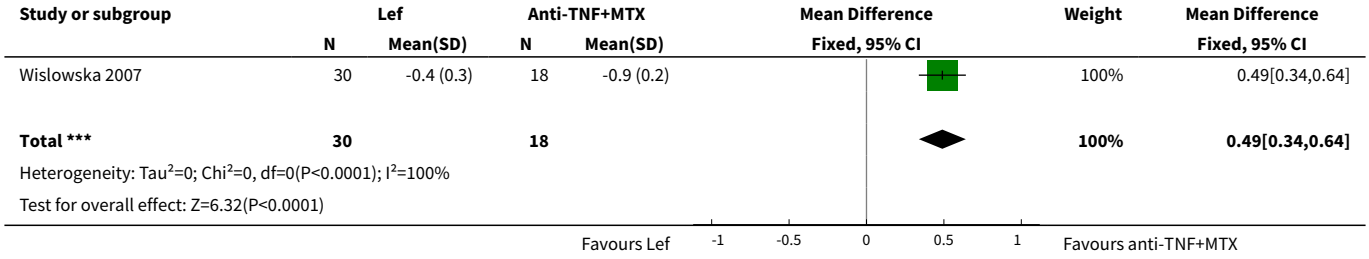
Analysis 12.30. Comparison 12 Changes in function and health-related quality of life, Outcome 30 Change of SF-36 physical component scores in Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 12.31. Comparison 12 Changes in function and health-related quality of life, Outcome 31 Change of SF-36 mental component scores in Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 12.32. Comparison 12 Changes in function and health-related quality of life, Outcome 32 Changes of HAQ score, leflunomide vs. anti-TNF, at 24 weeks.



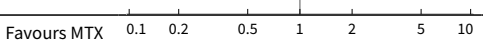
Comparison 13. Response rate in Chinese and Indian leflunomide studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response rate, Lef vs. MTX, at 3 months	5	361	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.88, 1.37]
2 Response rate, Lef vs. MTX, at 6 months	3	208	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Overall effective rate, Lef vs. MTX, at 12 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.04]
4 Overall effective rate, Lef vs. MTX, at 24 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.81, 1.00]
5 Remarkable improvement rate, Lef vs. MTX, at 12 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.01]
6 Remarkable improvement rate, Lef vs. MTX, at 24 weeks	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.10]
7 Significant improvement rate, Lef+MTX vs. MTX, at 3 years	1	466	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.62, 0.86]
8 Significant improvement rate, Lef+MTX vs MTX, at 2 years	1	166	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.52, 0.91]
9 Remarkable improvement rate, Lef+MTX vs. MTX, at 24 weeks	1	64	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.27, 0.68]
10 Remission rate, Lef+MTX vs. MTX+CQ +SSZ, at 12 weeks	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.16, 0.91]

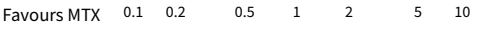
Analysis 13.1. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 1 Response rate, Lef vs. MTX, at 3 months.

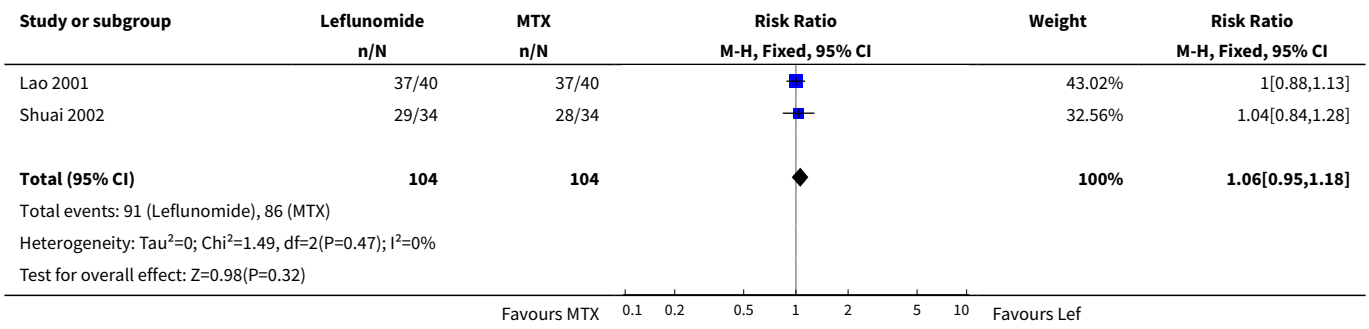
Study or subgroup	Leflunomide n/N	MTX n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bao 2000	24/30	21/30		22.97%	1.14[0.85,1.53]
Hu 2001	41/56	11/25		14.22%	1.66[1.04,2.66]
Jiang 2001	25/30	22/30		24.64%	1.14[0.87,1.49]
Lao 2001	31/40	36/40		29.54%	0.86[0.71,1.05]
Shuai 2002	12/40	12/40		8.63%	1[0.51,1.95]
Total (95% CI)	**196**	**165**		**100%**	**1.09[0.88,1.37]**
Total events: 133 (Leflunomide), 102 (MTX)					
Heterogeneity: Tau^2=0.03; Chi^2=9.28, df=4(P=0.05); I^2=56.88%					
Test for overall effect: Z=0.79(P=0.43)					



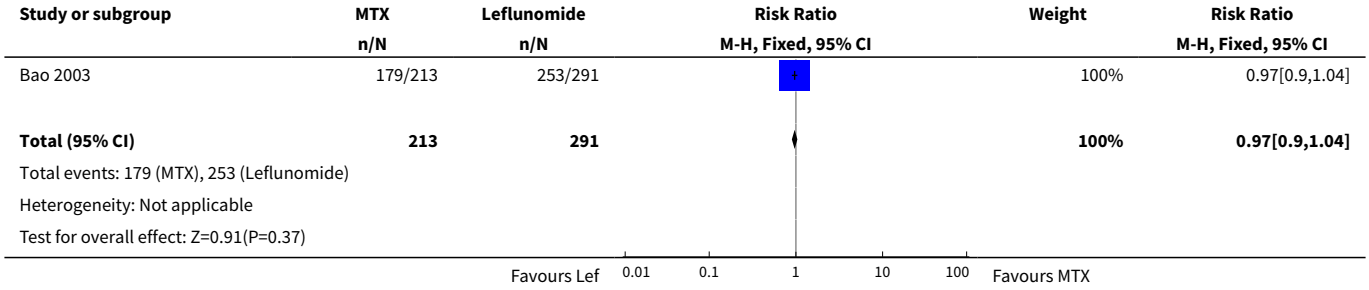
Analysis 13.2. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 2 Response rate, Lef vs. MTX, at 6 months.

Study or subgroup	Leflunomide n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bao 2000	25/30	21/30		24.42%	1.19[0.9,1.58]

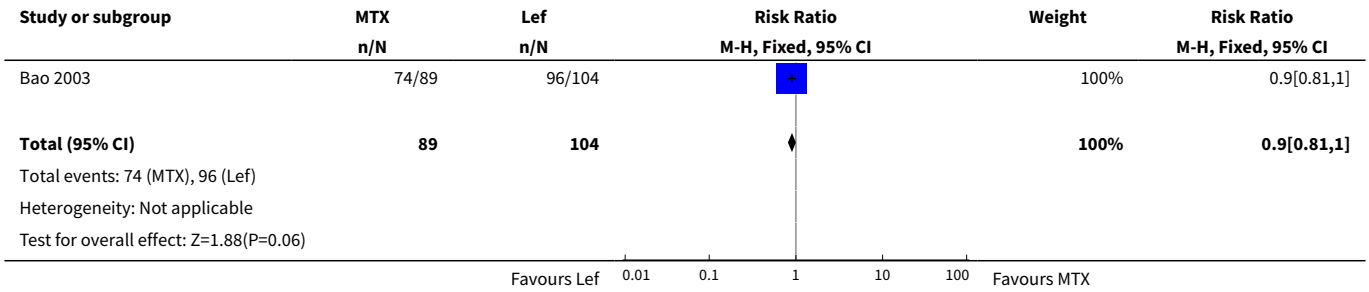




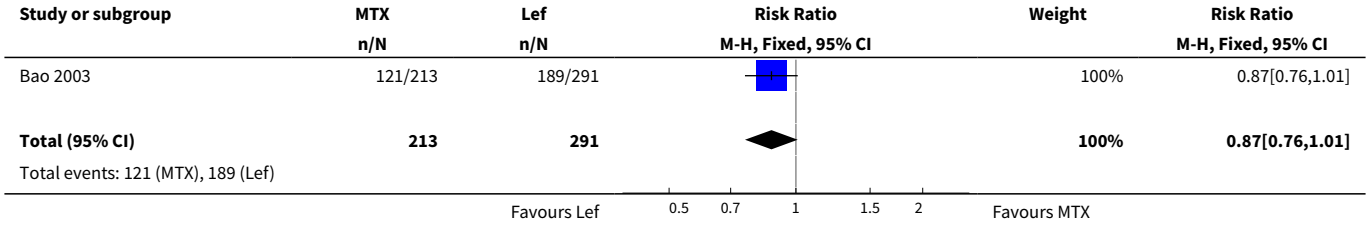
Analysis 13.3. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 3 Overall effective rate, Lef vs. MTX, at 12 weeks.

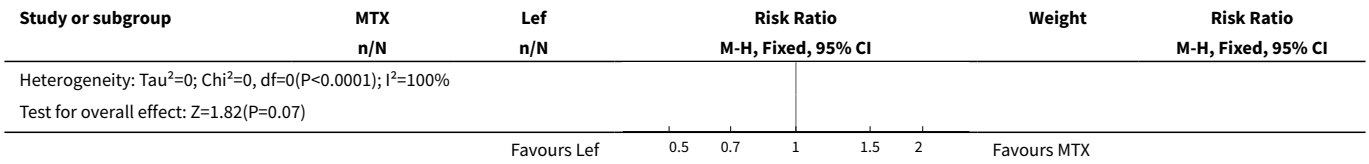


Analysis 13.4. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 4 Overall effective rate, Lef vs. MTX, at 24 weeks.

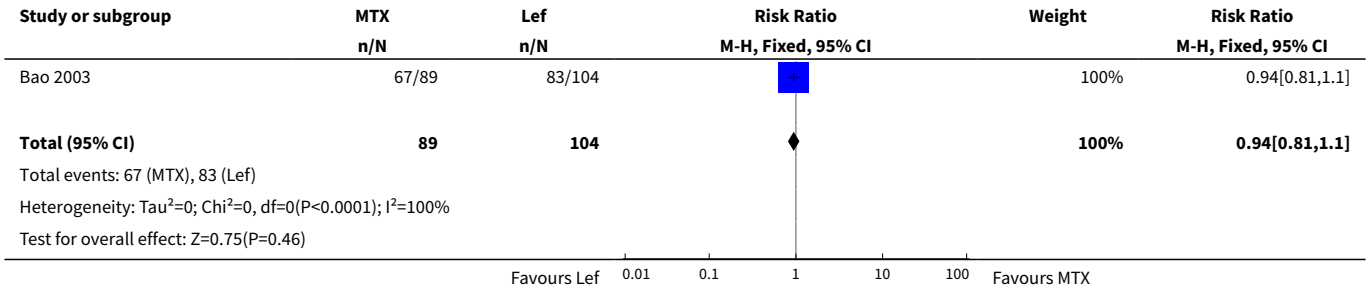


Analysis 13.5. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 5 Remarkable improvement rate, Lef vs. MTX, at 12 weeks.

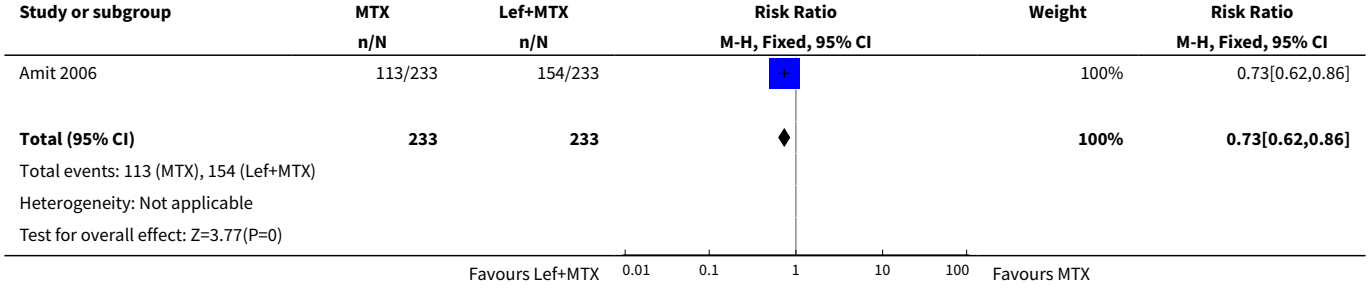




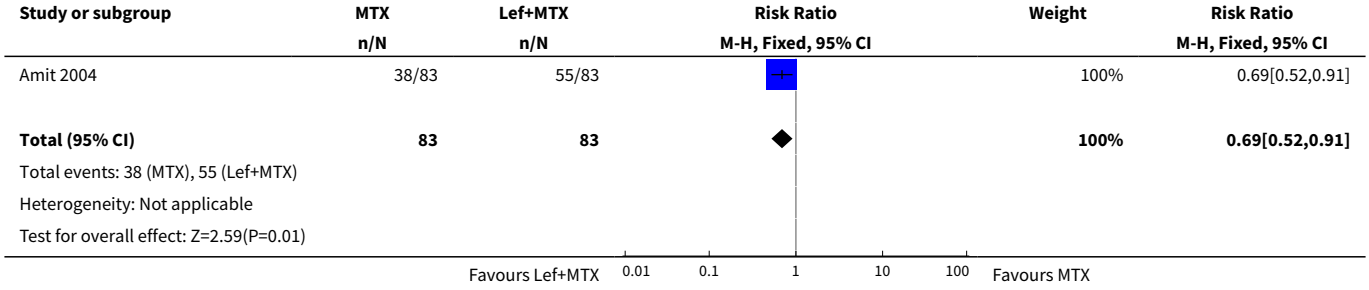
Analysis 13.6. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 6 Remarkable improvement rate, Lef vs. MTX, at 24 weeks.



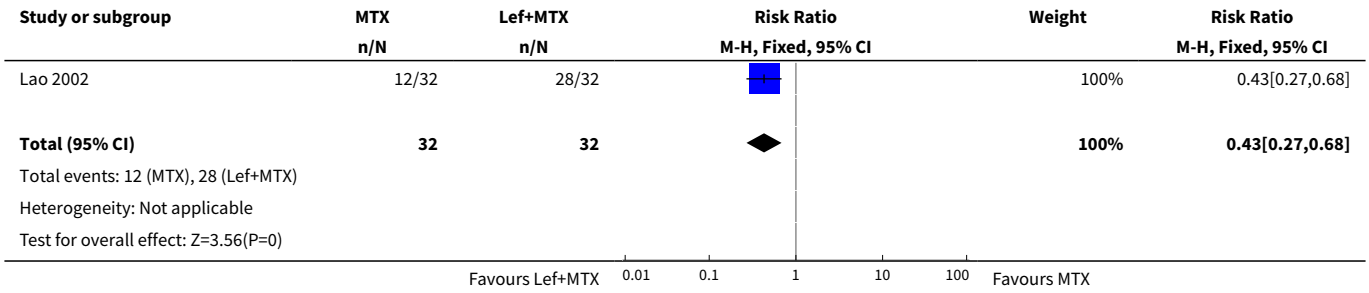
Analysis 13.7. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 7 Significant improvement rate, Lef+MTX vs. MTX, at 3 years.



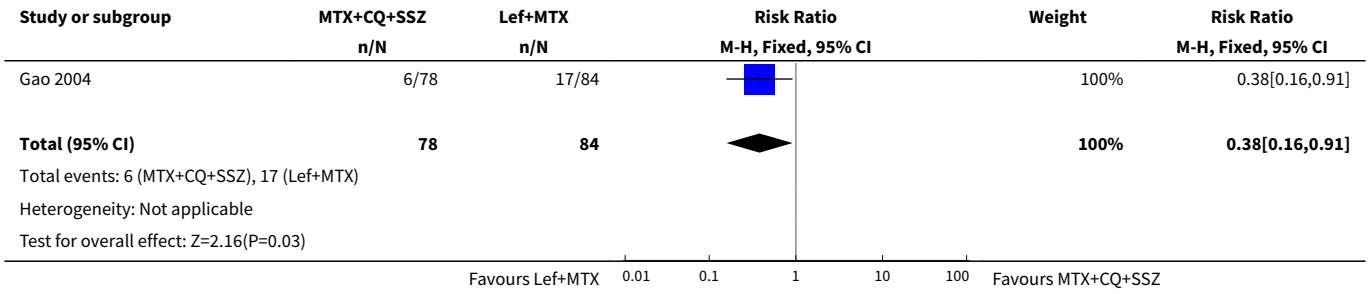
Analysis 13.8. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 8 Significant improvement rate, Lef+MTX vs MTX, at 2 years.



Analysis 13.9. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 9 Remarkable improvement rate, Lef+MTX vs. MTX, at 24 weeks.



Analysis 13.10. Comparison 13 Response rate in Chinese and Indian leflunomide studies, Outcome 10 Remission rate, Lef+MTX vs. MTX+CQ+SSZ, at 12 weeks.



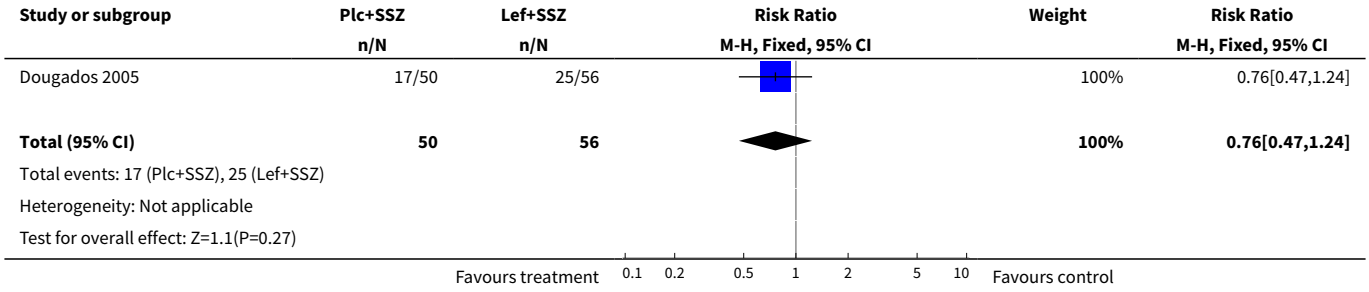
Comparison 14. DAS28 score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS28 response rate, Lef+SSZ vs. SSZ, at 24 weeks	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.47, 1.24]
2 Mean DAS28 score change, Lef+SSZ vs. SSZ, at 24 weeks	1	106	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.41, 0.61]
3 DAS28 responders for 24-week completers, Lef+SSZ vs. SSZ	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.36, 1.04]
4 Mean DAS28 score change, Lef vs. CsA, at 12 months	1	60	Mean Difference (IV, Fixed, 95% CI)	0.25 [0.15, 0.35]
5 Mean DAS28 score change, Lef vs. MTX, at 16 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	0.57 [0.24, 0.90]
6 EULAR remission (DAS28 <3.2), Lef vs MTX, at 16 weeks	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.64, 2.42]
7 Mean DAS28 score change, Lef vs. MTX, at 24 weeks	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.41, 0.21]

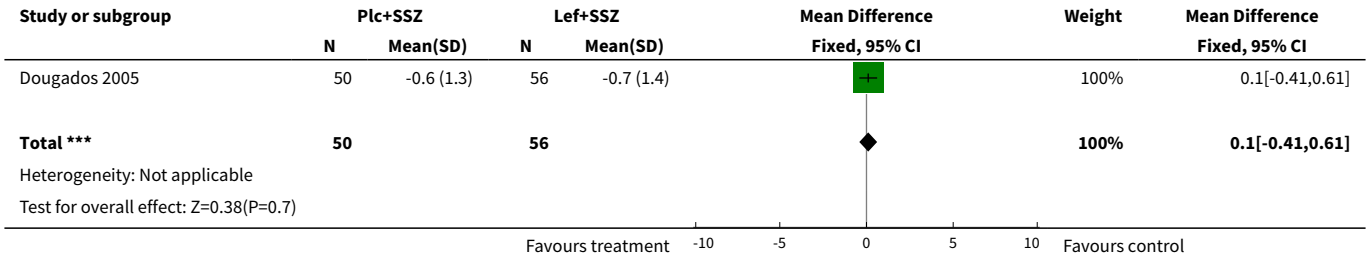
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Mean DAS28 score change, Lef vs. anti-TNF+MTX, at 24 weeks	1	48	Mean Difference (IV, Fixed, 95% CI)	0.80 [0.43, 1.17]
9 DAS28 remission, Lef vs. MTX, at 24 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.22, 4.56]
10 DAS28 low disease activity, Lef vs. MTX, at 24 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.28, 3.63]
11 DAS28 moderate disease activity, Lef vs. MTX, at 24 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.76, 1.44]
12 DAS28 high disease activity, Lef vs. MTX, at 24 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.22]
13 DAS28 remission, Lef vs. anti-TNF +MTX, at 24 weeks	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.38, 7.39]
14 DAS28 low disease activity, Lef vs. anti-TNF+MTX, at 24 weeks	1	48	Risk Ratio (M-H, Fixed, 95% CI)	3.33 [1.17, 9.51]
15 DAS28 moderate disease activity, Lef vs. anti-TNF+MTX, at 24 weeks	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.30, 1.04]
16 DAS28 high disease activity, Lef vs. anti-TNF+MTX, at 24 weeks	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.44]
17 Mean DAS28 score change, Lef vs. Lef +CsA, at 12 months	1	58	Mean Difference (IV, Fixed, 95% CI)	0.46 [0.35, 0.57]
18 DAS28 <3.2, Lef vs. CsA, at 12 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.34, 2.87]
19 DAS28 <3.2, Lef vs. Lef+CsA, at 12 months	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.68, 4.47]
20 EULAR good response, Lef vs. Lef+MTX, at 3 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.10, 1.34]
21 EULAR moderate response, Lef vs. Lef +MTX, at 3 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.47, 1.35]
22 EULAR response-no improvement, Lef vs. Lef+MTX, at 3 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	4.27 [0.64, 28.56]
23 DAS28 remission, Lef vs. Lef+MTX, at 3 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.18, 10.09]
24 EULAR good response, Lef+ADA vs. ADA, at 12 weeks	1	357	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.47, 1.05]
25 EULAR moderate response, Lef+ADA vs. ADA, at 12 weeks	1	357	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.73, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26 EULAR response rate, Lef vs. MTX, at 16 weeks	1	301	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.89, 1.23]

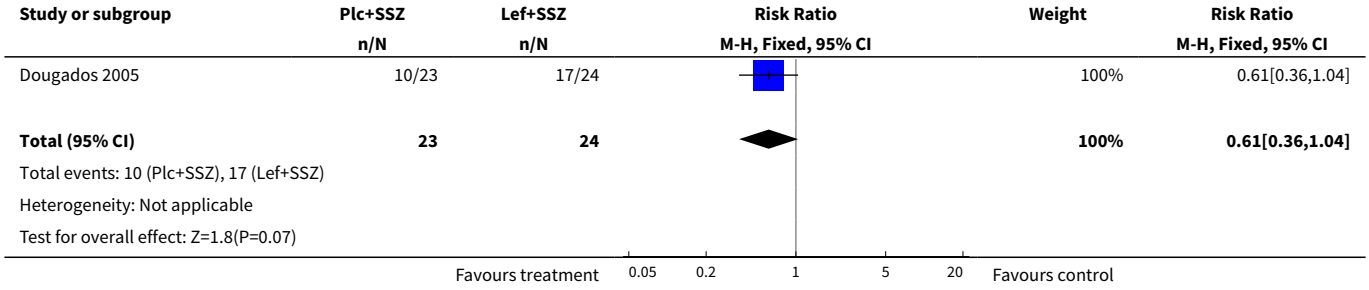
Analysis 14.1. Comparison 14 DAS28 score, Outcome 1 DAS28 response rate, Lef+SSZ vs. SSZ, at 24 weeks.



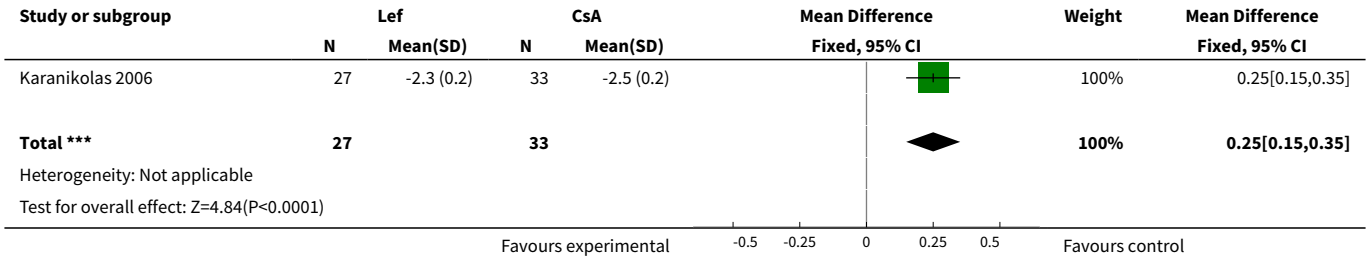
Analysis 14.2. Comparison 14 DAS28 score, Outcome 2 Mean DAS28 score change, Lef+SSZ vs. SSZ, at 24 weeks.



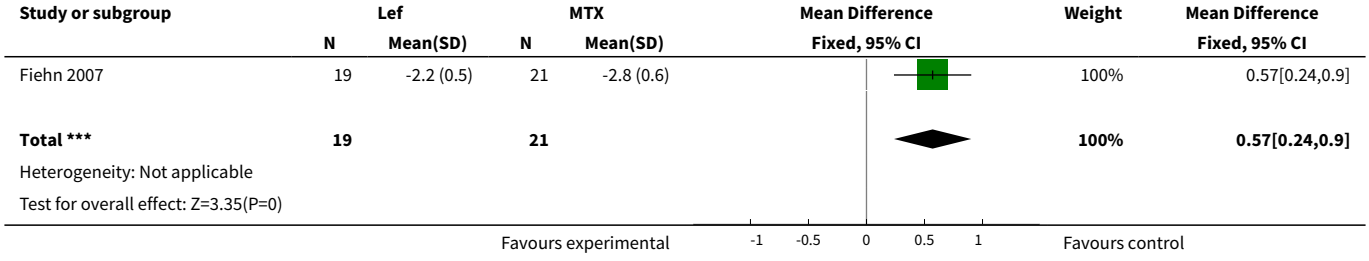
Analysis 14.3. Comparison 14 DAS28 score, Outcome 3 DAS28 responders for 24-week completers, Lef+SSZ vs. SSZ.



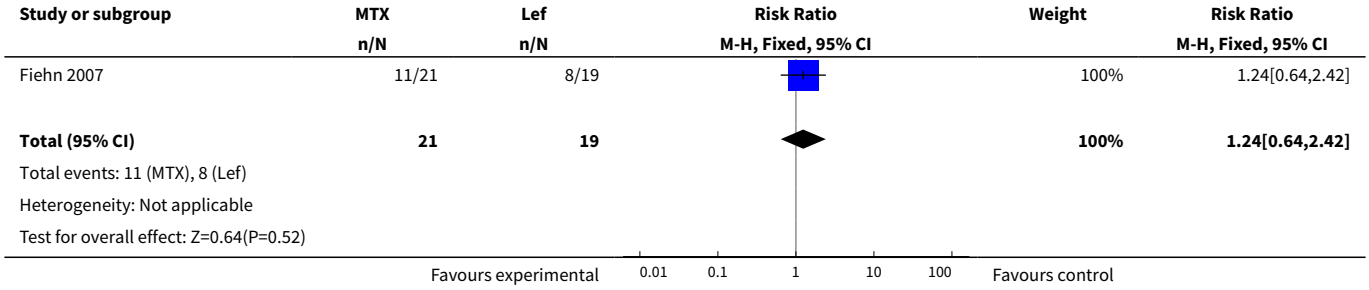
Analysis 14.4. Comparison 14 DAS28 score, Outcome 4 Mean DAS28 score change, Lef vs. CsA, at 12 months.



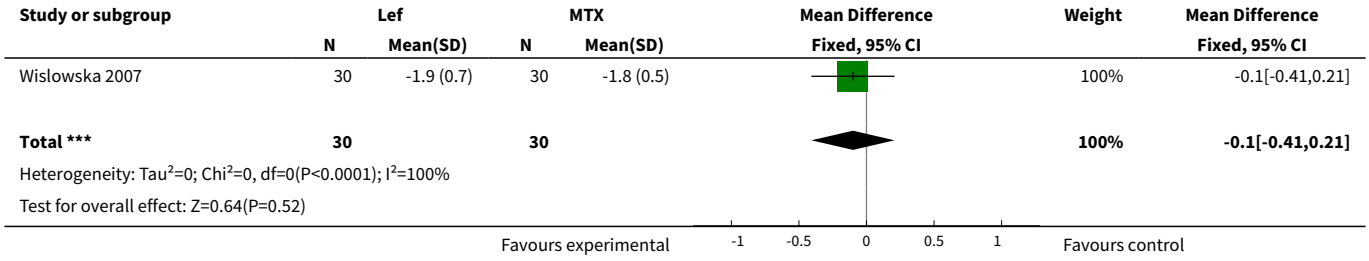
Analysis 14.5. Comparison 14 DAS28 score, Outcome 5 Mean DAS28 score change, Lef vs. MTX, at 16 weeks.



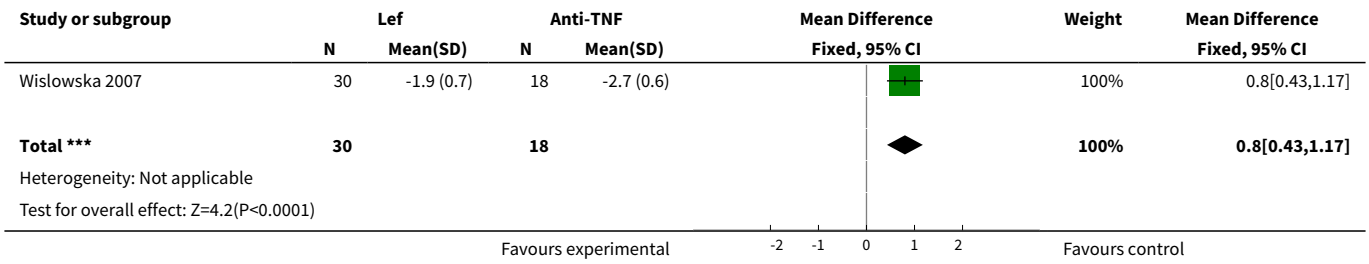
Analysis 14.6. Comparison 14 DAS28 score, Outcome 6 EULAR remission (DAS28 <3.2), Lef vs MTX, at 16 weeks.



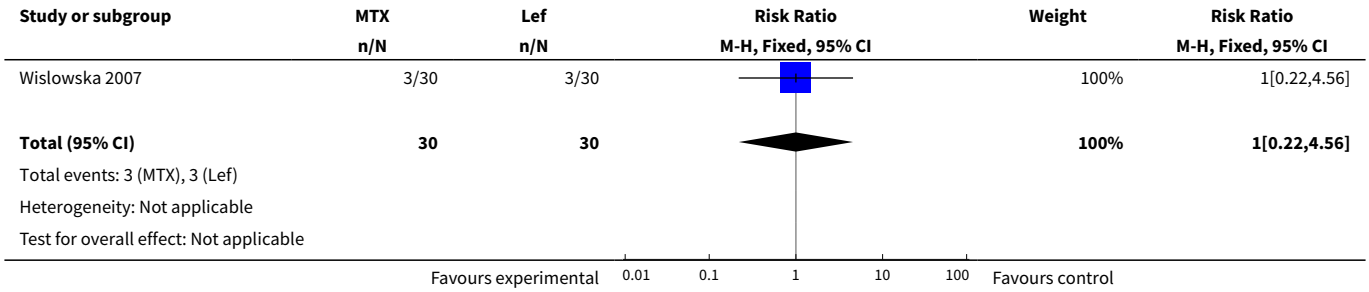
Analysis 14.7. Comparison 14 DAS28 score, Outcome 7 Mean DAS28 score change, Lef vs. MTX, at 24 weeks.



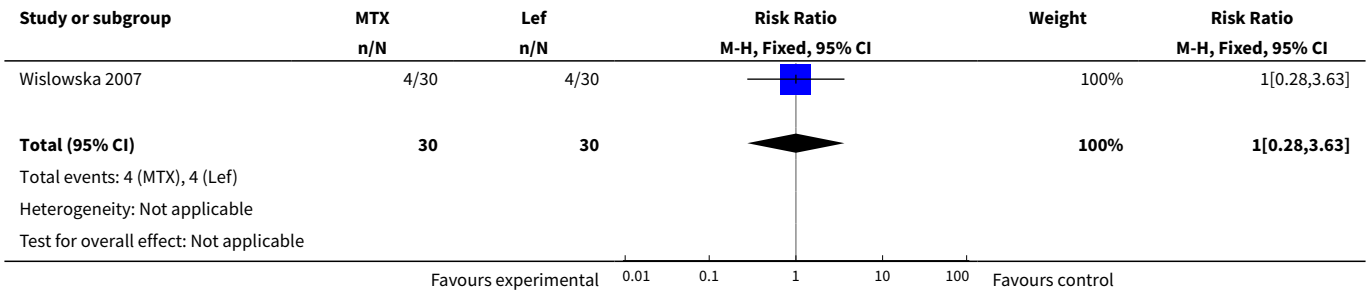
Analysis 14.8. Comparison 14 DAS28 score, Outcome 8 Mean DAS28 score change, Lef vs. anti-TNF+MTX, at 24 weeks.



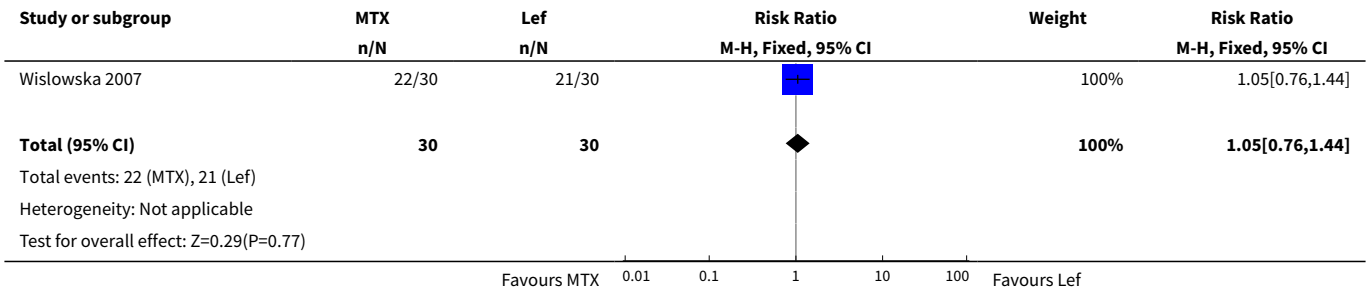
Analysis 14.9. Comparison 14 DAS28 score, Outcome 9 DAS28 remission, Lef vs. MTX, at 24 weeks.



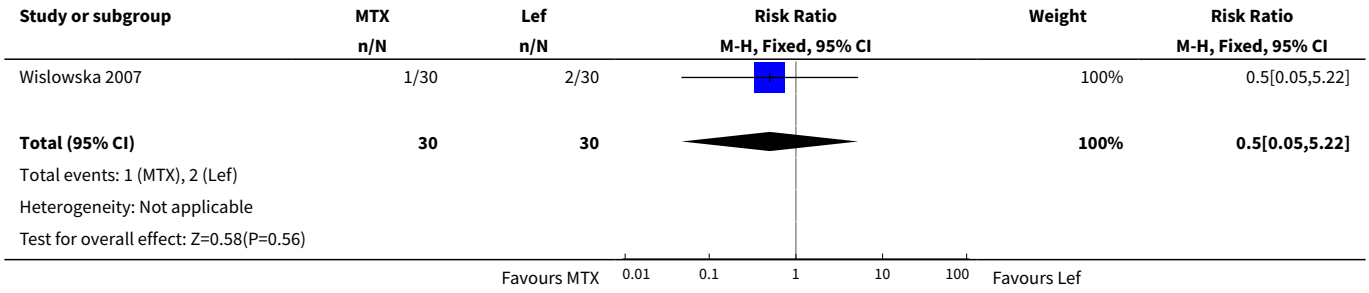
Analysis 14.10. Comparison 14 DAS28 score, Outcome 10 DAS28 low disease activity, Lef vs. MTX, at 24 weeks.



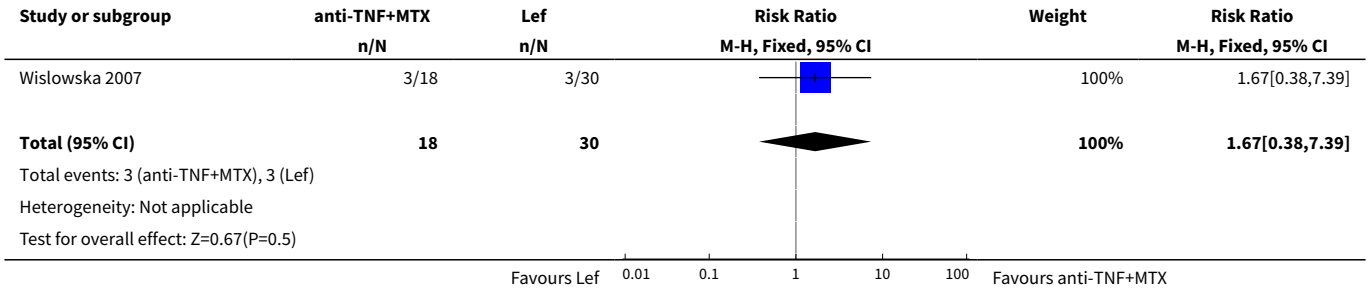
Analysis 14.11. Comparison 14 DAS28 score, Outcome 11 DAS28 moderate disease activity, Lef vs. MTX, at 24 weeks.



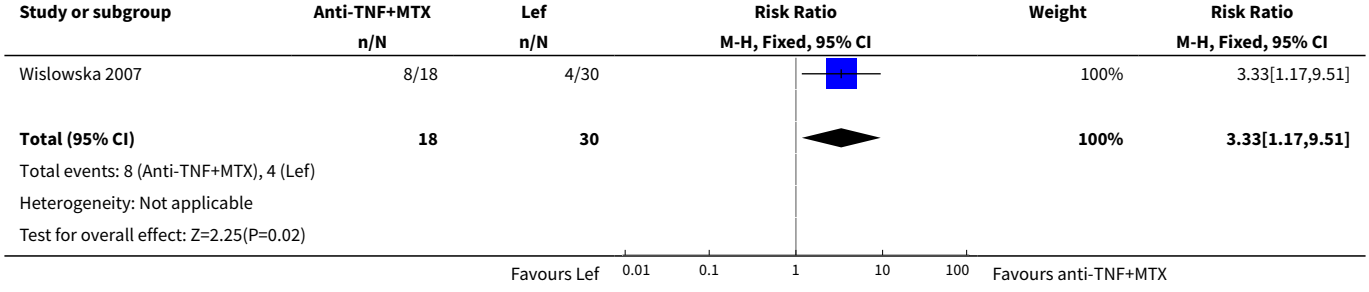
Analysis 14.12. Comparison 14 DAS28 score, Outcome 12 DAS28 high disease activity, Lef vs. MTX, at 24 weeks.



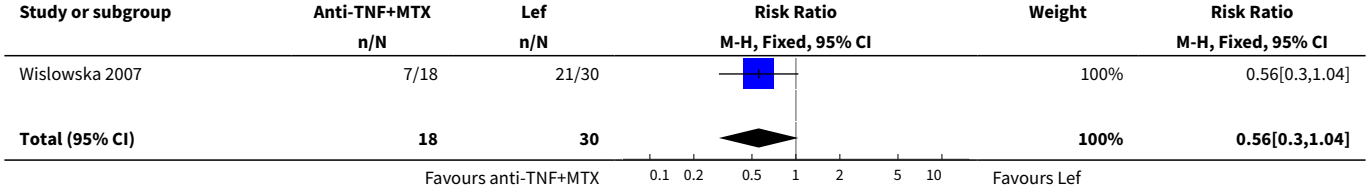
Analysis 14.13. Comparison 14 DAS28 score, Outcome 13 DAS28 remission, Lef vs. anti-TNF+MTX, at 24 weeks.

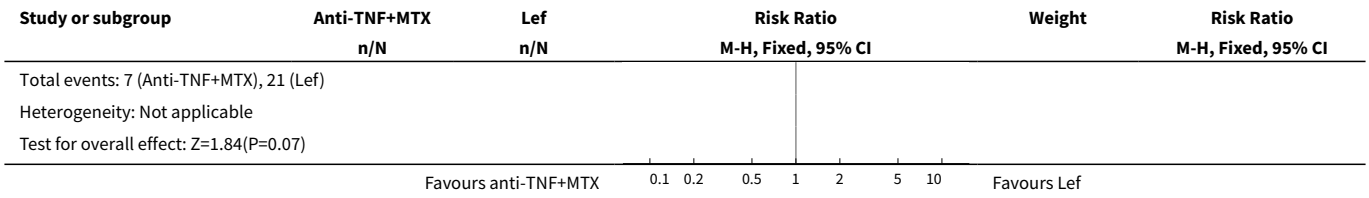


Analysis 14.14. Comparison 14 DAS28 score, Outcome 14 DAS28 low disease activity, Lef vs. anti-TNF+MTX, at 24 weeks.

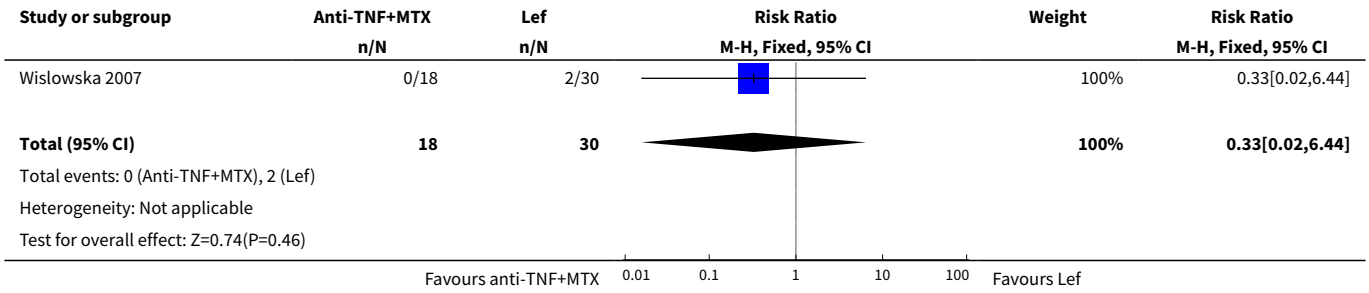


Analysis 14.15. Comparison 14 DAS28 score, Outcome 15 DAS28 moderate disease activity, Lef vs. anti-TNF+MTX, at 24 weeks.

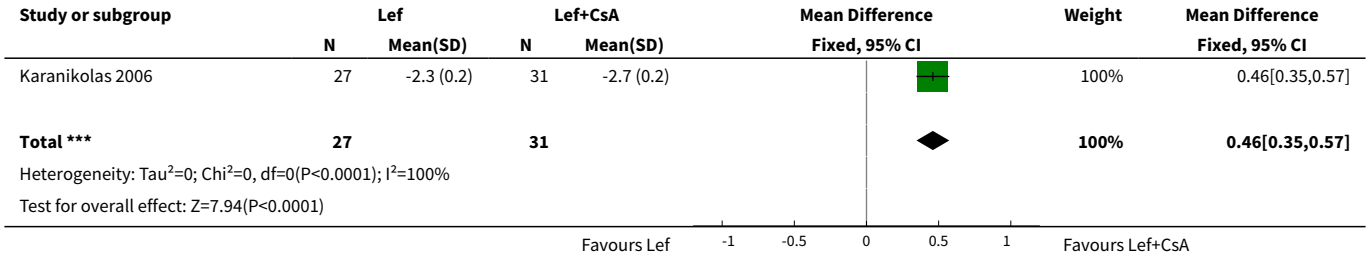




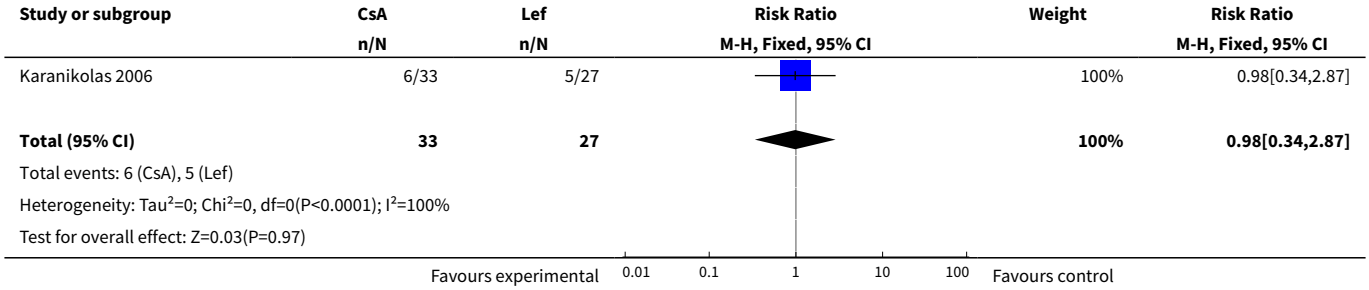
Analysis 14.16. Comparison 14 DAS28 score, Outcome 16 DAS28 high disease activity, Lef vs. anti-TNF+MTX, at 24 weeks.



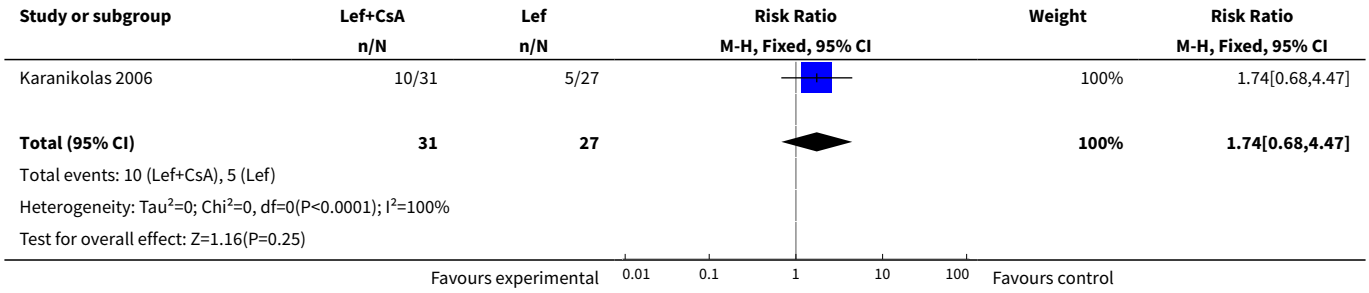
Analysis 14.17. Comparison 14 DAS28 score, Outcome 17 Mean DAS28 score change, Lef vs. Lef+CsA, at 12 months.



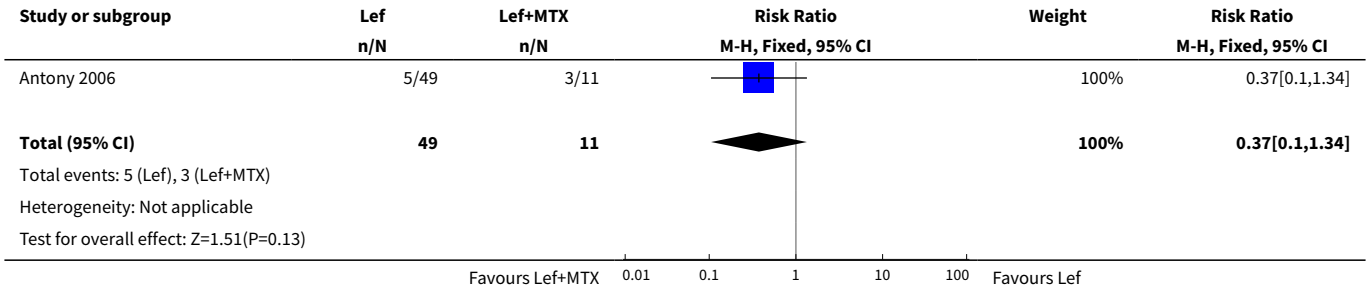
Analysis 14.18. Comparison 14 DAS28 score, Outcome 18 DAS28 <3.2, Lef vs. CsA, at 12 months.



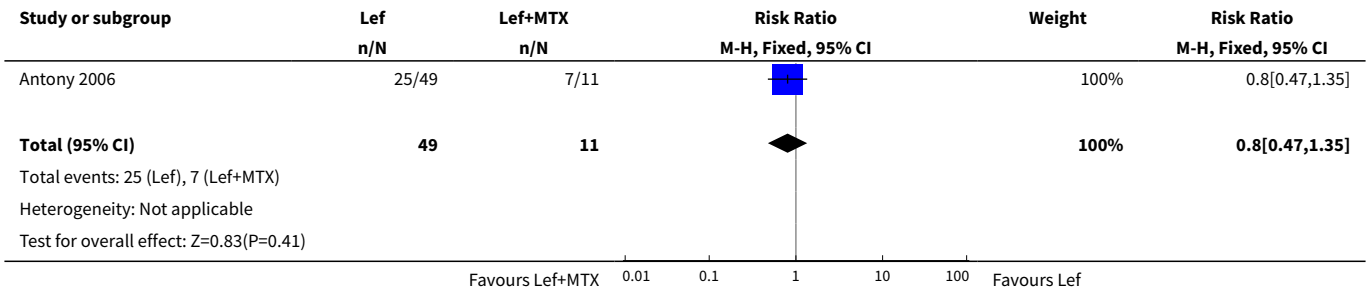
Analysis 14.19. Comparison 14 DAS28 score, Outcome 19 DAS28 <3.2, Lef vs. Lef+CsA, at 12 months.



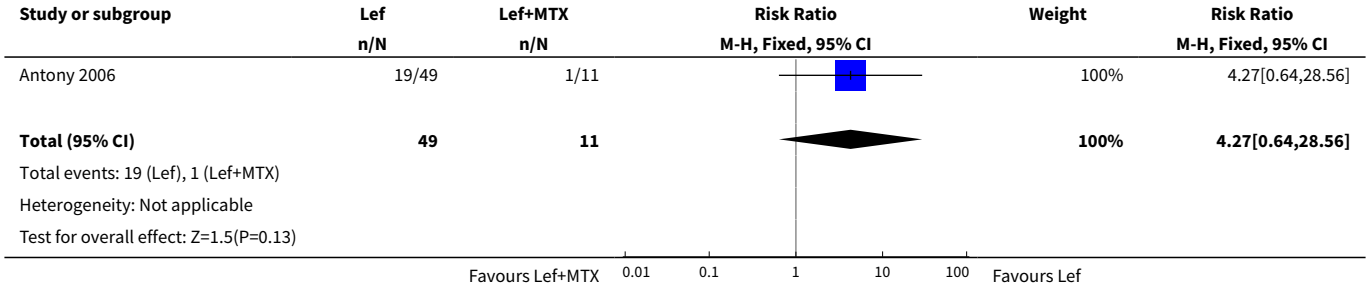
Analysis 14.20. Comparison 14 DAS28 score, Outcome 20 EULAR good response, Lef vs. Lef+MTX, at 3 months.



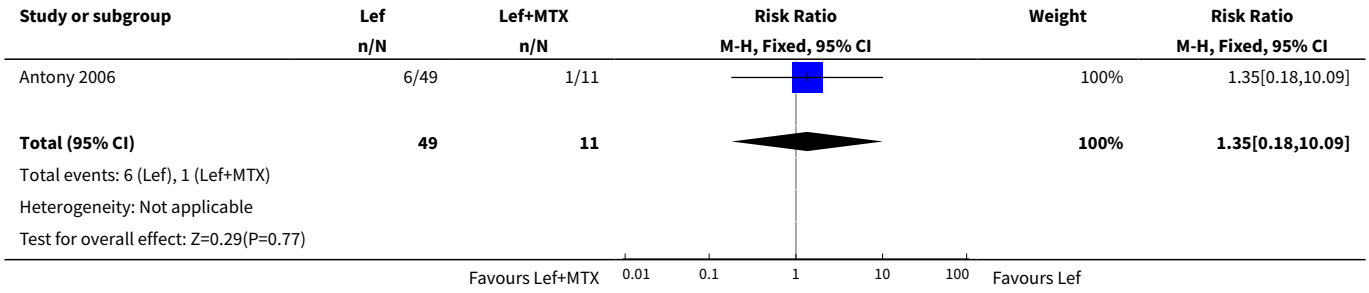
Analysis 14.21. Comparison 14 DAS28 score, Outcome 21 EULAR moderate response, Lef vs. Lef+MTX, at 3 months.



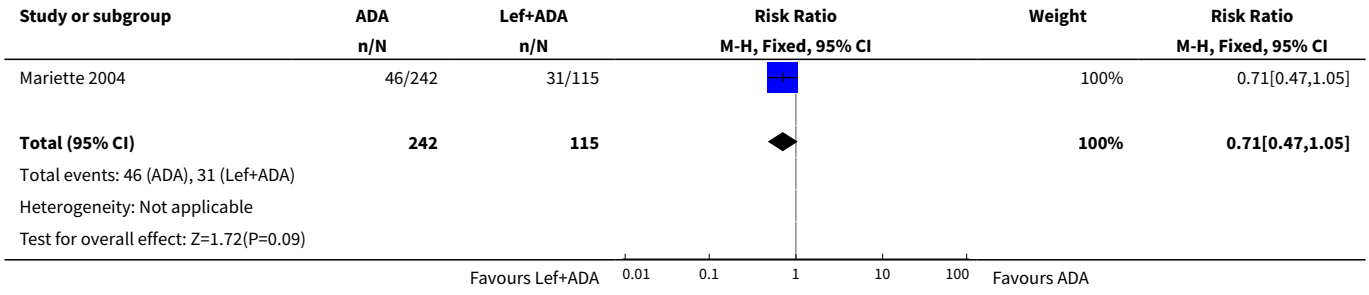
Analysis 14.22. Comparison 14 DAS28 score, Outcome 22 EULAR response-no improvement, Lef vs. Lef+MTX, at 3 months.



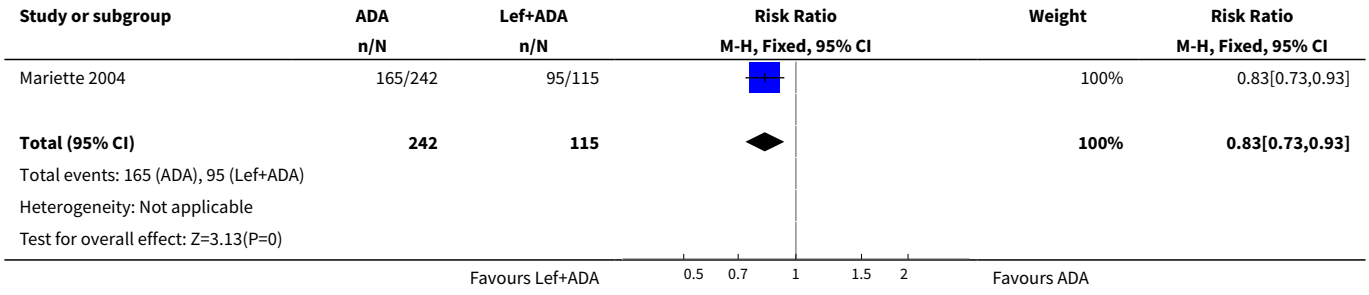
Analysis 14.23. Comparison 14 DAS28 score, Outcome 23 DAS28 remission, Lef vs. Lef+MTX, at 3 months.



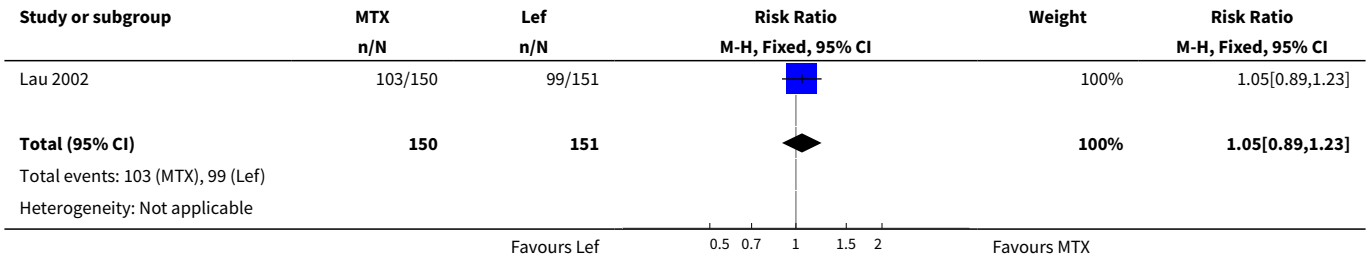
Analysis 14.24. Comparison 14 DAS28 score, Outcome 24 EULAR good response, Lef+ADA vs. ADA, at 12 weeks.

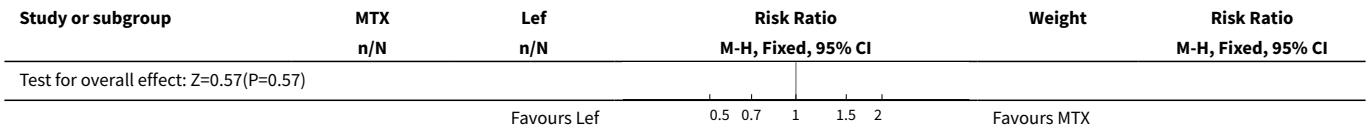


Analysis 14.25. Comparison 14 DAS28 score, Outcome 25 EULAR moderate response, Lef+ADA vs. ADA, at 12 weeks.



Analysis 14.26. Comparison 14 DAS28 score, Outcome 26 EULAR response rate, Lef vs. MTX, at 16 weeks.

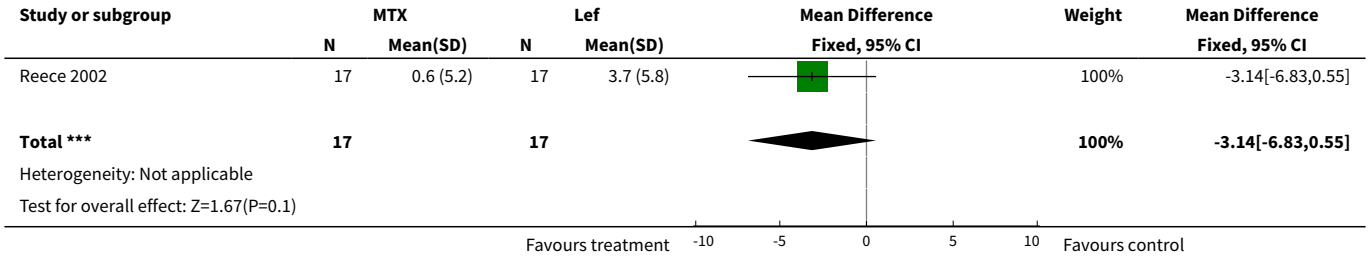




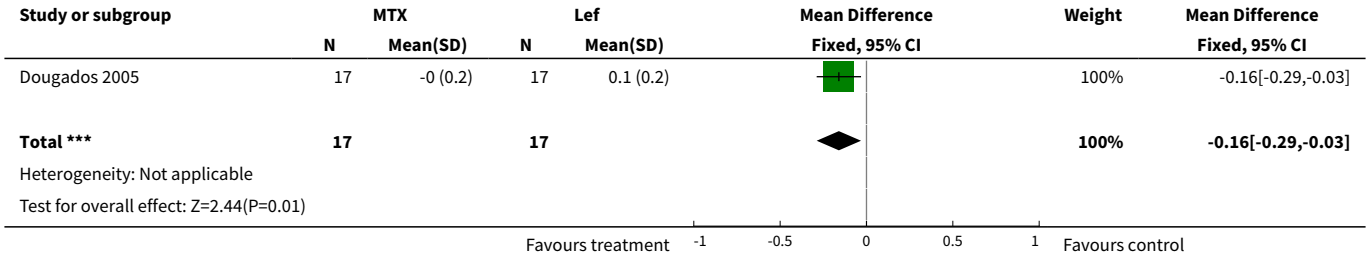
Comparison 15. Dynamic enhanced MRI assessment of knee joint, at 4 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximal signal intensity enhancement (ME) (/100), at 4 months	1	34	Mean Difference (IV, Fixed, 95% CI)	-3.14 [-6.83, 0.55]
2 Initial rate of enhancement (IRE) (/100), at 4 months	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.29, -0.03]

Analysis 15.1. Comparison 15 Dynamic enhanced MRI assessment of knee joint, at 4 months, Outcome 1 Maximal signal intensity enhancement (ME) (/100), at 4 months.



Analysis 15.2. Comparison 15 Dynamic enhanced MRI assessment of knee joint, at 4 months, Outcome 2 Initial rate of enhancement (IRE) (/100), at 4 months.



Comparison 16. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total withdrawals in leflunomide vs. placebo	3	727	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.59, 0.83]
2 Withdrawals due to adverse events in leflunomide vs. placebo	3	727	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.67, 4.47]
3 Total withdrawals in leflunomide vs.SSZ, at 6 months	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.53, 1.07]
4 Withdrawals due to adverse events in leflunomide vs. SSZ, at 6 months	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.45, 1.33]
5 Total withdrawals in leflunomide vs. MTX, at 12 months	2	1363	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.08, 1.48]
6 Withdrawals due to adverse events in leflunomide vs. MTX, at 12 months	2	1363	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.13, 1.83]
7 alopecia, leflunomide vs. placebo	3	728	Risk Ratio (M-H, Fixed, 95% CI)	6.60 [2.36, 18.44]
8 alopecia, leflunomide vs. SSZ	1	266	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.63, 3.93]
9 alopecia, leflunomide vs. MTX	6	2329	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.32, 2.24]
10 Elevated liver function tests, leflunomide vs. placebo	3	728	Risk Ratio (M-H, Fixed, 95% CI)	3.74 [1.86, 7.54]
11 Elevated liver function tests, leflunomide vs. SSZ	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.15, 2.46]
12 Elevated liver function tests, leflunomide vs. MTX	5	2028	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.31, 1.39]
13 GI symptoms, leflunomide vs. placebo	3	728	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.28, 1.99]
14 GI symptoms, leflunomide vs. SSZ	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.63, 1.22]
15 GI symptoms, leflunomide vs. MTX	6	2088	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.28, 0.92]
16 Allergy or rash, leflunomide vs. placebo	3	728	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.07, 2.37]
17 Allergy or rash, leflunomide vs. SSZ	1	266	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.52, 1.92]
18 Allergy or rash, leflunomide vs. MTX	4	1948	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.19, 1.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 hypertension, leflunomide vs. placebo	2	525	Risk Ratio (M-H, Fixed, 95% CI)	3.36 [0.58, 19.32]
20 hypertension, leflunomide vs. SSZ	1	266	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.87]
21 hypertension, leflunomide vs. MTX	2	1363	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.42, 3.69]
22 Weight loss, leflunomide vs. placebo	2	428	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.44, 2.87]
23 Weight loss, leflunomide vs. SSZ	1	266	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.62, 14.60]
24 Weight loss, leflunomide vs. MTX	1	999	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.39, 1.66]
25 Infections, leflunomide vs. placebo	3	728	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.34]
26 Infections, leflunomide vs. SSZ	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.21]
27 Infections, leflunomide vs. MTX	2	1363	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.15]
28 Total withdrawals in leflunomide vs. MTX, at 2 years	1	612	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.83, 1.61]
29 Withdrawals due to adverse events in leflunomide vs. MTX, at 2 years	1	612	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.77, 2.47]
30 Total withdrawals in leflunomide vs.SSZ, at 12 months	1	156	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.43, 2.63]
31 Withdrawals due to adverse events in leflunomide vs. SSZ, at 12 months	1	156	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.90]
32 Total withdrawals in leflunomide vs.SSZ, at 24 months	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.39, 1.59]
33 Withdrawals due to adverse events in leflunomide vs. SSZ, at 24 months	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.76]
34 Reported adverse events in leflunomide vs. MTX, at 6 months	4	724	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.42, 0.73]
35 Withdrawals due to adverse events in leflunomide vs. MTX, at 6 months	4	724	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.57]
36 **Elevated liver function tests, reported as adverse event	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.1 Leflunomide vs. placebo, at 6 months	2	431	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.02, 5.87]
36.2 Leflunomide vs. placebo, at 1 year	1	300	Risk Ratio (M-H, Random, 95% CI)	5.84 [1.81, 18.80]
36.3 Leflunomide vs. placebo, at 2 years	1	318	Risk Ratio (M-H, Random, 95% CI)	3.23 [1.27, 8.25]
36.4 Leflunomide vs. SSZ, at 6 months	1	266	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.15, 2.46]
36.5 Leflunomide vs. MTX, at 6 months	2	584	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.24, 1.15]
36.6 Leflunomide vs. MTX, at 1 year	2	1363	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.17, 2.45]
36.7 Leflunomide vs. MTX, at 2 years	2	992	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.30, 2.14]
37 **Elevated liver function tests, withdrawals	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
37.1 Leflunomide vs. placebo, at 6 months	2	431	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.13, 15.03]
37.2 Leflunomide vs. placebo, at 1 year	1	300	Risk Ratio (M-H, Random, 95% CI)	4.21 [0.97, 18.34]
37.3 Leflunomide vs. placebo, at 2 years	1	318	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.12, 14.70]
37.4 Leflunomide vs. SSZ, at 6 months	1	266	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.14, 6.99]
37.5 Leflunomide vs. MTX, at 6 months	1	504	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.02, 1.63]
37.6 Leflunomide vs. MTX, at 1 year	2	1363	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.28, 2.86]
37.7 Leflunomide vs. MTX, at 2 years	2	992	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.42]
38 Total withdrawals in leflunomide+MTX vs.MTX, at 24 weeks	1	263	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.60, 1.43]
39 Withdrawals due to adverse events in leflunomide+MTX vs. MTX, at 24 weeks	1	263	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.83, 3.97]
40 Reported adverse events in leflunomide10mg vs.leflunomide20mg, at 24 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.10]

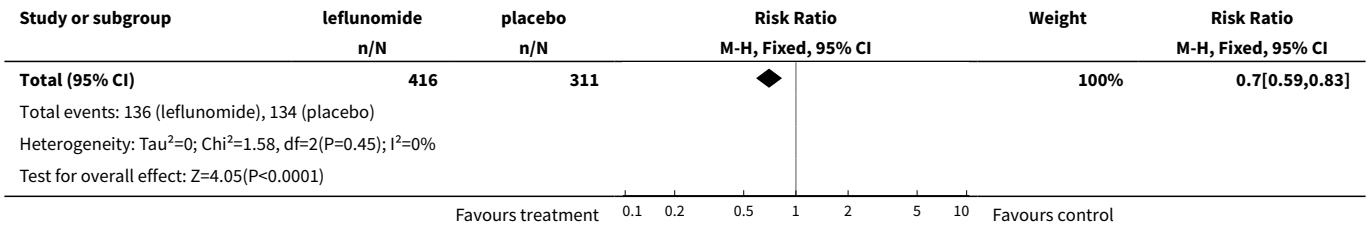
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41 Withdrawals due to adverse events in leflunomide10mg vs. leflunomide20mg, at 24 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.78, 2.10]
42 Related adverse events in Lef+SSZ vs.Plc+SSZ, at 24 weeks	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.20]
43 Serious adverse events in Lef+SSZ vs. Plc+SSZ, at 24 weeks	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.47, 6.77]
44 Withdrawals due to adverse events in Lef+SSZ vs. Plc+SSZ, at 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
44.1 Overall	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.77, 2.34]
44.2 Rash	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.32, 3.93]
44.3 Nausea	1	106	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.41, 30.90]
44.4 Diarrhea	1	106	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [0.29, 24.93]
45 Total withdrawals, Lef+SSZ vs. Plc +SSZ, at 24 weeks	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.85, 1.81]
46 Reported adverse events, Lef/Lef+MTX vs Plc/Lef+MTX, at 48 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
46.1 nausea	1	192	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.31, 5.80]
46.2 diarrhea	1	192	Risk Ratio (M-H, Fixed, 95% CI)	5.33 [1.61, 17.71]
46.3 rash	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.30, 2.46]
46.4 alopecia	1	192	Risk Ratio (M-H, Fixed, 95% CI)	8.0 [1.02, 62.74]
46.5 infection	1	192	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.81, 7.70]
46.6 elevated liver enzymes	1	191	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.53, 2.15]
47 Serious adverse events in Lef/Lef+MTX vs. Plc/Lef+MTX, at 48 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.44, 1.72]
48 Total withdrawals, Lef/Lef+MTX vs. Plc/Lef+MTX, at 48 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.65, 3.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49 Withdrawals due to adverse events, Lef/Lef+MTX vs. Plc/Lef+MTX, at 48 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.83]
50 Total withdrawals, Lef vs. CsA, at 12 months	1	71	Risk Ratio (M-H, Fixed, 95% CI)	4.38 [1.02, 18.84]
51 Withdrawals due to adverse events, Lef vs. CsA, at 12 months	1	71	Risk Ratio (M-H, Fixed, 95% CI)	8.76 [0.49, 156.85]
52 Total withdrawals, Lef vs. Lef+CsA, at 12 months	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.15, 1.35]
53 Withdrawals due to adverse events, Lef vs. Lef+CsA, at 12 months	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.63]
54 Withdrawals due to adverse events, Lef vs. Lef+MTX, at 3 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.03, 8.03]
55 Total withdrawals, Lef+MTX vs. MTX, at 36 months	1	466	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.39, 1.43]
56 Withdrawals due to adverse events, Lef +MTX vs. MTX, at 36 months	1	466	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.41, 1.81]
57 Reported adverse events, weekly Lef vs. daily Lef	1	16	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.85, 10.63]
58 Withdrawals due to adverse events, weekly Lef vs. daily Lef	1	16	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.28, 90.18]
59 Total withdrawals, Lef+MTX vs. MTX, at 24 months	1	166	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.52, 3.01]
60 Withdrawals due to adverse events, Lef +MTX vs. MTX, at 24 months	1	166	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.46, 4.23]
61 Reported adverse events in Lef+MTX vs. MTX, at 24 weeks	1	64	Risk Ratio (M-H, Fixed, 95% CI)	3.5 [1.29, 9.49]
62 Withdrawals due to adverse events, weekly Lef200 vs. weekly Lef100, at 6 months	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 4.93]

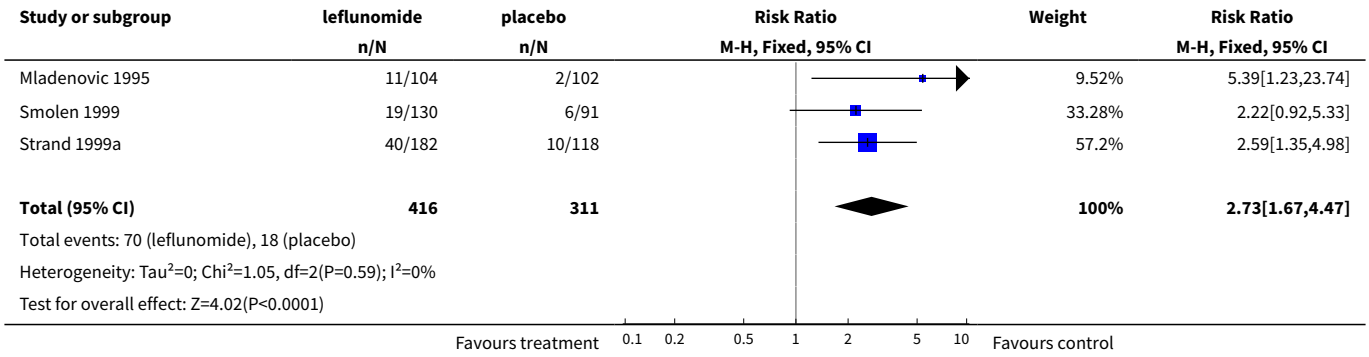
Analysis 16.1. Comparison 16 Adverse events, Outcome 1 Total withdrawals in leflunomide vs. placebo.

Study or subgroup	leflunomide n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mladenovic 1995	13/104	12/102		7.64%	1.06[0.51,2.22]
Smolen 1999	37/130	41/91		30.41%	0.63[0.44,0.9]
Strand 1999a	86/182	81/118		61.95%	0.69[0.57,0.84]

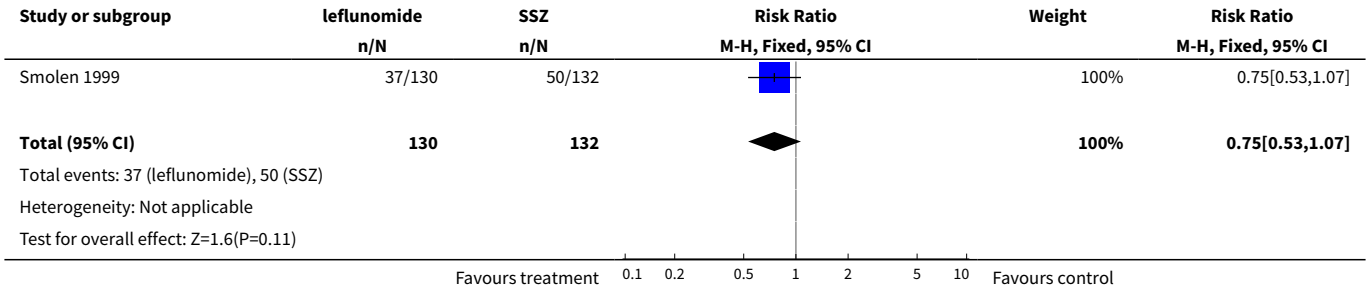
Favours treatment — Favours control



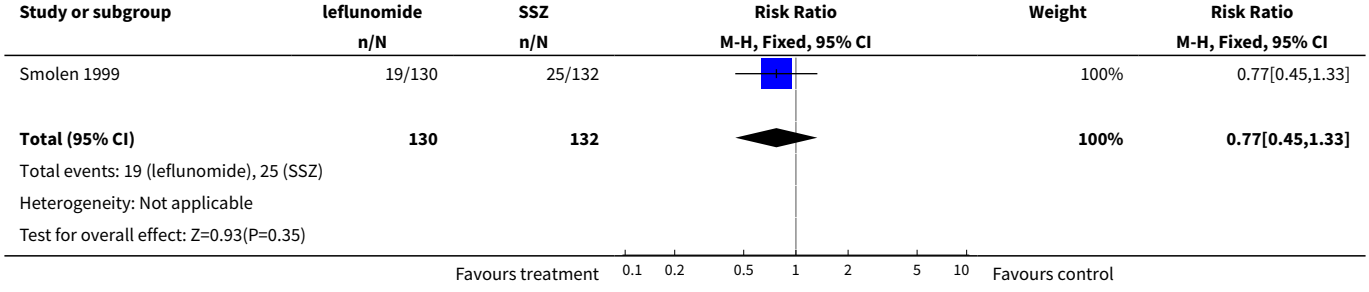
Analysis 16.2. Comparison 16 Adverse events, Outcome 2 Withdrawals due to adverse events in leflunomide vs. placebo.



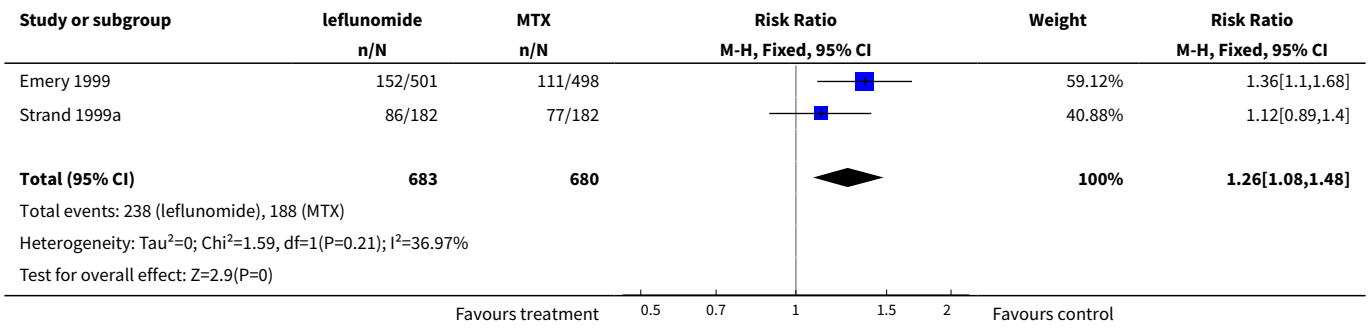
Analysis 16.3. Comparison 16 Adverse events, Outcome 3 Total withdrawals in leflunomide vs.SSZ, at 6 months.



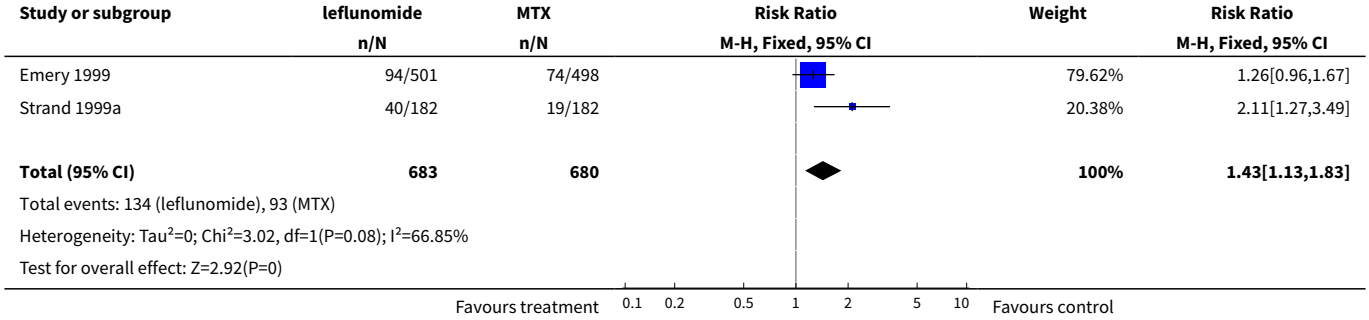
Analysis 16.4. Comparison 16 Adverse events, Outcome 4 Withdrawals due to adverse events in leflunomide vs. SSZ, at 6 months.



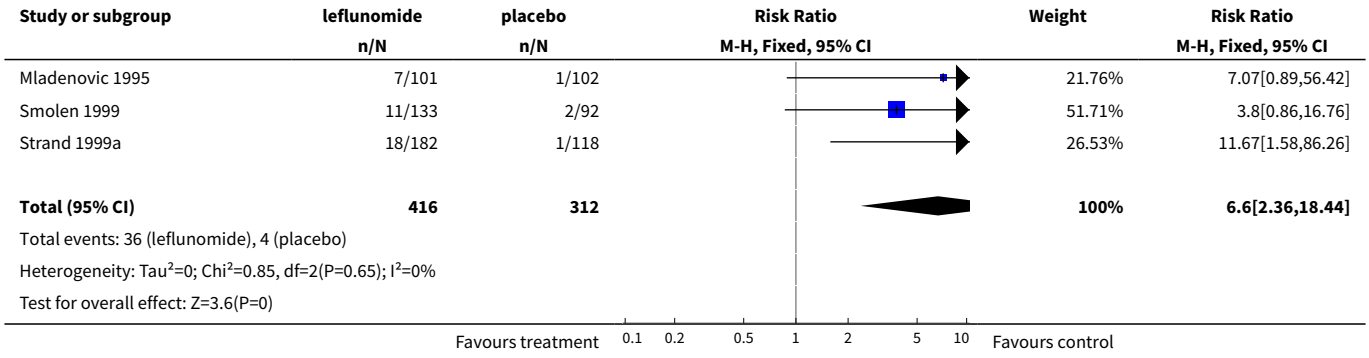
Analysis 16.5. Comparison 16 Adverse events, Outcome 5 Total withdrawals in leflunomide vs. MTX, at 12 months.



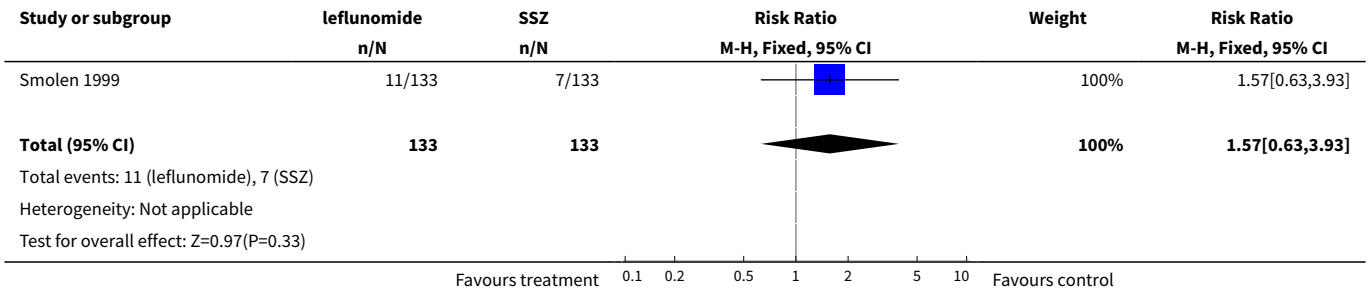
Analysis 16.6. Comparison 16 Adverse events, Outcome 6 Withdrawals due to adverse events in leflunomide vs. MTX, at 12 months.



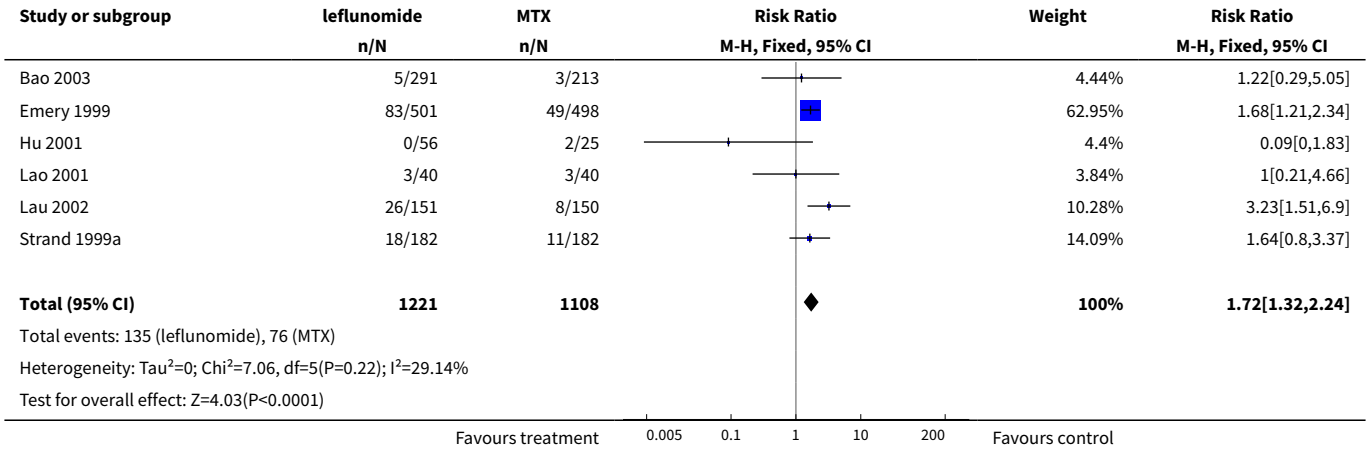
Analysis 16.7. Comparison 16 Adverse events, Outcome 7 alopecia, leflunomide vs. placebo.



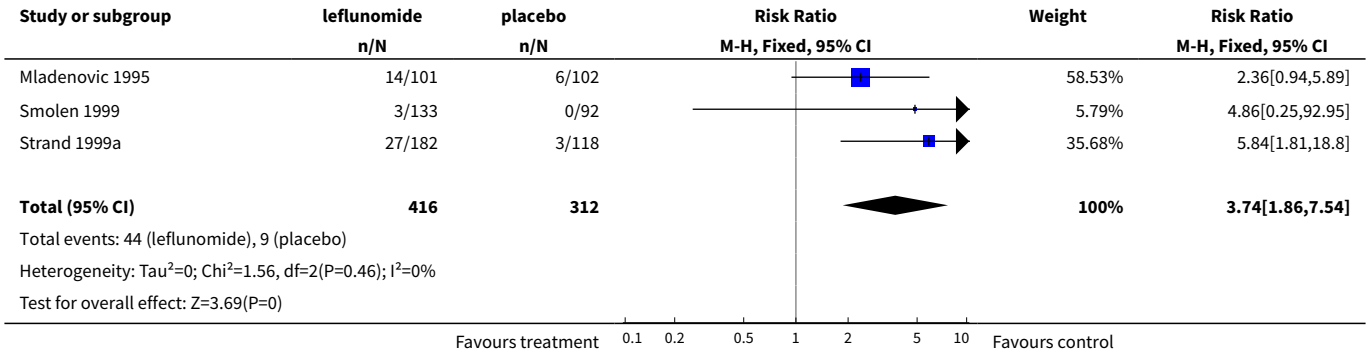
Analysis 16.8. Comparison 16 Adverse events, Outcome 8 alopecia, leflunomide vs. SSZ.



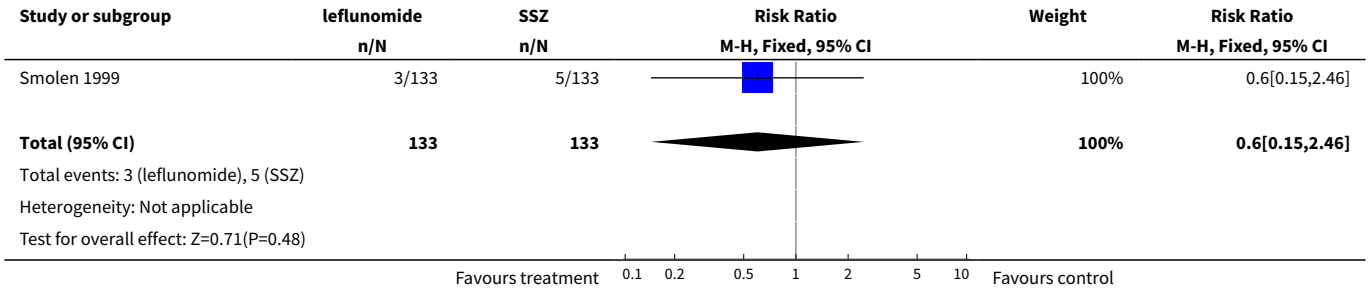
Analysis 16.9. Comparison 16 Adverse events, Outcome 9 alopecia, leflunomide vs. MTX.



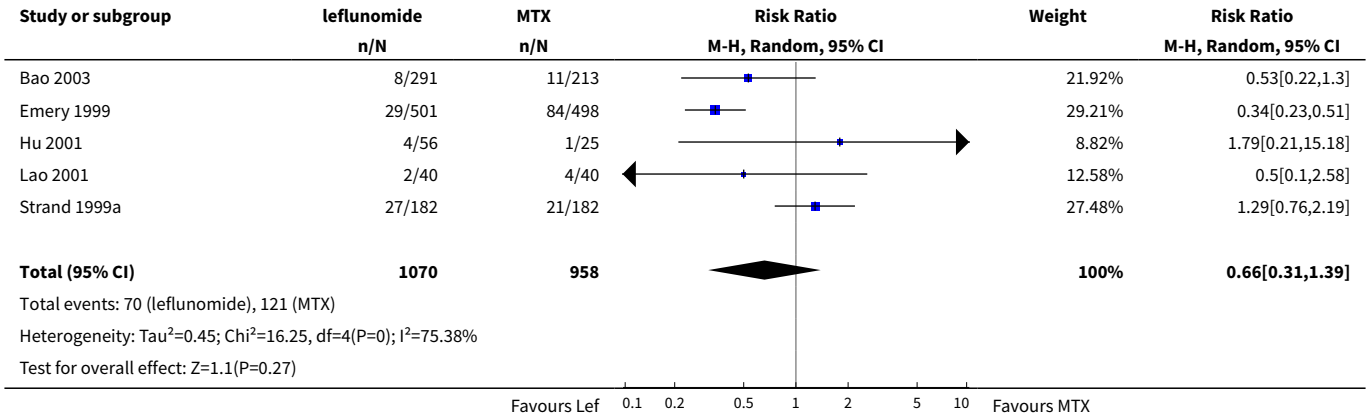
Analysis 16.10. Comparison 16 Adverse events, Outcome 10 Elevated liver function tests, leflunomide vs. placebo.



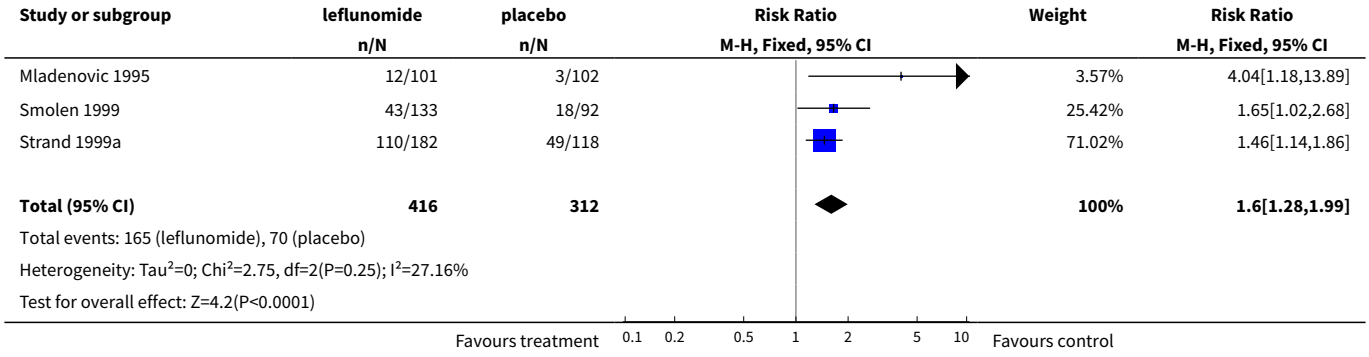
Analysis 16.11. Comparison 16 Adverse events, Outcome 11 Elevated liver function tests, leflunomide vs. SSZ.



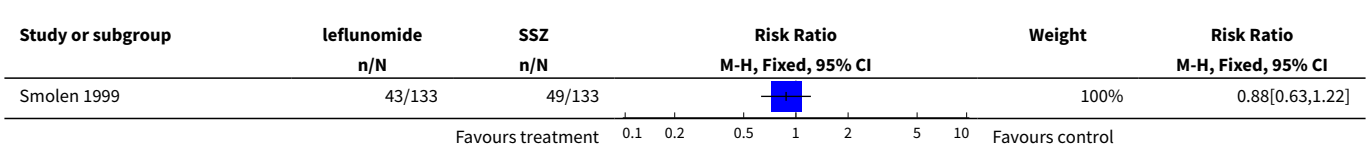
Analysis 16.12. Comparison 16 Adverse events, Outcome 12 Elevated liver function tests, leflunomide vs. MTX.

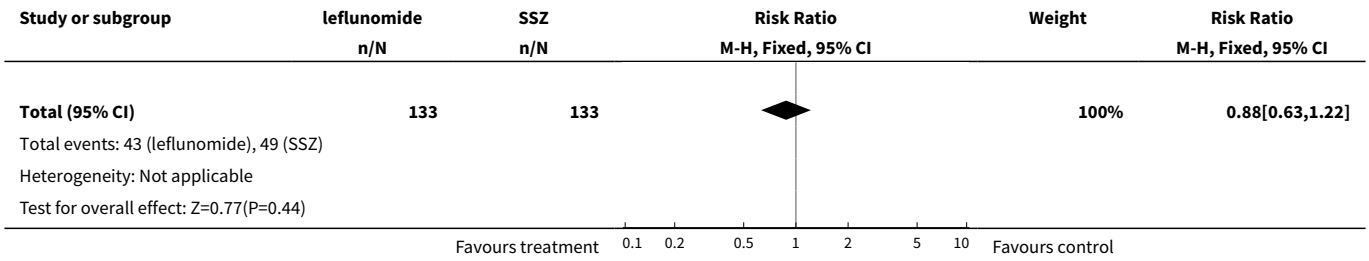


Analysis 16.13. Comparison 16 Adverse events, Outcome 13 GI symptoms, leflunomide vs. placebo.

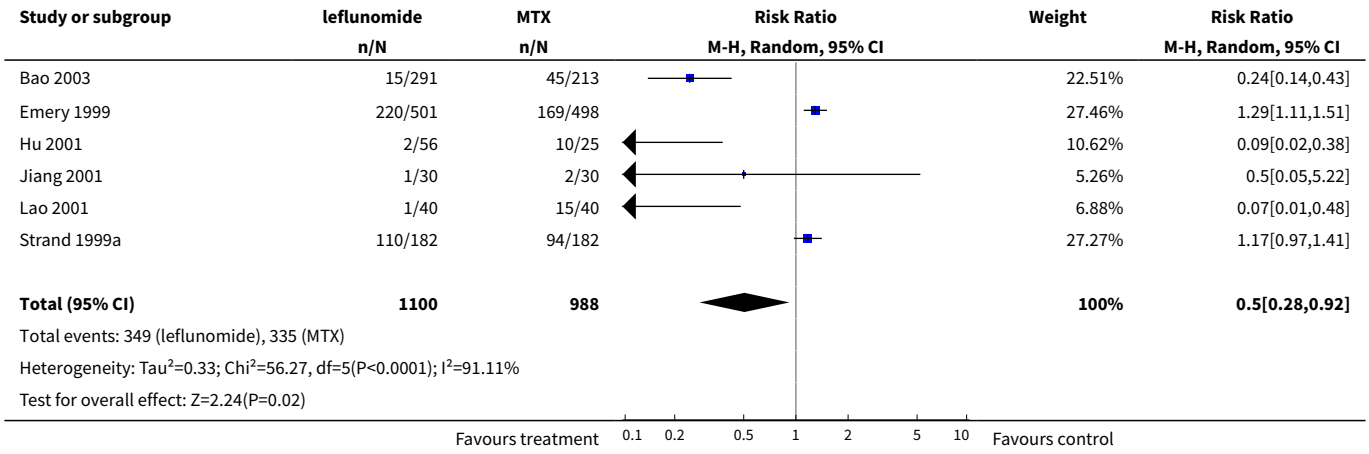


Analysis 16.14. Comparison 16 Adverse events, Outcome 14 GI symptoms, leflunomide vs. SSZ.

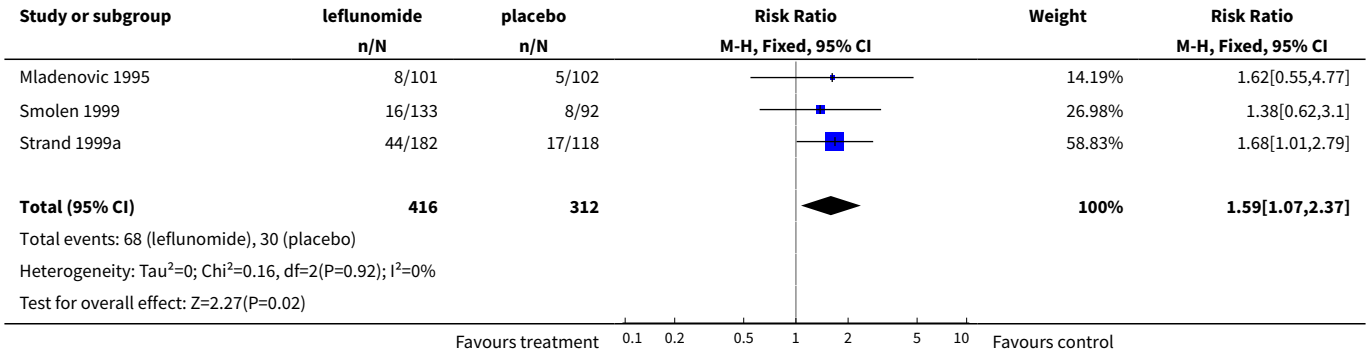




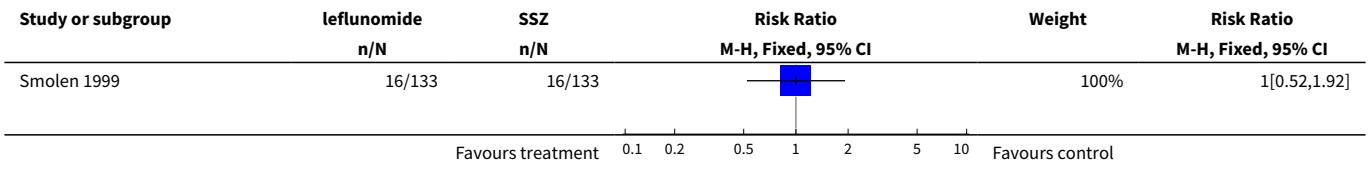
Analysis 16.15. Comparison 16 Adverse events, Outcome 15 GI symptoms, leflunomide vs. MTX.

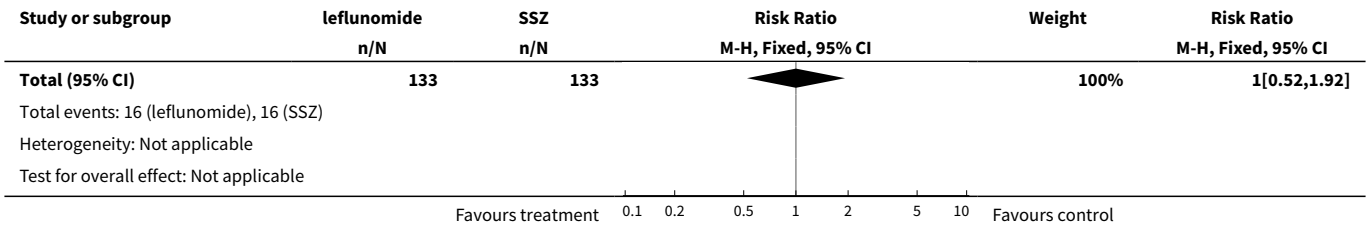


Analysis 16.16. Comparison 16 Adverse events, Outcome 16 Allergy or rash, leflunomide vs. placebo.

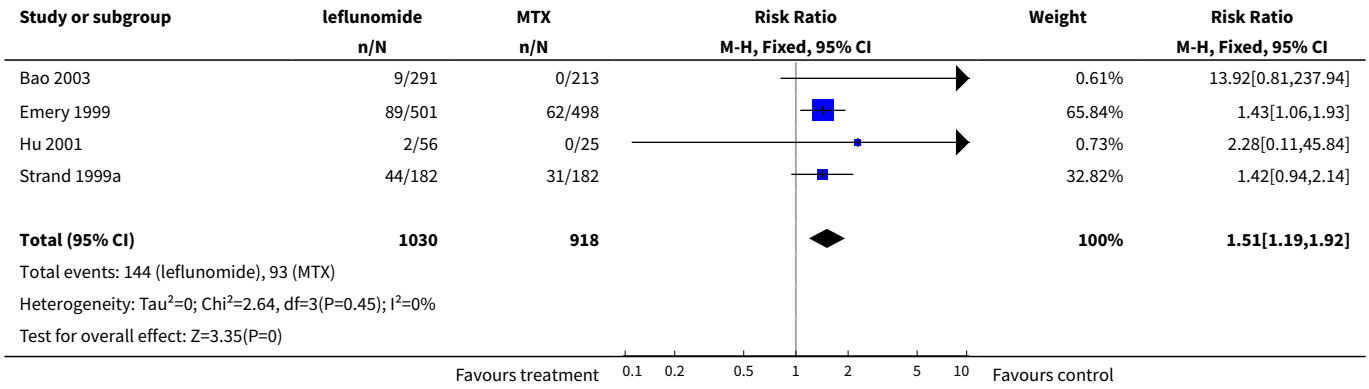


Analysis 16.17. Comparison 16 Adverse events, Outcome 17 Allergy or rash, leflunomide vs. SSZ.

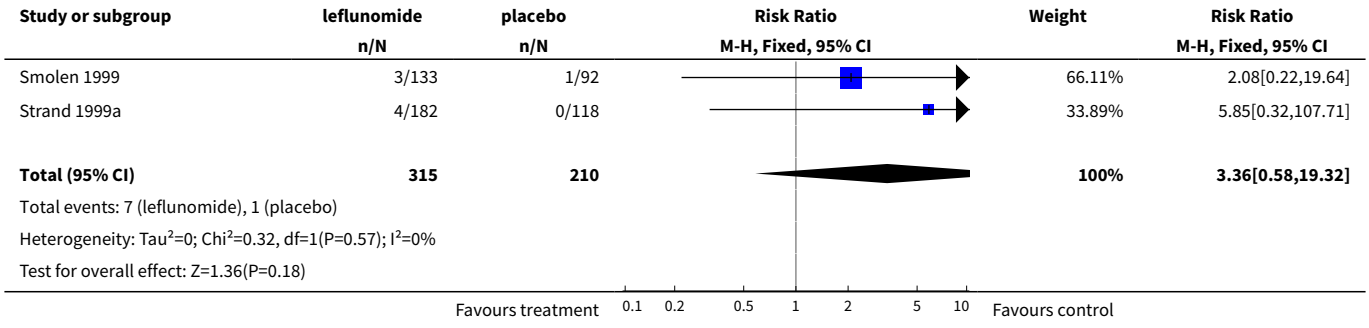




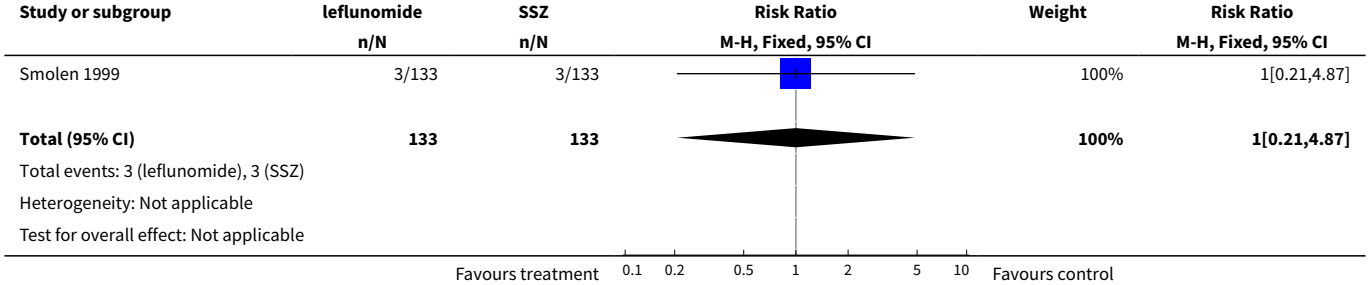
Analysis 16.18. Comparison 16 Adverse events, Outcome 18 Allergy or rash, leflunomide vs. MTX.



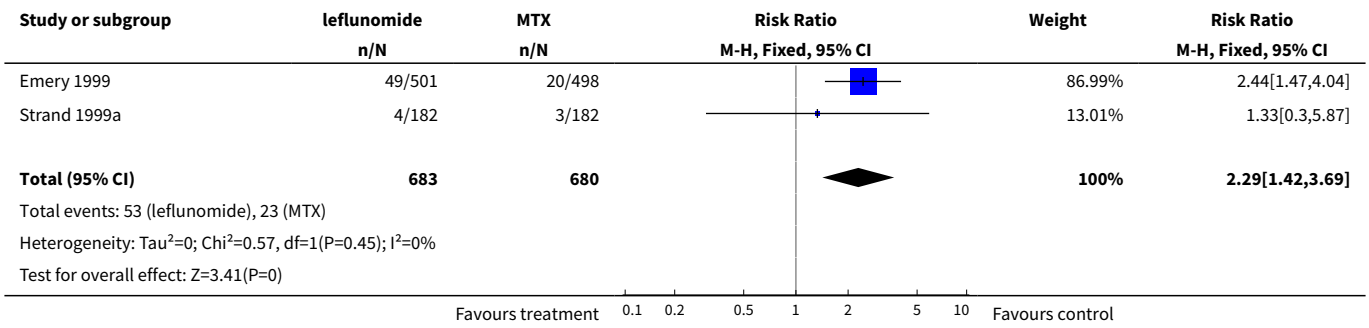
Analysis 16.19. Comparison 16 Adverse events, Outcome 19 hypertension, leflunomide vs. placebo.



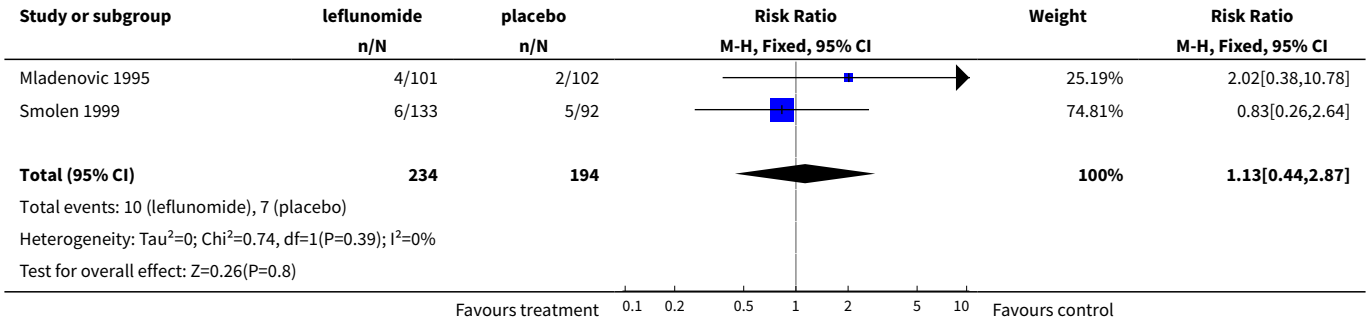
Analysis 16.20. Comparison 16 Adverse events, Outcome 20 hypertension, leflunomide vs. SSZ.



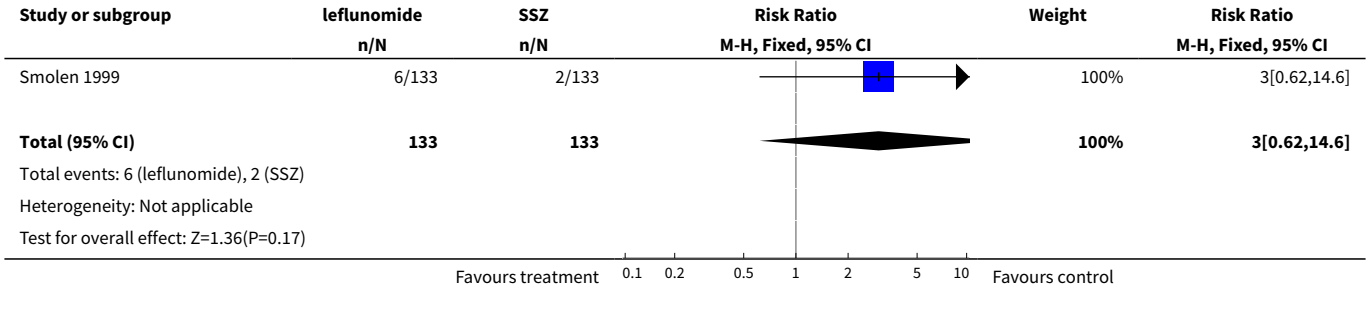
Analysis 16.21. Comparison 16 Adverse events, Outcome 21 hypertension, leflunomide vs. MTX.



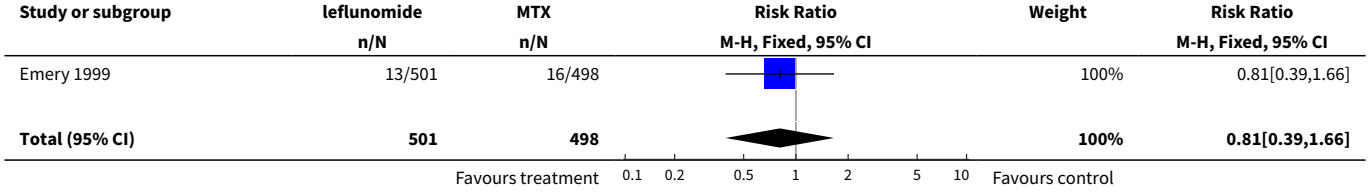
Analysis 16.22. Comparison 16 Adverse events, Outcome 22 Weight loss, leflunomide vs. placebo.



Analysis 16.23. Comparison 16 Adverse events, Outcome 23 Weight loss, leflunomide vs. SSZ.



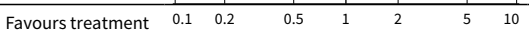
Analysis 16.24. Comparison 16 Adverse events, Outcome 24 Weight loss, leflunomide vs. MTX.



Study or subgroup	leflunomide n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 13 (leflunomide), 16 (MTX)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					

Analysis 16.25. Comparison 16 Adverse events, Outcome 25 Infections, leflunomide vs. placebo.

Study or subgroup	leflunomide n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mladenovic 1995	16/101	18/102		19.77%	0.9[0.49,1.66]
Smolen 1999	1/133	3/92		3.91%	0.23[0.02,2.18]
Strand 1999a	103/182	57/118		76.32%	1.17[0.93,1.47]
Total (95% CI)	**416**	**312**		**100%**	**1.08[0.87,1.34]**
Total events: 120 (leflunomide), 78 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.66, df=2(P=0.26); I^2=24.7%					
Test for overall effect: Z=0.71(P=0.48)					



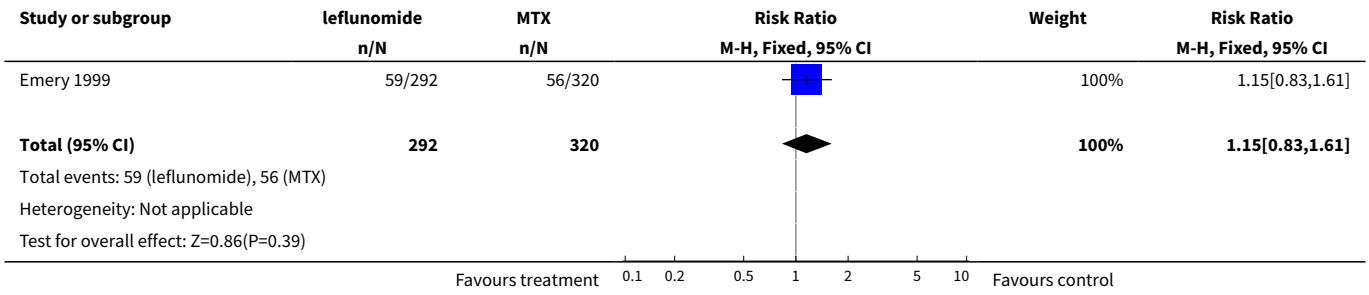
Analysis 16.26. Comparison 16 Adverse events, Outcome 26 Infections, leflunomide vs. SSZ.

Study or subgroup	leflunomide n/N	SSZ n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Smolen 1999	1/133	4/133		100%	0.25[0.03,2.21]
Total (95% CI)	**133**	**133**		**100%**	**0.25[0.03,2.21]**
Total events: 1 (leflunomide), 4 (SSZ)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.25(P=0.21)					

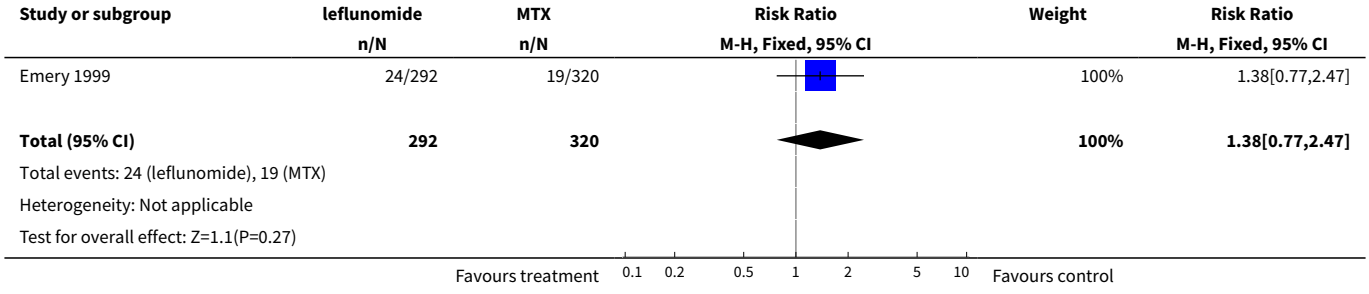
Analysis 16.27. Comparison 16 Adverse events, Outcome 27 Infections, leflunomide vs. MTX.

Study or subgroup	leflunomide n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Emery 1999	10/501	8/498		6.86%	1.24[0.49,3.12]
Strand 1999a	103/182	109/182		93.14%	0.94[0.79,1.12]
Total (95% CI)	**683**	**680**		**100%**	**0.97[0.81,1.15]**
Total events: 113 (leflunomide), 117 (MTX)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=0.39(P=0.69)					

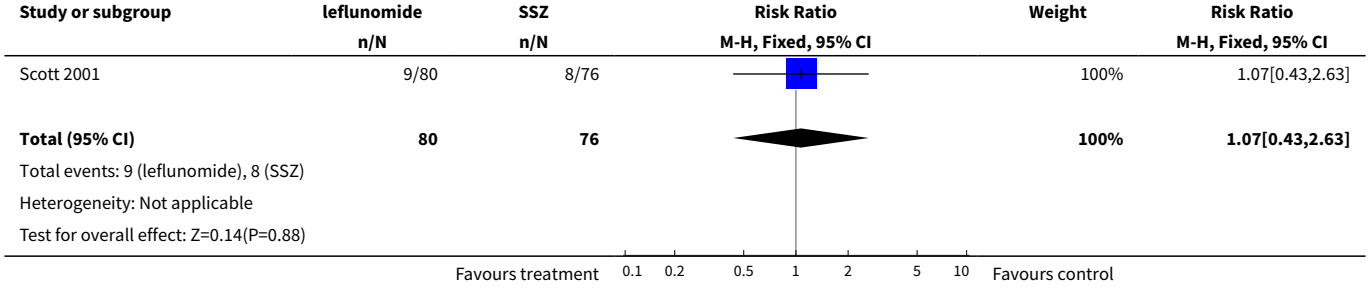
Analysis 16.28. Comparison 16 Adverse events, Outcome 28 Total withdrawals in leflunomide vs. MTX, at 2 years.



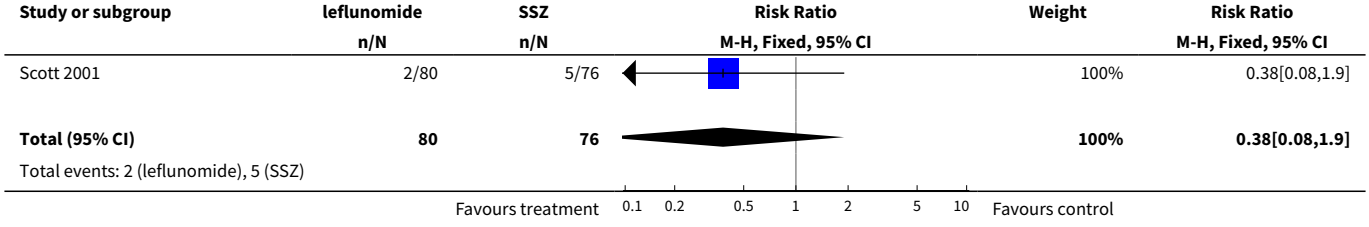
Analysis 16.29. Comparison 16 Adverse events, Outcome 29 Withdrawals due to adverse events in leflunomide vs. MTX, at 2 years.



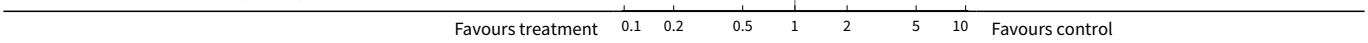
Analysis 16.30. Comparison 16 Adverse events, Outcome 30 Total withdrawals in leflunomide vs.SSZ, at 12 months.



Analysis 16.31. Comparison 16 Adverse events, Outcome 31 Withdrawals due to adverse events in leflunomide vs. SSZ, at 12 months.

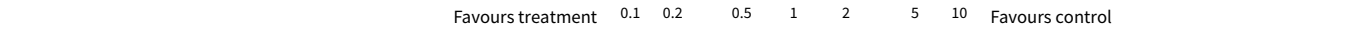


Study or subgroup	leflunomide n/N	SSZ n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.18(P=0.24)					



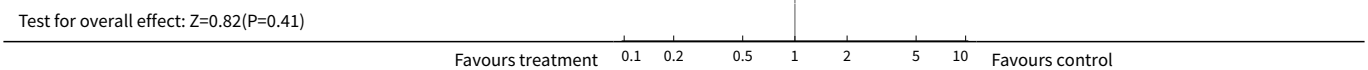
Analysis 16.32. Comparison 16 Adverse events, Outcome 32 Total withdrawals in leflunomide vs.SSZ, at 24 months.

Study or subgroup	leflunomide n/N	SSZ n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	11/60	14/60		100%	0.79[0.39,1.59]
Total (95% CI)	**60**	**60**		**100%**	**0.79[0.39,1.59]**
Total events: 11 (leflunomide), 14 (SSZ)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					



Analysis 16.33. Comparison 16 Adverse events, Outcome 33 Withdrawals due to adverse events in leflunomide vs. SSZ, at 24 months.

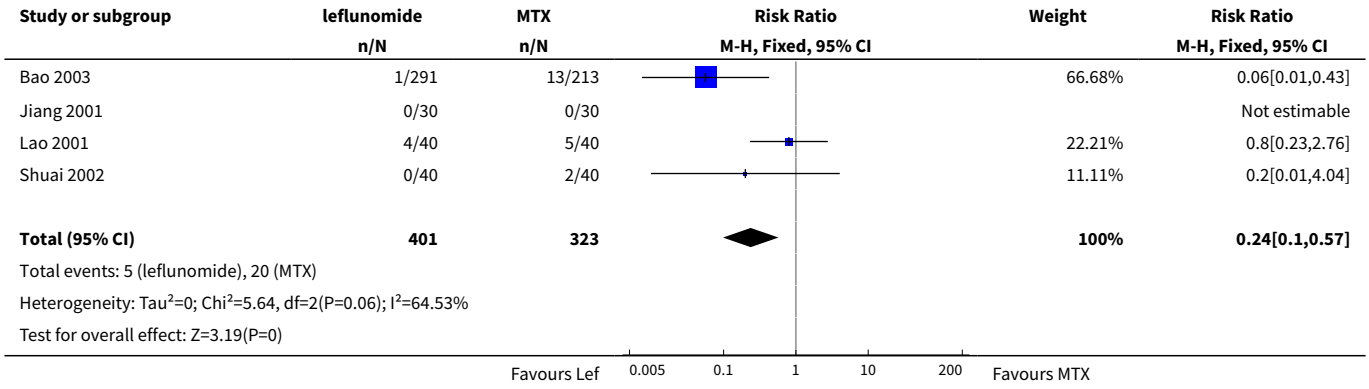
Study or subgroup	leflunomide n/N	SSZ n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	6/60	9/60		100%	0.67[0.25,1.76]
Total (95% CI)	**60**	**60**		**100%**	**0.67[0.25,1.76]**
Total events: 6 (leflunomide), 9 (SSZ)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					



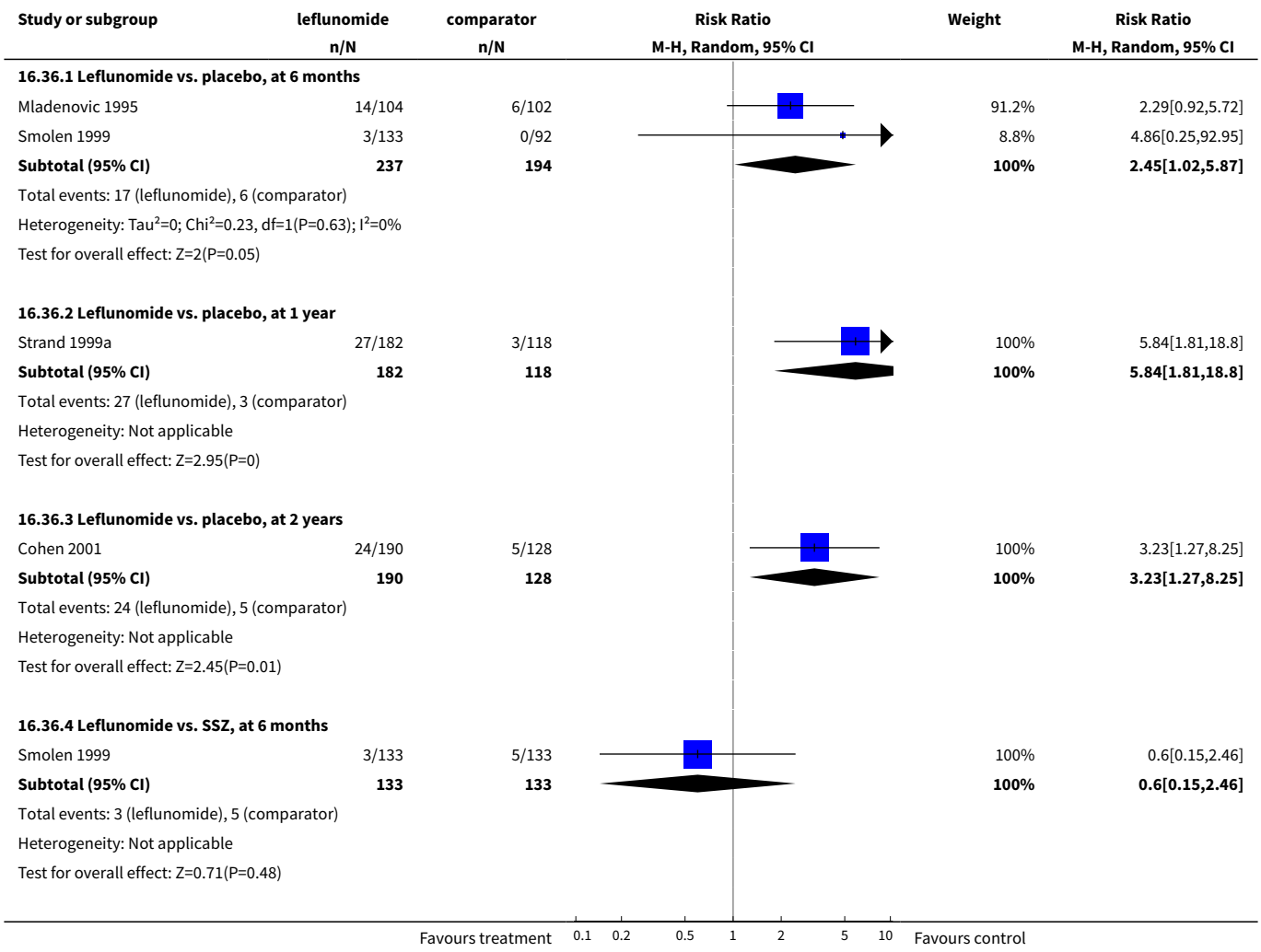
Analysis 16.34. Comparison 16 Adverse events, Outcome 34 Reported adverse events in leflunomide vs. MTX, at 6 months.

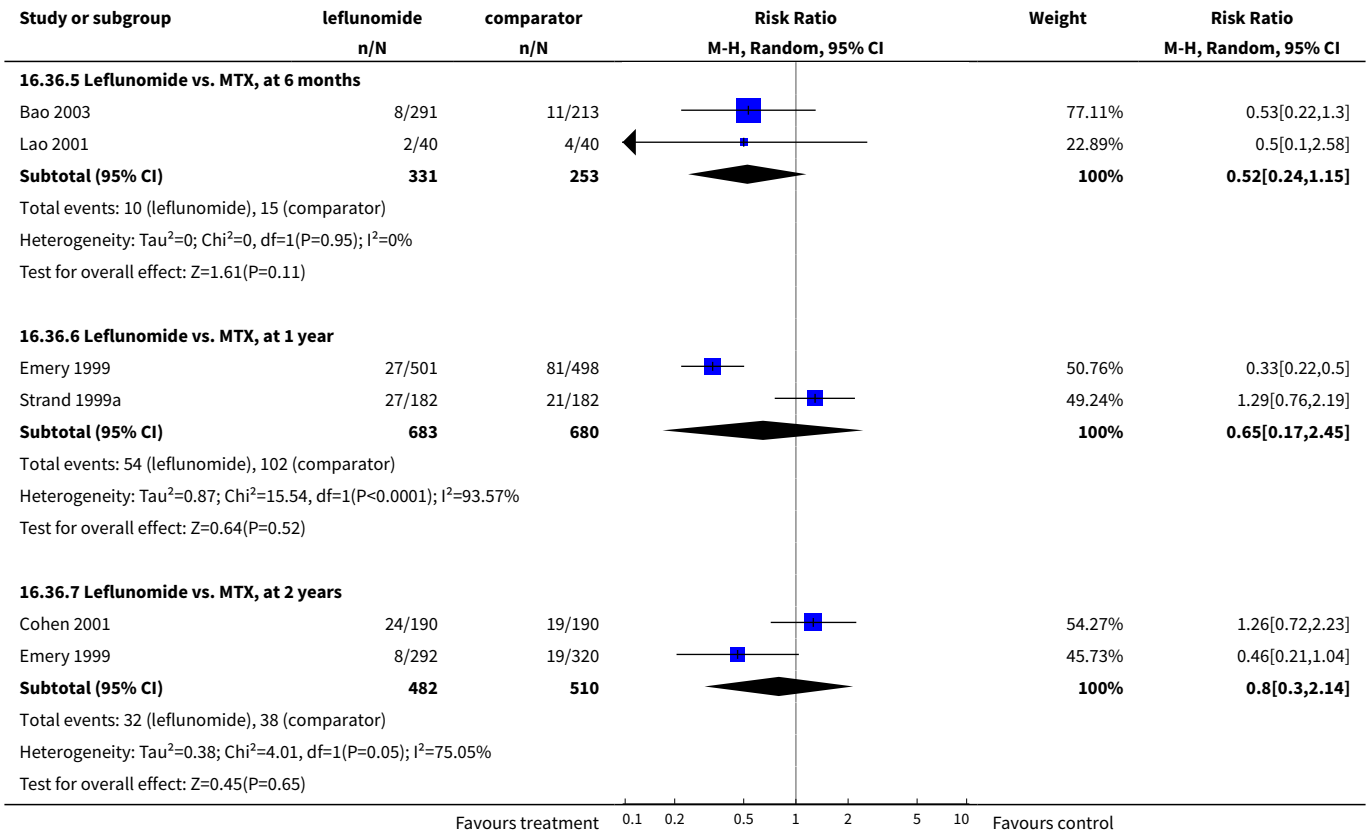
Study or subgroup	leflunomide n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bao 2003	49/291	60/213		66.44%	0.6[0.43,0.83]
Jiang 2001	2/30	9/30		8.63%	0.22[0.05,0.94]
Lao 2001	9/40	17/40		16.3%	0.53[0.27,1.04]
Shuai 2002	5/40	9/40		8.63%	0.56[0.2,1.51]
Total (95% CI)	**401**	**323**		**100%**	**0.55[0.42,0.73]**
Total events: 65 (leflunomide), 95 (MTX)					
Heterogeneity: Tau^2=0; Chi^2=1.76, df=3(P=0.62); I^2=0%					
Test for overall effect: Z=4.16(P<0.0001)					

Analysis 16.35. Comparison 16 Adverse events, Outcome 35
Withdrawals due to adverse events in leflunomide vs. MTX, at 6 months.

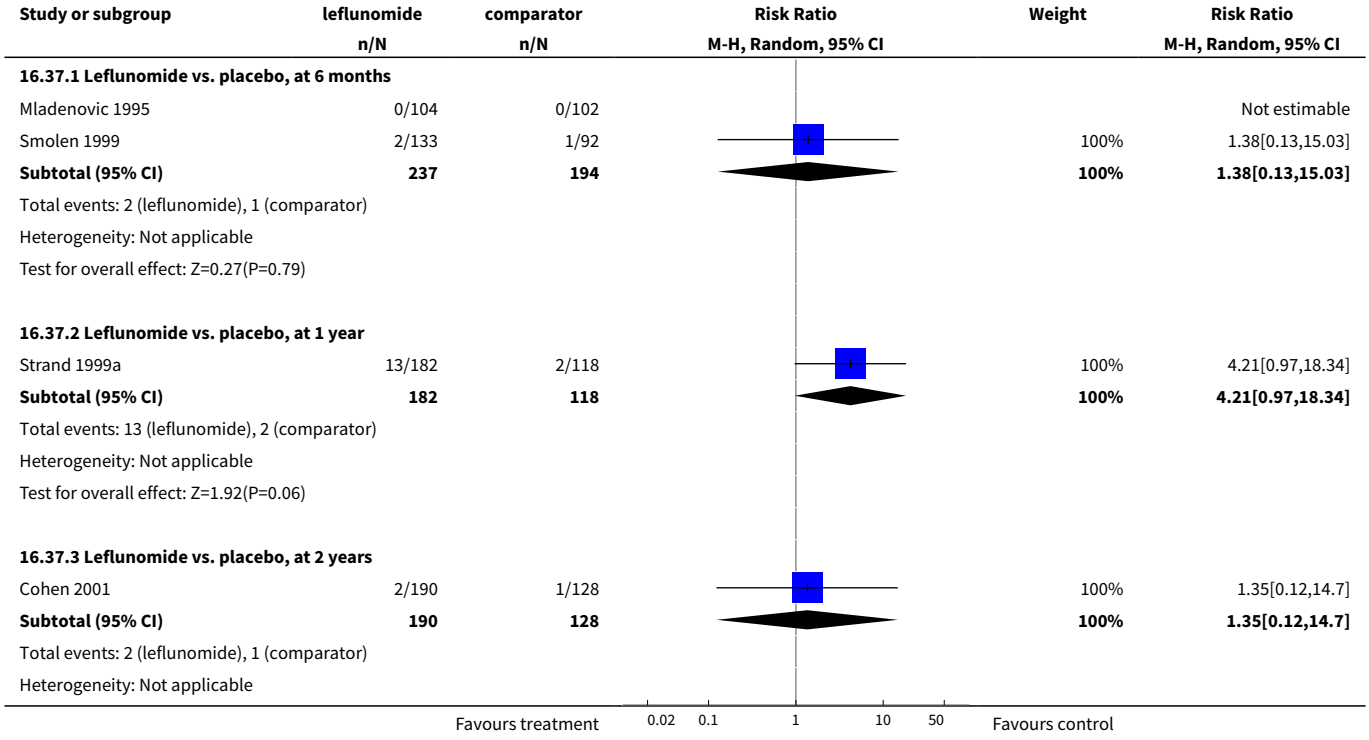


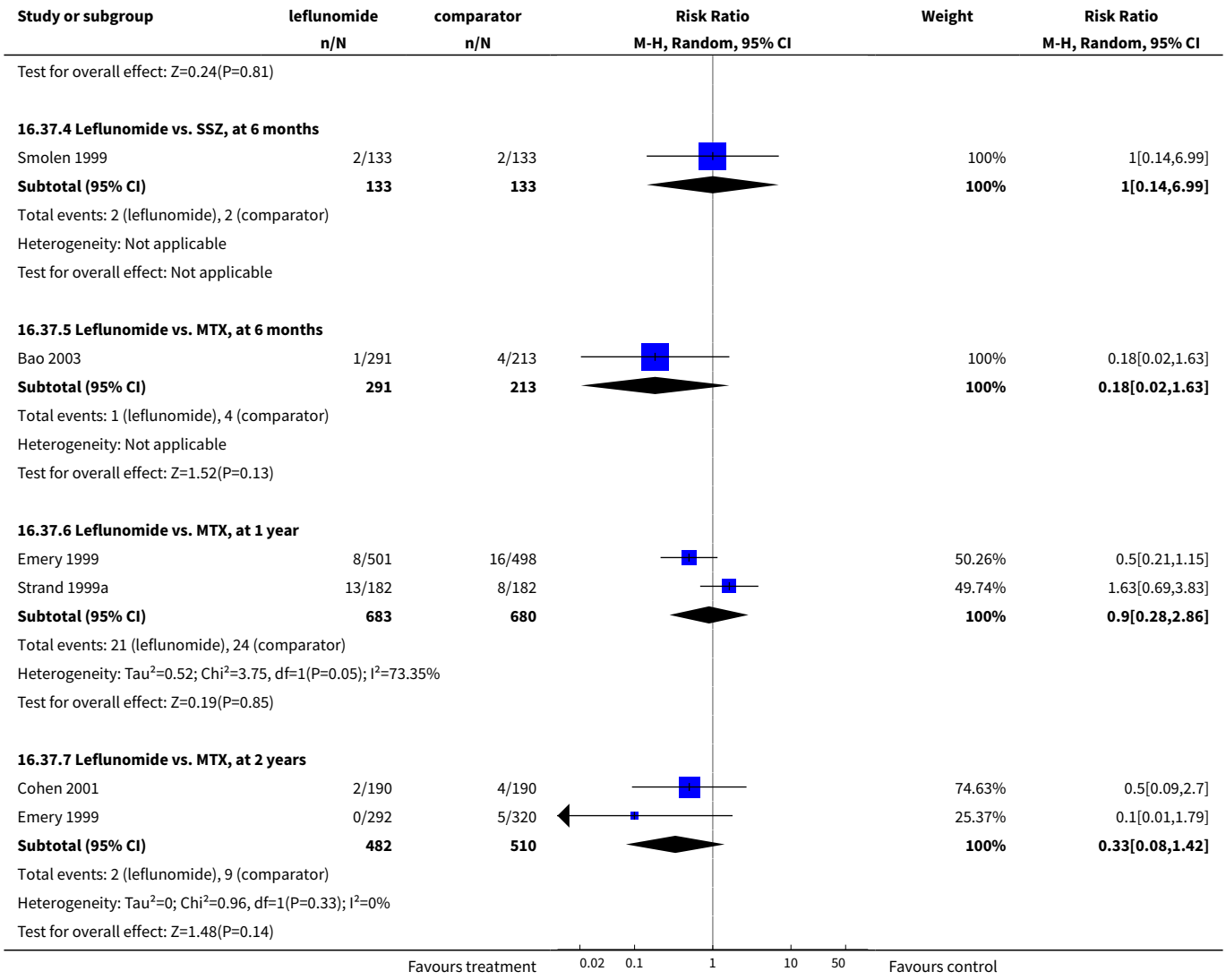
Analysis 16.36. Comparison 16 Adverse events, Outcome 36
**Elevated liver function tests, reported as adverse event.



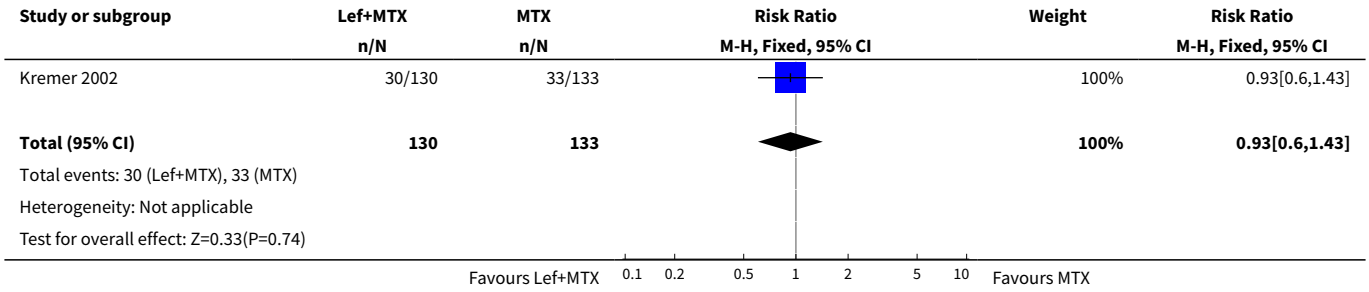


Analysis 16.37. Comparison 16 Adverse events, Outcome 37 **Elevated liver function tests, withdrawals.

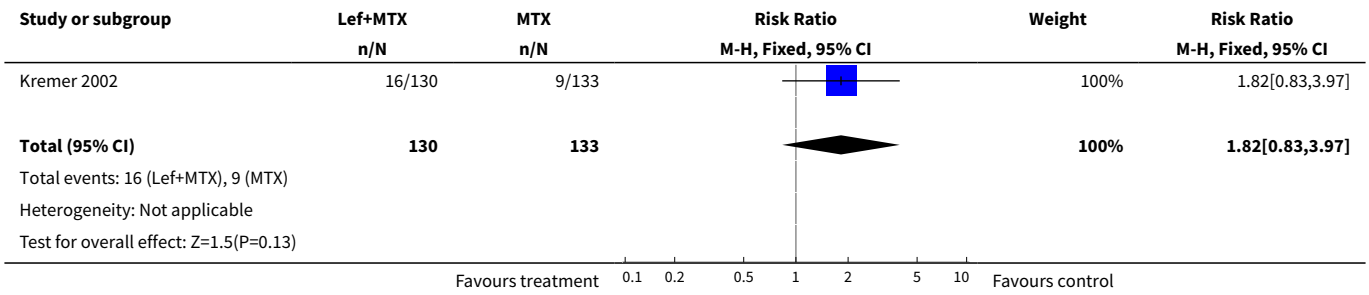




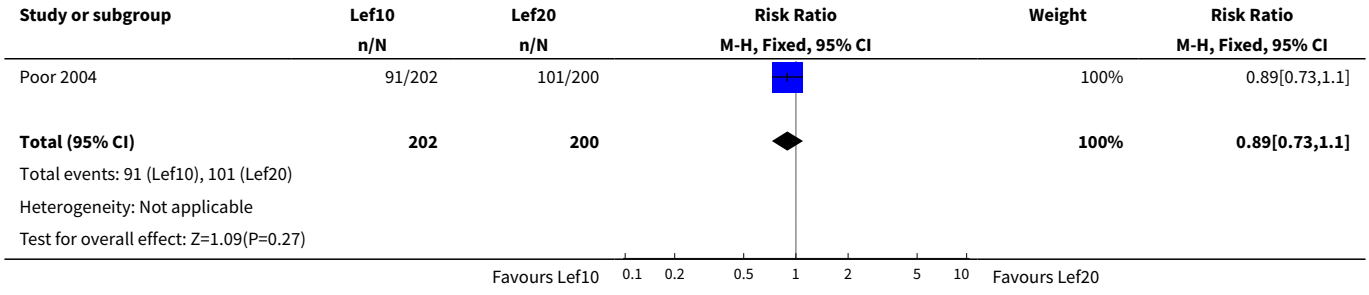
Analysis 16.38. Comparison 16 Adverse events, Outcome 38 Total withdrawals in leflunomide+MTX vs.MTX, at 24 weeks.



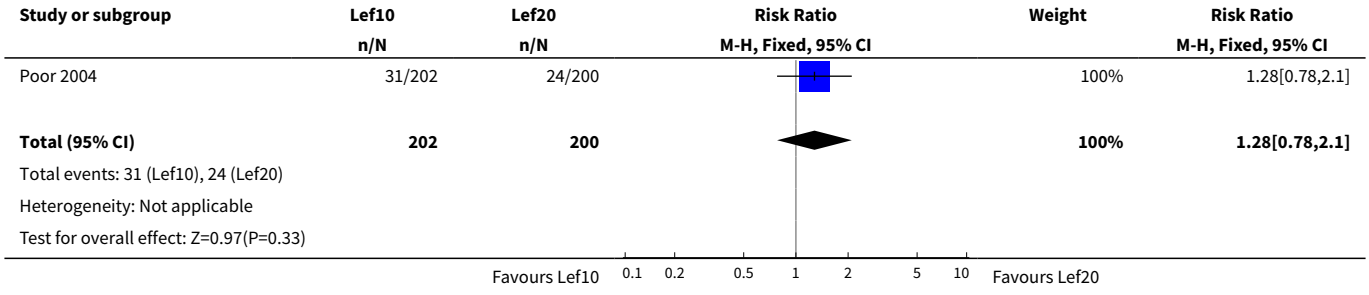
Analysis 16.39. Comparison 16 Adverse events, Outcome 39 Withdrawals due to adverse events in leflunomide+MTX vs. MTX, at 24 weeks.



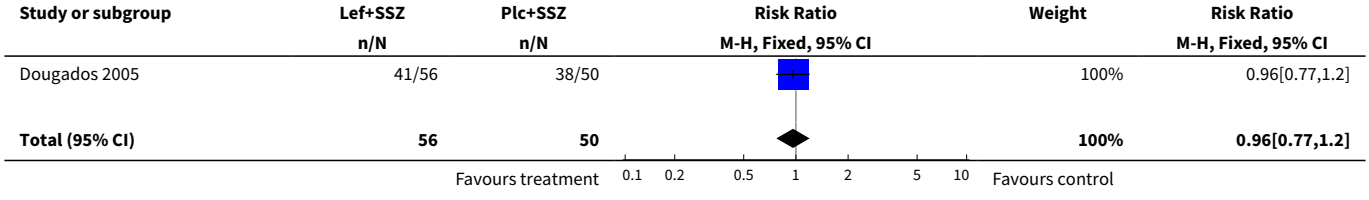
Analysis 16.40. Comparison 16 Adverse events, Outcome 40 Reported adverse events in leflunomide10mg vs.leflunomide20mg, at 24 weeks.

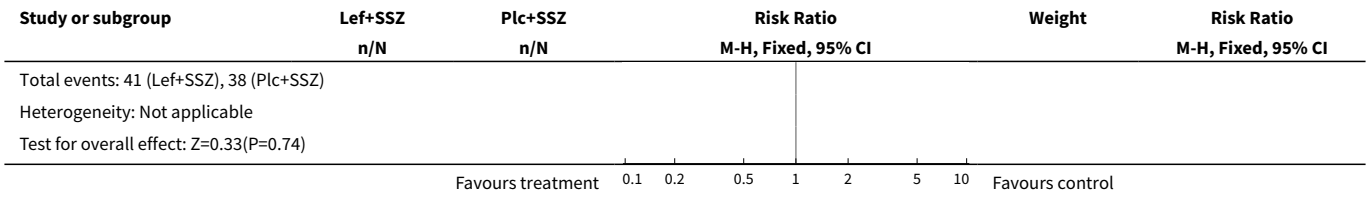


Analysis 16.41. Comparison 16 Adverse events, Outcome 41 Withdrawals due to adverse events in leflunomide10mg vs. leflunomide20mg, at 24 weeks.

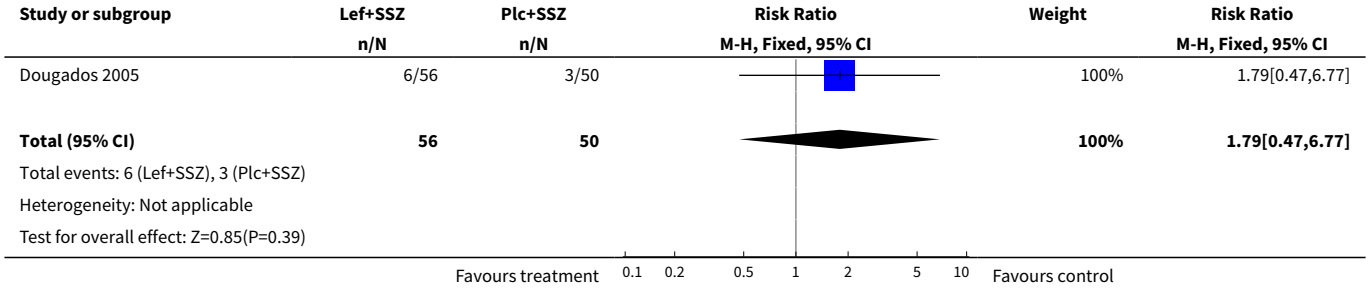


Analysis 16.42. Comparison 16 Adverse events, Outcome 42 Related adverse events in Lef+SSZ vs.Plc+SSZ, at 24 weeks.

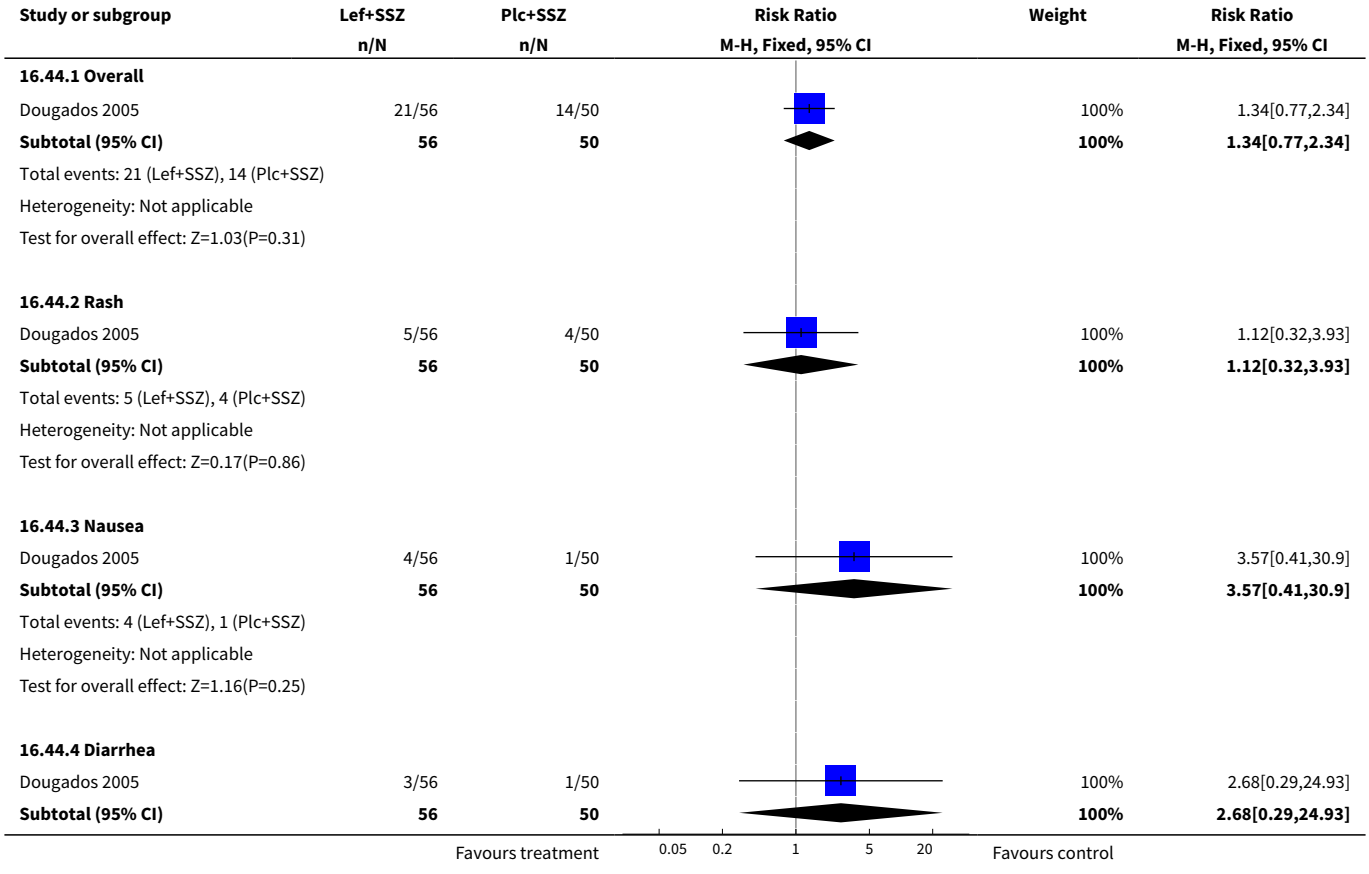


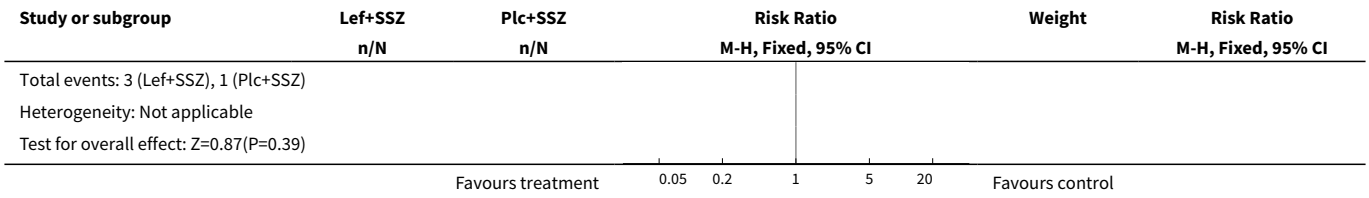


Analysis 16.43. Comparison 16 Adverse events, Outcome 43 Serious adverse events in Lef+SSZ vs. Plc+SSZ, at 24 weeks.

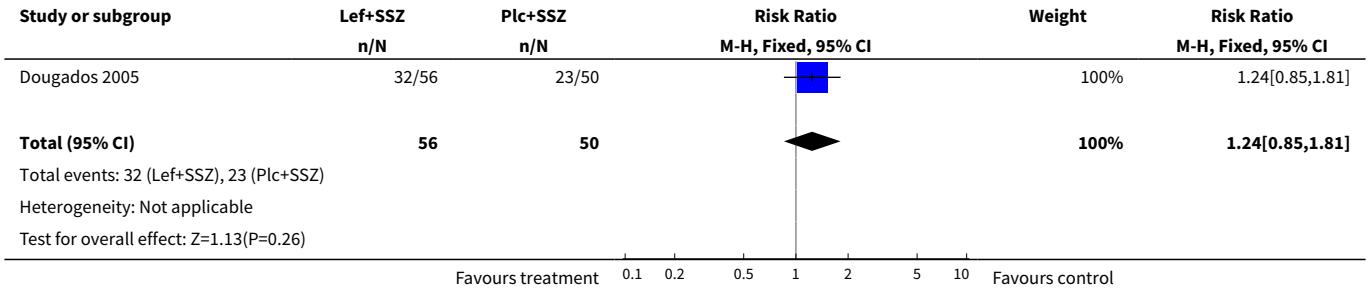


Analysis 16.44. Comparison 16 Adverse events, Outcome 44 Withdrawals due to adverse events in Lef+SSZ vs. Plc+SSZ, at 24 weeks.

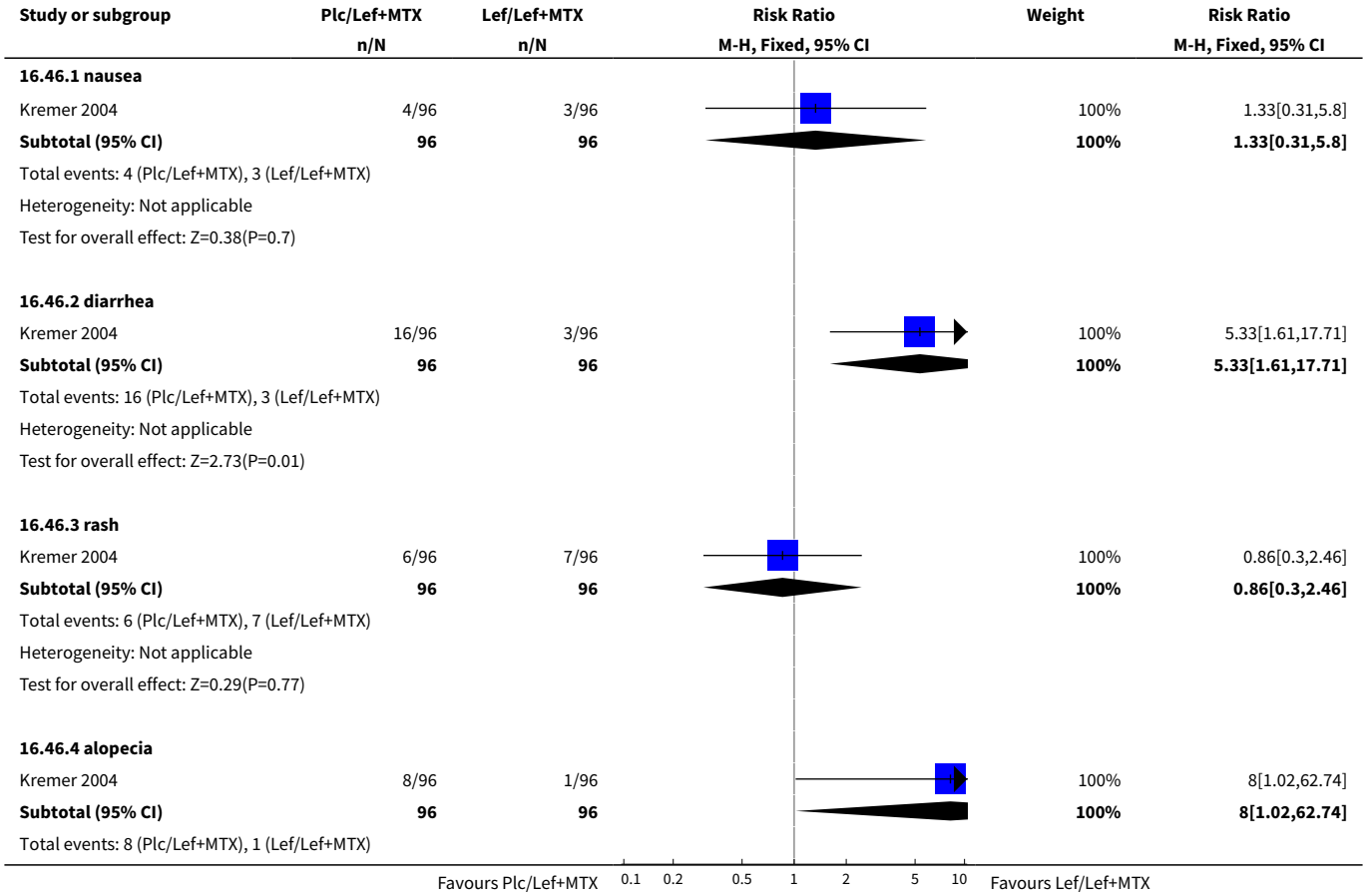


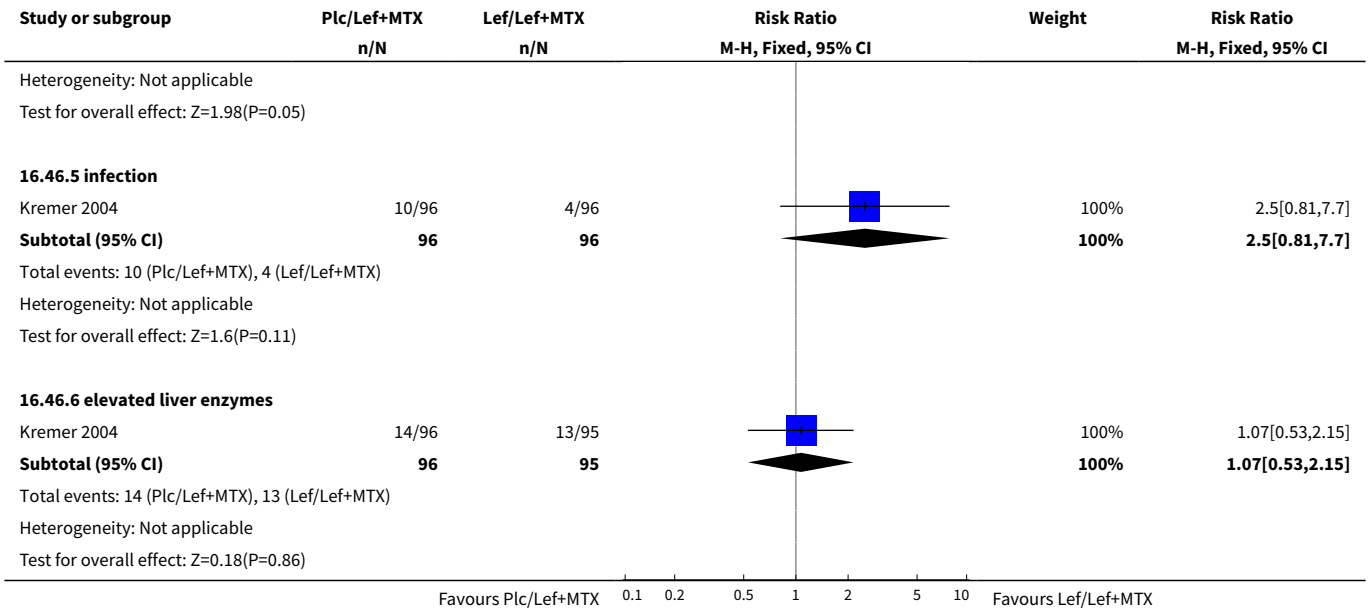


Analysis 16.45. Comparison 16 Adverse events, Outcome 45 Total withdrawals, Lef+SSZ vs. Plc+SSZ, at 24 weeks.

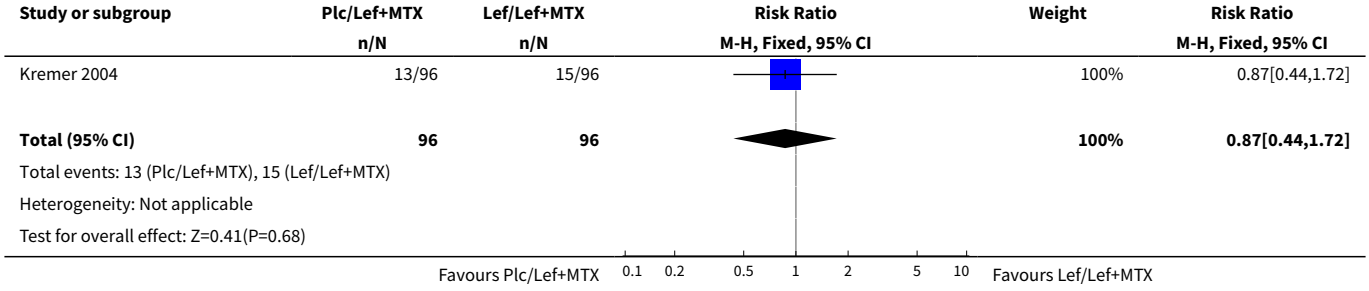


Analysis 16.46. Comparison 16 Adverse events, Outcome 46 Reported adverse events, Lef/Lef+MTX vs Plc/Lef+MTX, at 48 weeks.

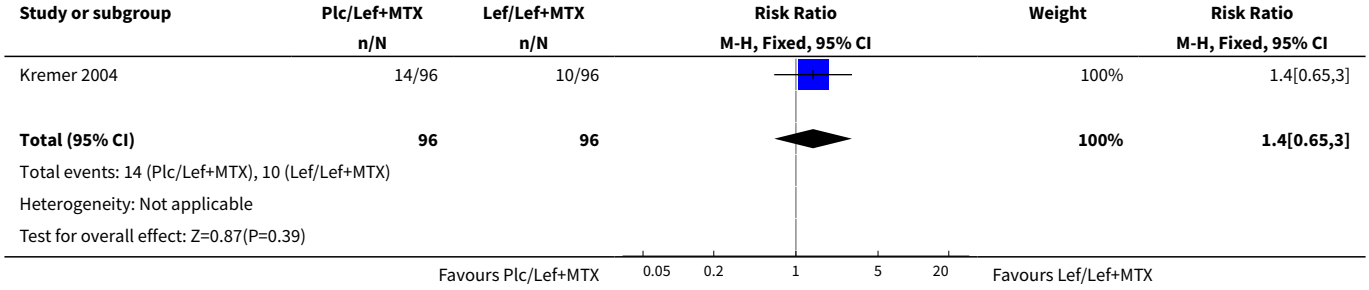




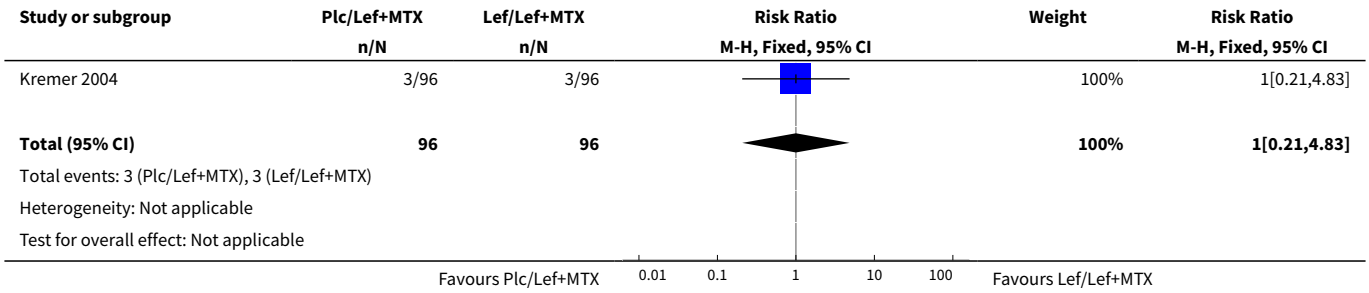
Analysis 16.47. Comparison 16 Adverse events, Outcome 47 Serious adverse events in Lef/Lef+MTX vs. Plc/Lef+MTX, at 48 weeks.



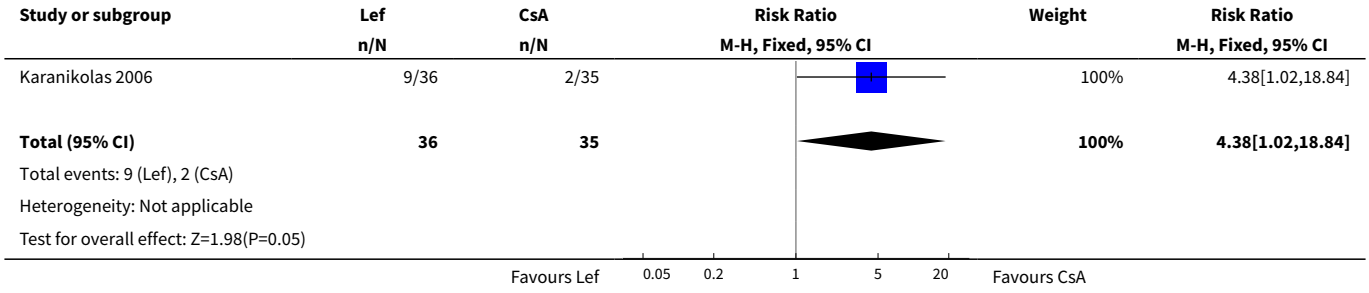
Analysis 16.48. Comparison 16 Adverse events, Outcome 48 Total withdrawals, Lef/Lef+MTX vs. Plc/Lef+MTX, at 48 weeks.



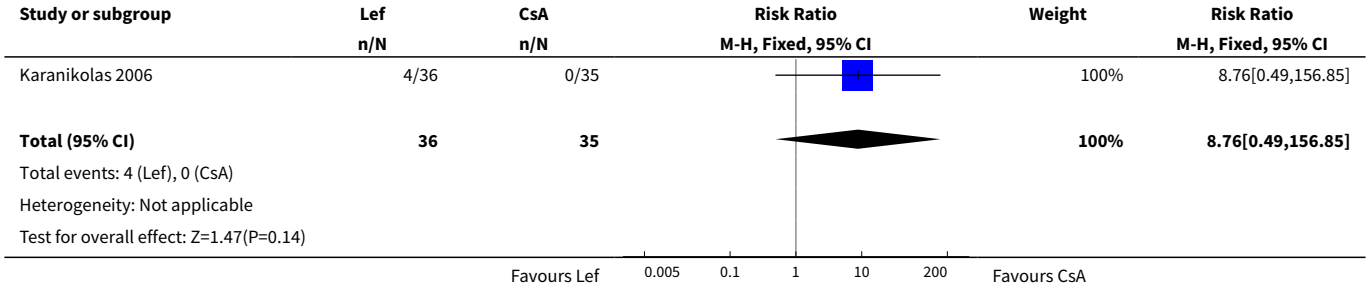
Analysis 16.49. Comparison 16 Adverse events, Outcome 49 Withdrawals due to adverse events, Lef/Lef+MTX vs. Plc/Lef+MTX, at 48 weeks.



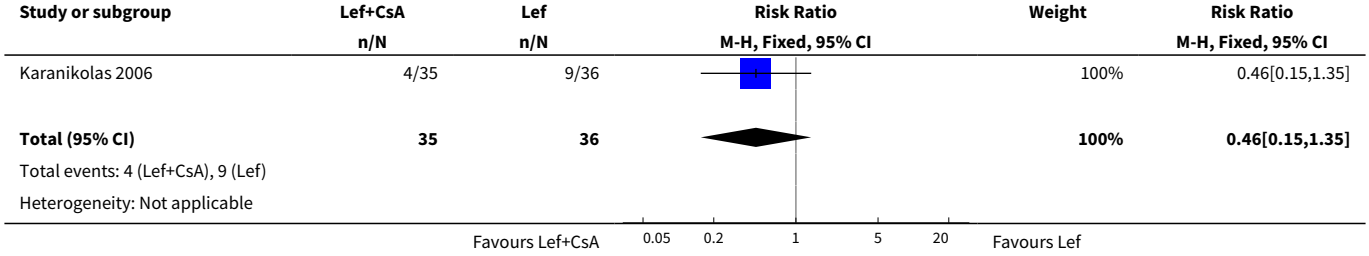
Analysis 16.50. Comparison 16 Adverse events, Outcome 50 Total withdrawals, Lef vs. CsA, at 12 months.

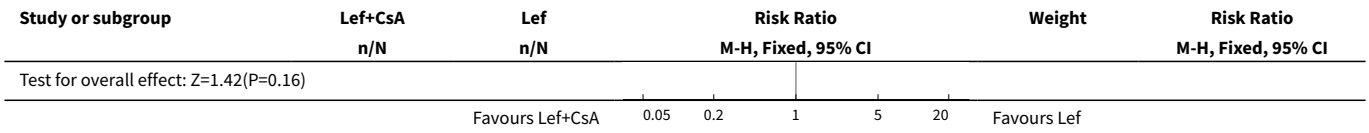


Analysis 16.51. Comparison 16 Adverse events, Outcome 51 Withdrawals due to adverse events, Lef vs. CsA, at 12 months.

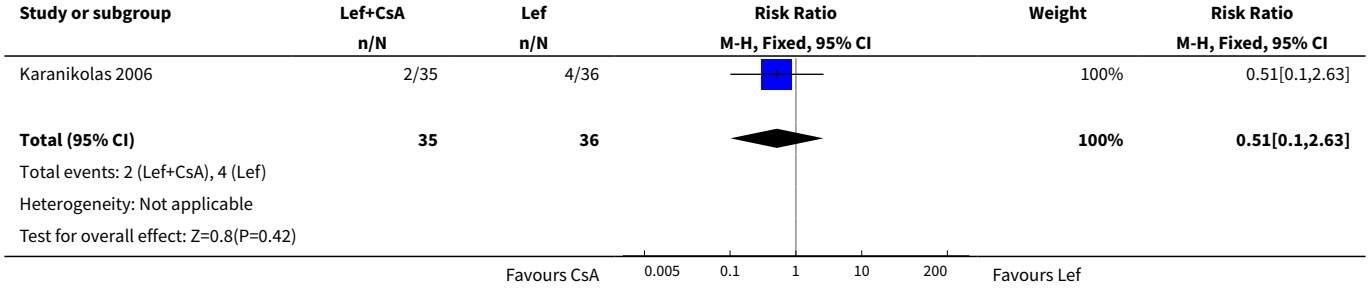


Analysis 16.52. Comparison 16 Adverse events, Outcome 52 Total withdrawals, Lef vs. Lef+CsA, at 12 months.

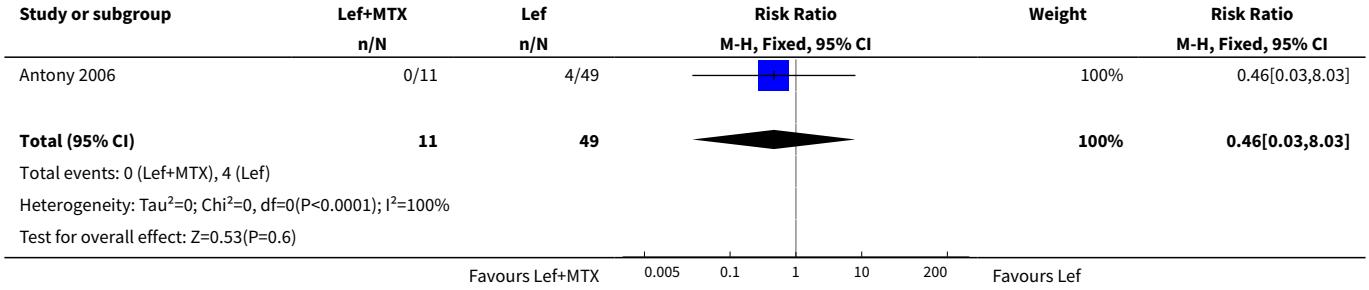




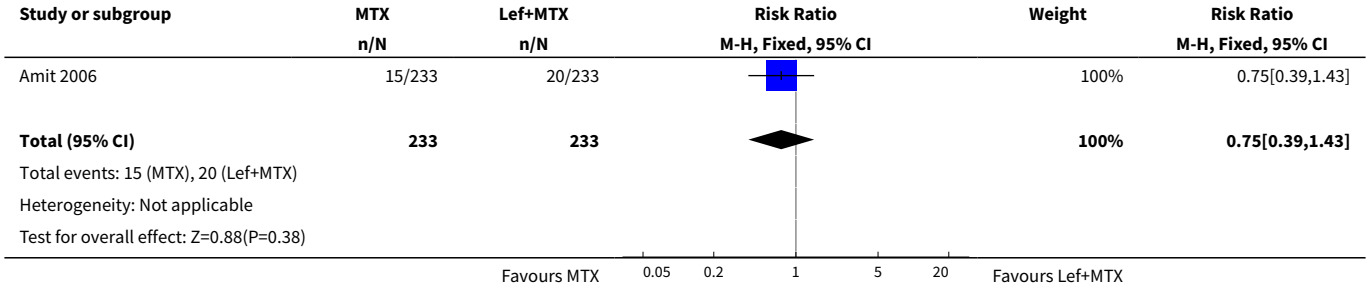
Analysis 16.53. Comparison 16 Adverse events, Outcome 53 Withdrawals due to adverse events, Lef vs. Lef+CsA, at 12 months.



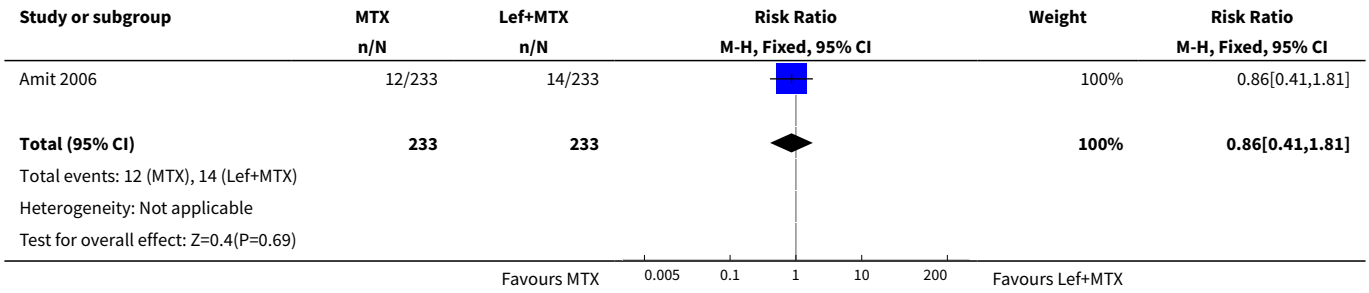
Analysis 16.54. Comparison 16 Adverse events, Outcome 54 Withdrawals due to adverse events, Lef vs. Lef+MTX, at 3 months.



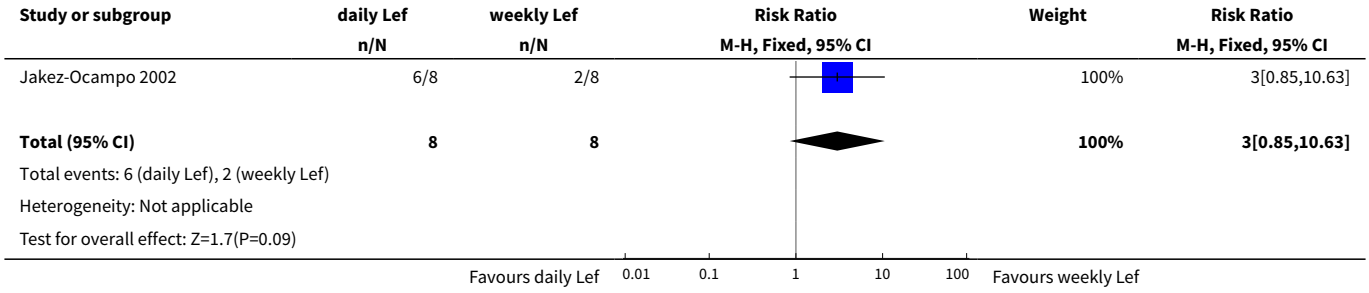
Analysis 16.55. Comparison 16 Adverse events, Outcome 55 Total withdrawals, Lef+MTX vs. MTX, at 36 months.



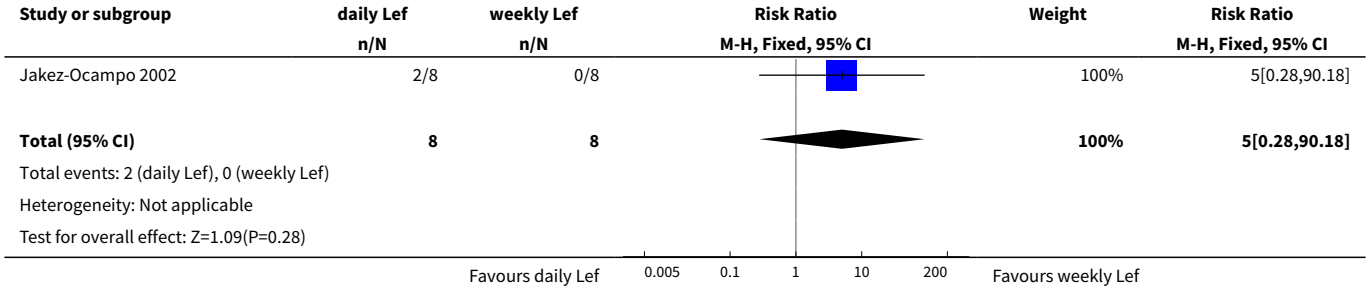
Analysis 16.56. Comparison 16 Adverse events, Outcome 56 Withdrawals due to adverse events, Lef+MTX vs. MTX, at 36 months.



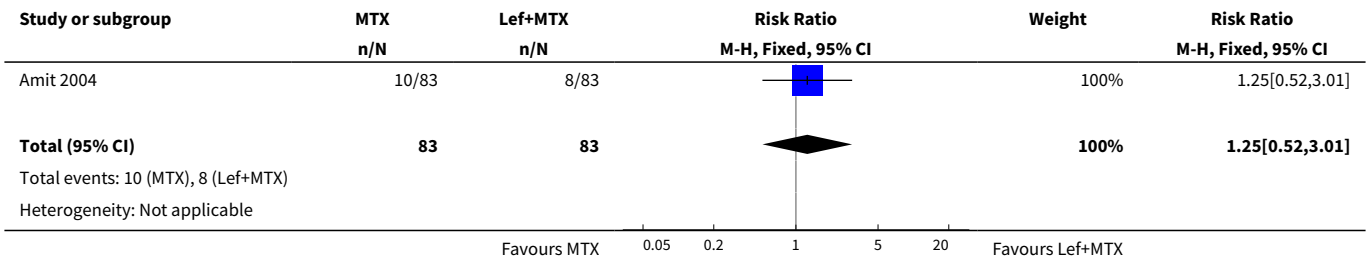
Analysis 16.57. Comparison 16 Adverse events, Outcome 57 Reported adverse events, weekly Lef vs. daily Lef.

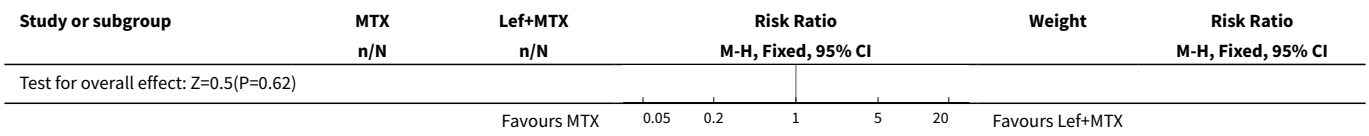


Analysis 16.58. Comparison 16 Adverse events, Outcome 58 Withdrawals due to adverse events, weekly Lef vs. daily Lef.

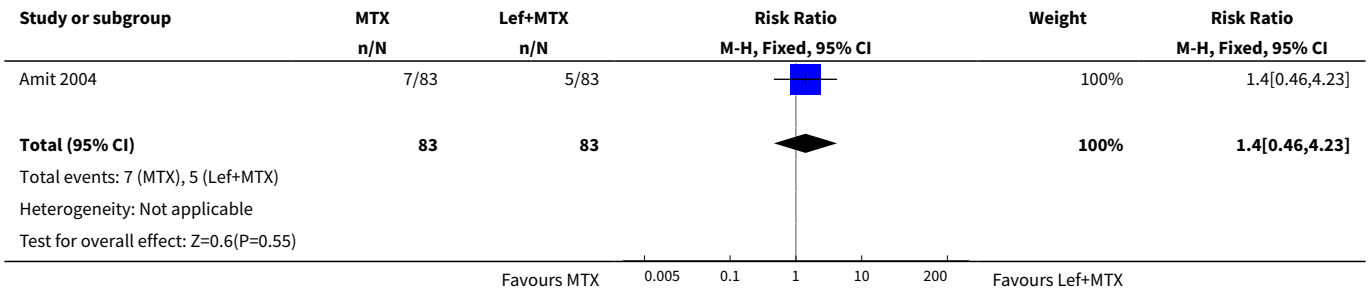


Analysis 16.59. Comparison 16 Adverse events, Outcome 59 Total withdrawals, Lef+MTX vs. MTX, at 24 months.

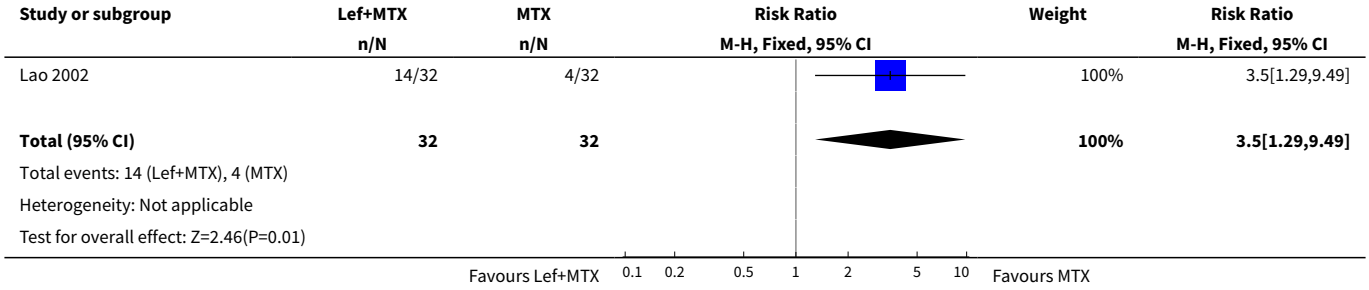




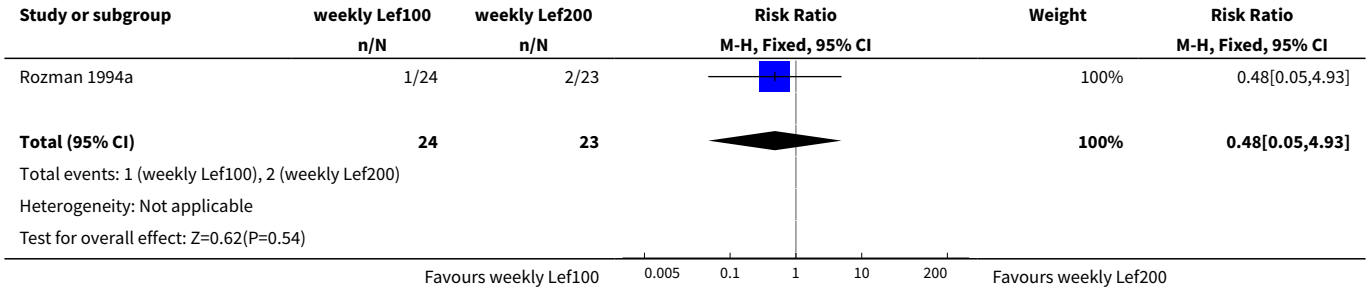
Analysis 16.60. Comparison 16 Adverse events, Outcome 60 Withdrawals due to adverse events, Lef+MTX vs. MTX, at 24 months.



Analysis 16.61. Comparison 16 Adverse events, Outcome 61 Reported adverse events in Lef+MTX vs. MTX, at 24 weeks.



Analysis 16.62. Comparison 16 Adverse events, Outcome 62 Withdrawals due to adverse events, weekly Lef200 vs. weekly Lef100, at 6 months.

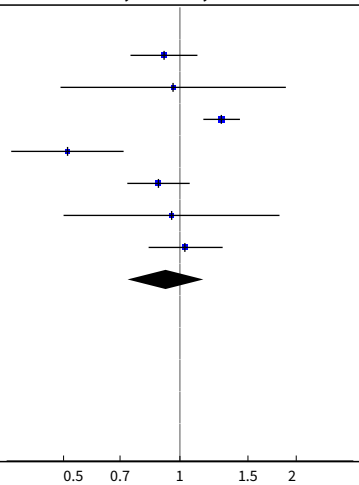


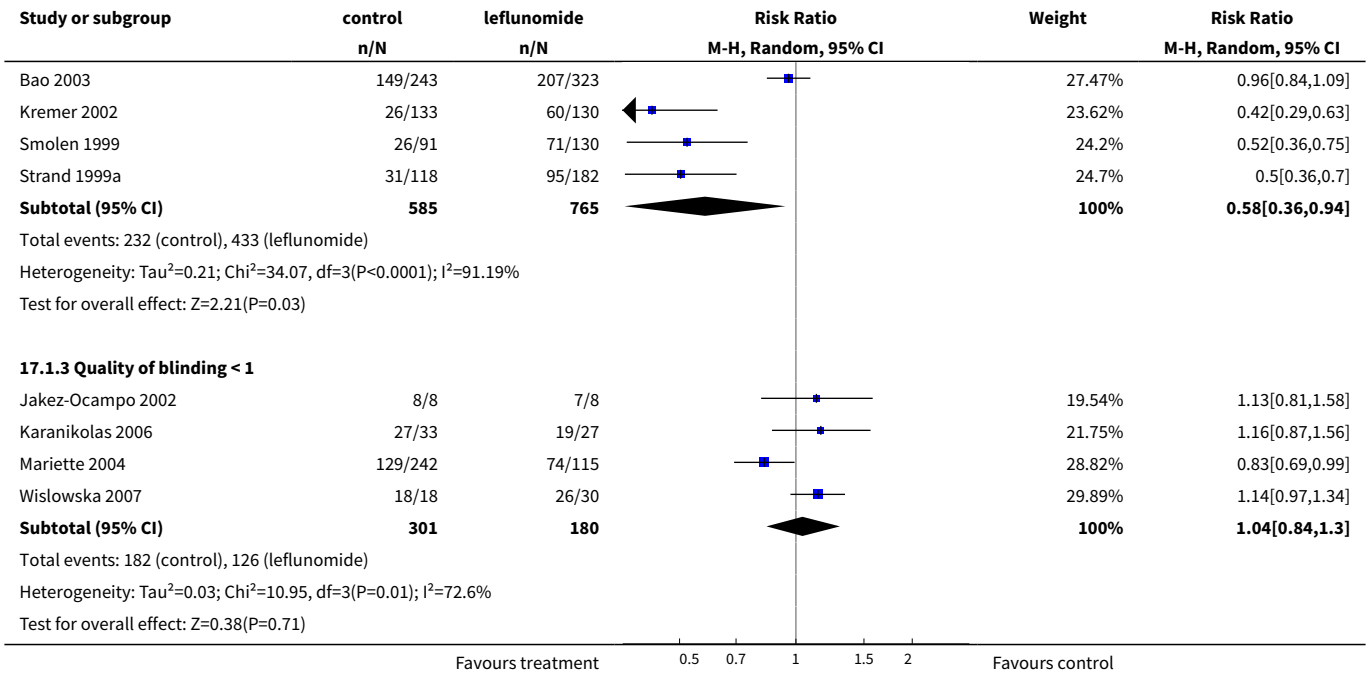
Comparison 17. Subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20 Treatment responder	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Quality of blinding = 1	7	2263	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.15]
1.2 Quality of blinding > 1	4	1350	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.36, 0.94]
1.3 Quality of blinding < 1	4	481	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.84, 1.30]
2 ACR20 Treatment responder	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 RA duration < 5 years	1	984	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.15, 1.43]
2.2 RA duration => 5 years	7	1799	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.05]
3 ACR20 Treatment responder	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Concomitant steroid use <50%	2	424	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.40, 0.66]
3.2 Concomitant steroid use => 50%	3	1026	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.51, 1.03]
4 ACR20 Treatment responder	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Withdrawals < 50% patients randomized	7	2277	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.67, 1.11]
4.2 Withdrawals => 50% patients randomized	3	893	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.49, 1.23]

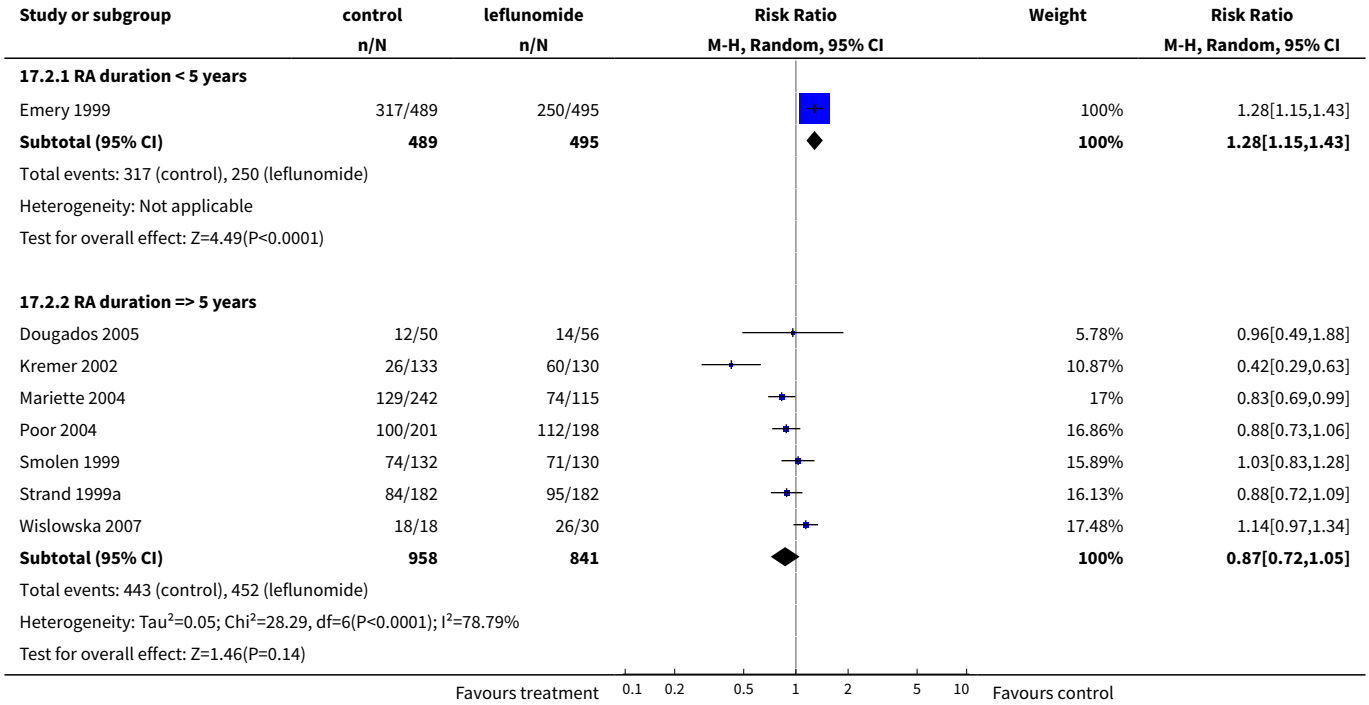
Analysis 17.1. Comparison 17 Subgroup analysis, Outcome 1 ACR20 Treatment responder.

Study or subgroup	control n/N	leflunomide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
17.1.1 Quality of blinding = 1					
Cohen 2001	91/190	100/190		17.34%	0.91[0.74,1.11]
Dougados 2005	12/50	14/56		7.28%	0.96[0.49,1.88]
Emery 1999	317/489	250/495		19.18%	1.28[1.15,1.43]
Mladenovic 1995	31/102	60/101		13.95%	0.51[0.37,0.72]
Poor 2004	100/201	112/198		17.7%	0.88[0.73,1.06]
Reece 2002	10/21	9/18		7.66%	0.95[0.5,1.81]
Scott 2001	51/74	52/78		16.89%	1.03[0.83,1.29]
Subtotal (95% CI)	**1127**	**1136**		**100%**	**0.92[0.73,1.15]**
Total events: 612 (control), 597 (leflunomide)					
Heterogeneity: Tau²=0.07; Chi²=36.74, df=6(P<0.0001); I²=83.67%					
Test for overall effect: Z=0.74(P=0.46)					
17.1.2 Quality of blinding > 1					



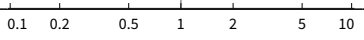


Analysis 17.2. Comparison 17 Subgroup analysis, Outcome 2 ACR20 Treatment responder.



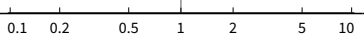
Analysis 17.3. Comparison 17 Subgroup analysis, Outcome 3 ACR20 Treatment responder.

Study or subgroup	control n/N	leflunomide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
17.3.1 Concomitant steroid use <50%					
Mladenovic 1995	31/102	60/101		53.68%	0.51[0.37,0.72]
Smolen 1999	26/91	71/130		46.32%	0.52[0.36,0.75]
Subtotal (95% CI)	**193**	**231**		**100%**	**0.52[0.4,0.66]**
Total events: 57 (control), 131 (leflunomide)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=5.27(P<0.0001)					
17.3.2 Concomitant steroid use => 50%					
Kremer 2002	26/133	60/130		27.25%	0.42[0.29,0.63]
Poor 2004	100/201	112/198		36.89%	0.88[0.73,1.06]
Strand 1999a	84/182	95/182		35.86%	0.88[0.72,1.09]
Subtotal (95% CI)	**516**	**510**		**100%**	**0.72[0.51,1.03]**
Total events: 210 (control), 267 (leflunomide)					
Heterogeneity: Tau^2=0.08; Chi^2=12.38, df=2(P=0); I^2=83.84%					
Test for overall effect: Z=1.81(P=0.07)					



Analysis 17.4. Comparison 17 Subgroup analysis, Outcome 4 ACR20 Treatment responder.

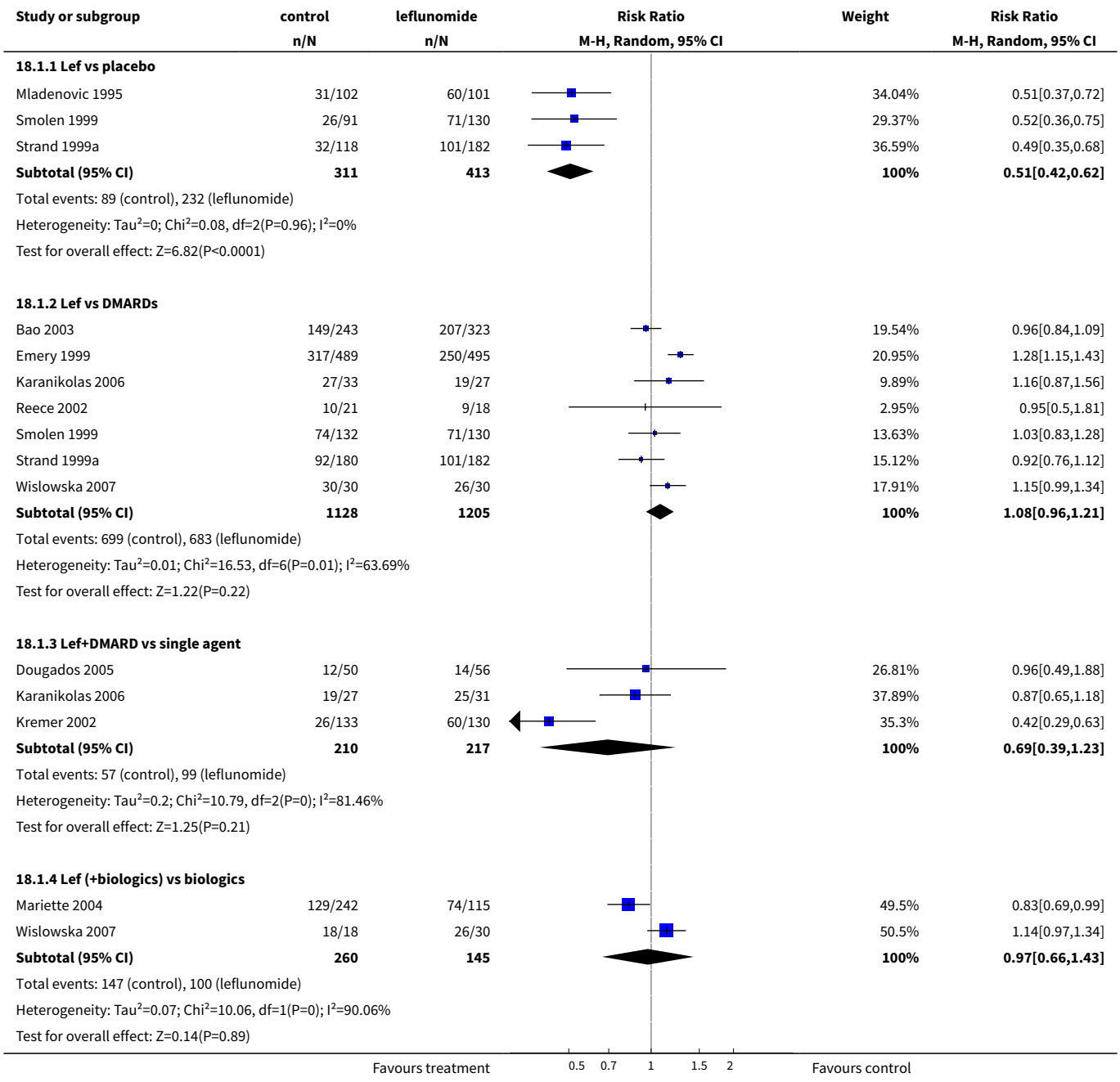
Study or subgroup	control n/N	leflunomide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
17.4.1 Withdrawals < 50% patients randomized					
Emery 1999	317/489	250/495		16.21%	1.28[1.15,1.43]
Jakez-Ocampo 2002	8/8	7/8		12.97%	1.13[0.81,1.58]
Kremer 2002	26/133	60/130		11.93%	0.42[0.29,0.63]
Mladenovic 1995	31/102	60/101		12.92%	0.51[0.37,0.72]
Poor 2004	100/201	112/198		15.34%	0.88[0.73,1.06]
Strand 1999a	84/182	95/182		14.99%	0.88[0.72,1.09]
Wislowska 2007	18/18	26/30		15.63%	1.14[0.97,1.34]
Subtotal (95% CI)	**1133**	**1144**		**100%**	**0.86[0.67,1.11]**
Total events: 584 (control), 610 (leflunomide)					
Heterogeneity: Tau^2=0.1; Chi^2=62.37, df=6(P<0.0001); I^2=90.38%					
Test for overall effect: Z=1.16(P=0.24)					
17.4.2 Withdrawals => 50% patients randomized					
Bao 2000	146/243	202/323		42.68%	0.96[0.84,1.1]
Dougados 2005	12/50	14/56		22.64%	0.96[0.49,1.88]
Smolen 1999	26/91	71/130		34.68%	0.52[0.36,0.75]
Subtotal (95% CI)	**384**	**509**		**100%**	**0.78[0.49,1.23]**
Total events: 184 (control), 287 (leflunomide)					
Heterogeneity: Tau^2=0.12; Chi^2=10.17, df=2(P=0.01); I^2=80.33%					
Test for overall effect: Z=1.08(P=0.28)					



Comparison 18. Summary of comparisons

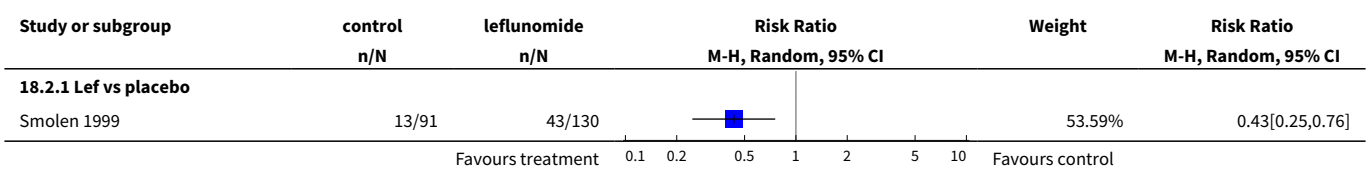
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20 Treatment responder	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Lef vs placebo	3	724	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.42, 0.62]
1.2 Lef vs DMARDs	7	2333	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.96, 1.21]
1.3 Lef+DMARD vs single agent	3	427	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.39, 1.23]
1.4 Lef (+biologics) vs biologics	2	405	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.66, 1.43]
2 ACR50 Treatment responder	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Lef vs placebo	2	521	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.61]
2.2 Lef vs DMARDs	4	1257	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.65, 1.16]
2.3 Lef+DMARD vs single agent	3	427	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.11, 1.03]
2.4 Lef (+biologics) vs biologics	2	405	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.62, 1.87]
3 ACR70 Treatment responder	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Lef vs placebo	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.09, 0.53]
3.2 Lef vs DMARDs	4	746	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.39, 0.80]
3.3 Lef+DMARD vs single agent	3	427	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.20, 0.63]
4 Reported adverse events	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Lef vs DMARDs	4	724	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.35, 2.36]
4.2 Lef+DMARD vs single agent	2	170	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.14, 2.47]
5 Withdrawals due to adverse events	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Lef vs placebo	3	727	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.61]
5.2 Lef vs DMARDs	8	2220	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.63, 2.19]
5.3 Lef+DMARD vs single agent	5	966	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.53, 1.12]

Analysis 18.1. Comparison 18 Summary of comparisons, Outcome 1 ACR20 Treatment responder.

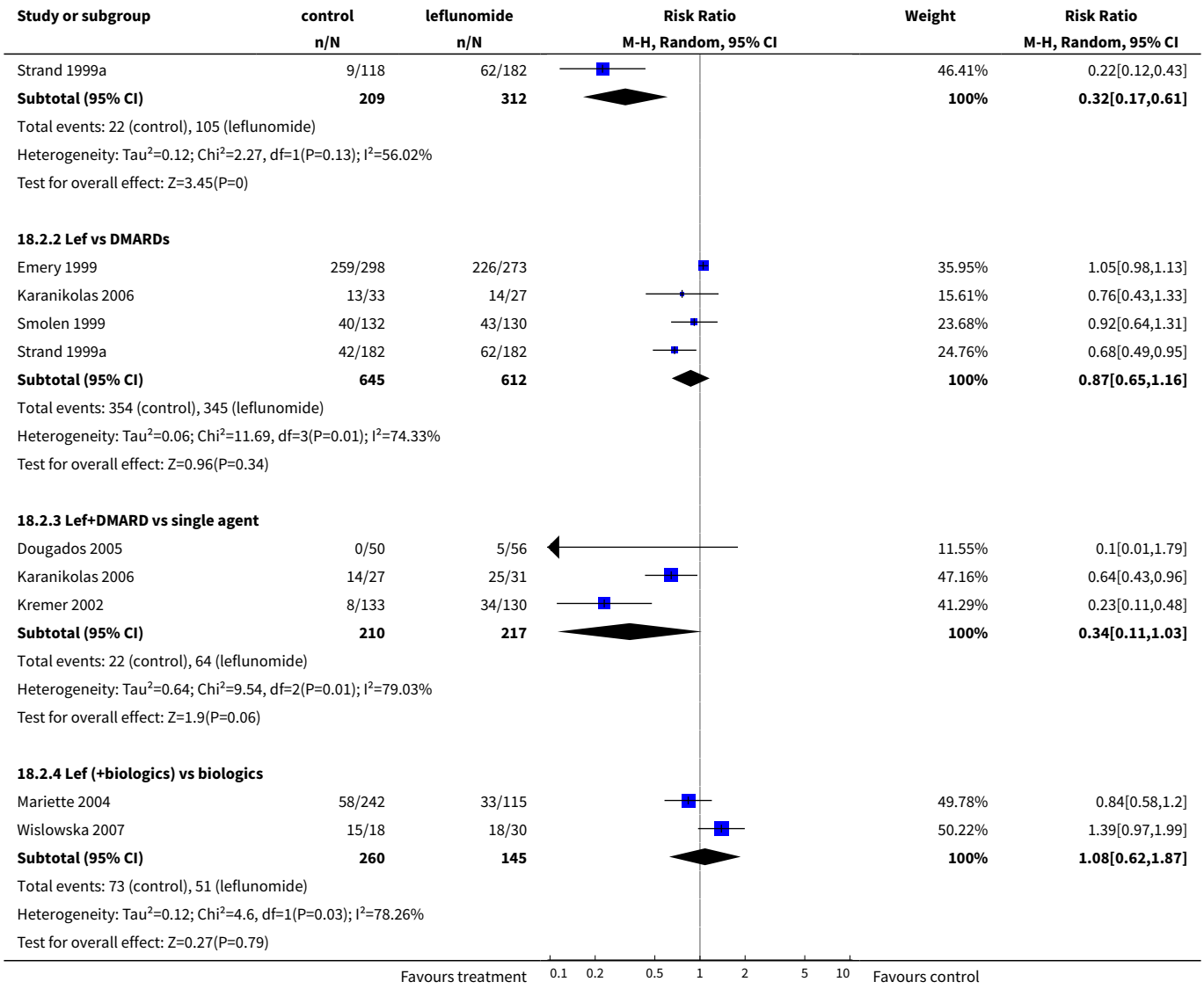


Study or subgroup	control n/N	leflunomide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
18.1.1 Lef vs placebo					
Mladenovic 1995	31/102	60/101		34.04%	0.51[0.37,0.72]
Smolen 1999	26/91	71/130		29.37%	0.52[0.36,0.75]
Strand 1999a	32/118	101/182		36.59%	0.49[0.35,0.68]
Subtotal (95% CI)	**311**	**413**		**100%**	**0.51[0.42,0.62]**
Total events: 89 (control), 232 (leflunomide)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=2(P=0.96); I^2=0%					
Test for overall effect: Z=6.82(P<0.0001)					
18.1.2 Lef vs DMARDs					
Bao 2003	149/243	207/323		19.54%	0.96[0.84,1.09]
Emery 1999	317/489	250/495		20.95%	1.28[1.15,1.43]
Karanikolas 2006	27/33	19/27		9.89%	1.16[0.87,1.56]
Reece 2002	10/21	9/18		2.95%	0.95[0.5,1.81]
Smolen 1999	74/132	71/130		13.63%	1.03[0.83,1.28]
Strand 1999a	92/180	101/182		15.12%	0.92[0.76,1.12]
Wislowska 2007	30/30	26/30		17.91%	1.15[0.99,1.34]
Subtotal (95% CI)	**1128**	**1205**		**100%**	**1.08[0.96,1.21]**
Total events: 699 (control), 683 (leflunomide)					
Heterogeneity: Tau^2=0.01; Chi^2=16.53, df=6(P=0.01); I^2=63.69%					
Test for overall effect: Z=1.22(P=0.22)					
18.1.3 Lef+DMARD vs single agent					
Dougados 2005	12/50	14/56		26.81%	0.96[0.49,1.88]
Karanikolas 2006	19/27	25/31		37.89%	0.87[0.65,1.18]
Kremer 2002	26/133	60/130		35.3%	0.42[0.29,0.63]
Subtotal (95% CI)	**210**	**217**		**100%**	**0.69[0.39,1.23]**
Total events: 57 (control), 99 (leflunomide)					
Heterogeneity: Tau^2=0.2; Chi^2=10.79, df=2(P=0); I^2=81.46%					
Test for overall effect: Z=1.25(P=0.21)					
18.1.4 Lef (+biologics) vs biologics					
Mariette 2004	129/242	74/115		49.5%	0.83[0.69,0.99]
Wislowska 2007	18/18	26/30		50.5%	1.14[0.97,1.34]
Subtotal (95% CI)	**260**	**145**		**100%**	**0.97[0.66,1.43]**
Total events: 147 (control), 100 (leflunomide)					
Heterogeneity: Tau^2=0.07; Chi^2=10.06, df=1(P=0); I^2=90.06%					
Test for overall effect: Z=0.14(P=0.89)					

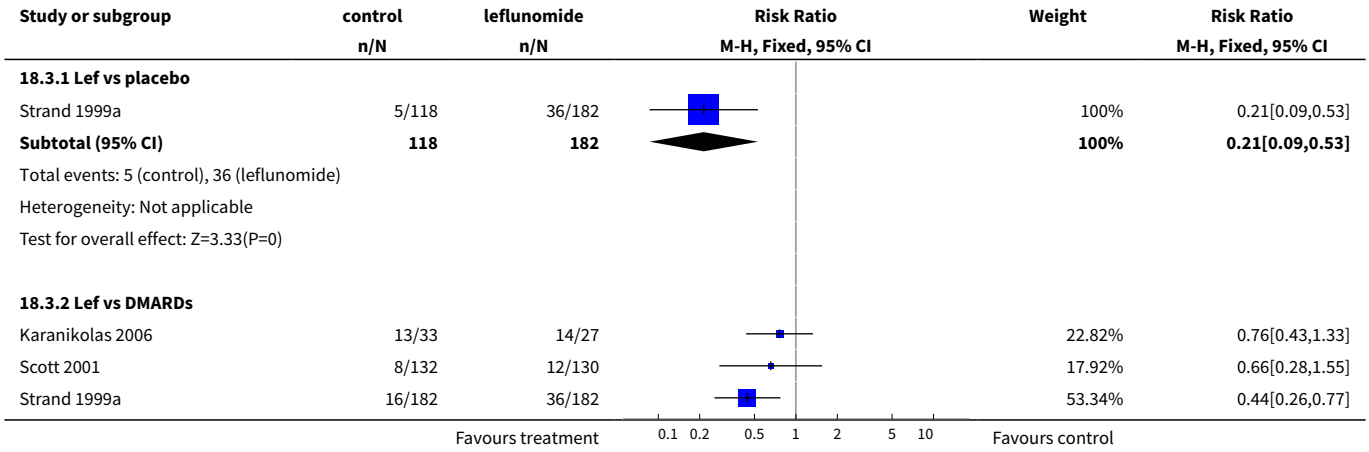
Analysis 18.2. Comparison 18 Summary of comparisons, Outcome 2 ACR50 Treatment responder.

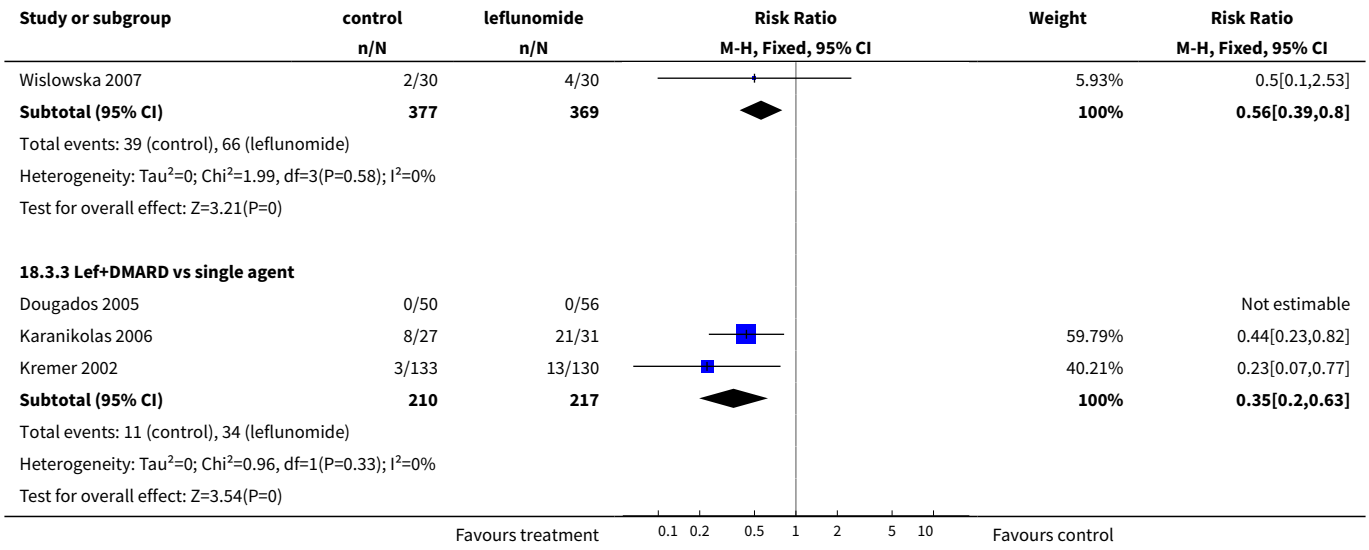


Study or subgroup	control n/N	leflunomide n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
18.2.1 Lef vs placebo					
Smolen 1999	13/91	43/130		53.59%	0.43[0.25,0.76]

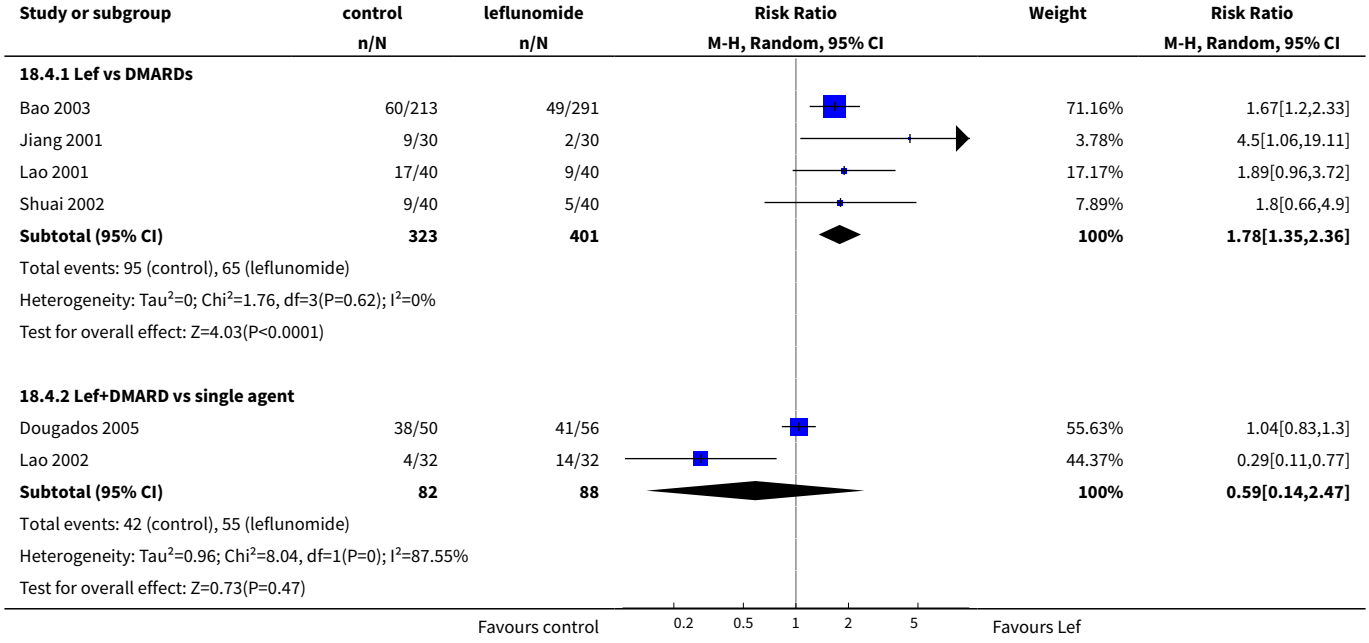


Analysis 18.3. Comparison 18 Summary of comparisons, Outcome 3 ACR70 Treatment responder.

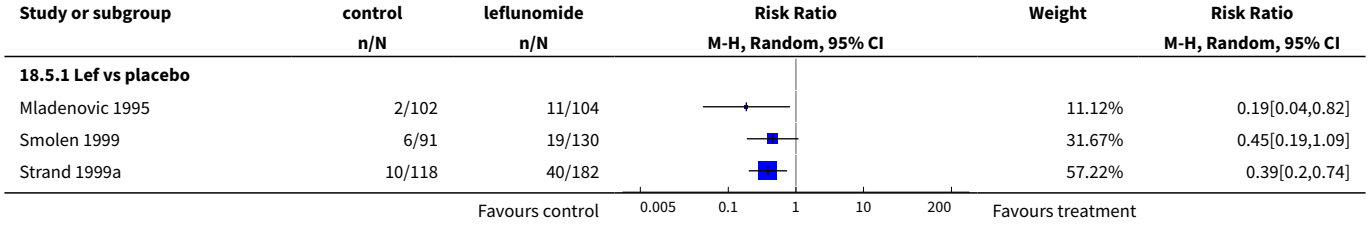


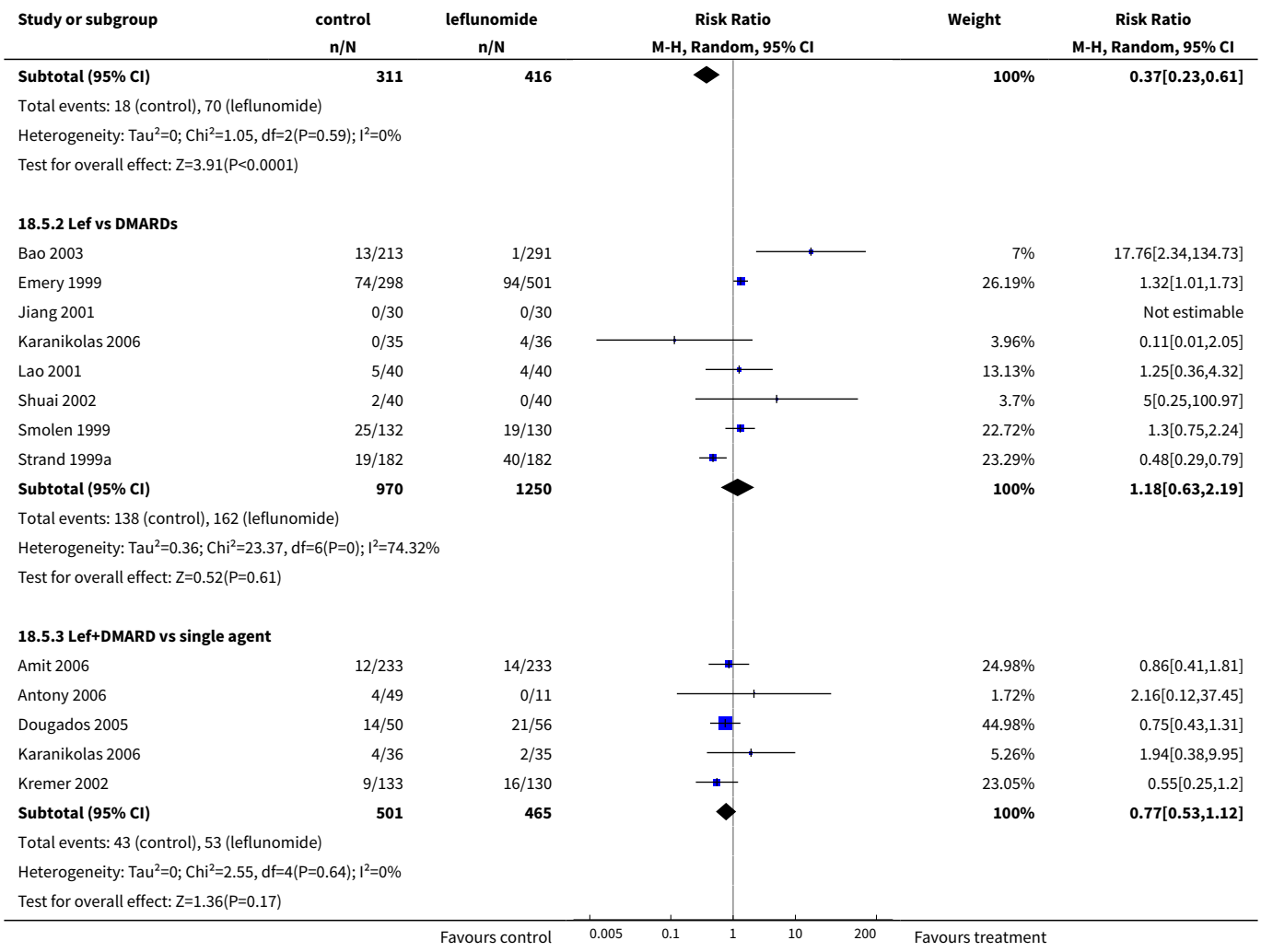


Analysis 18.4. Comparison 18 Summary of comparisons, Outcome 4 Reported adverse events.



Analysis 18.5. Comparison 18 Summary of comparisons, Outcome 5 Withdrawals due to adverse events.





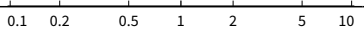
Comparison 19. Treatment responder - ACR50 for SoF

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 leflunomide vs. placebo, at 6 months	1	221	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [1.32, 4.05]
2 leflunomide vs. placebo, at 12 months	1	300	Risk Ratio (M-H, Fixed, 95% CI)	4.47 [2.31, 8.64]
3 leflunomide vs. methotrexate, at 12 months	2	935	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.69, 1.94]
4 leflunomide vs. methotrexate, at 2 years	1	380	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.91, 1.66]
5 leflunomide vs. sulfasalazine, at 6 months	1	262	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.76, 1.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 leflunomide vs. sulfasalazine, at 12 months	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.74, 1.59]
7 leflunomide vs. sulfasalazine, at 24 months	1	117	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [1.25, 3.53]
8 leflunomide+MTX vs MTX, at 24 weeks	1	263	Risk Ratio (M-H, Fixed, 95% CI)	4.35 [2.09, 9.03]
9 leflunomide10mg vs leflunomide 20 mg, at 24 weeks	1	399	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.88, 1.81]
10 leflunomide+SSZ vs. placebo+SSZ, at 24 weeks	1	106	Risk Ratio (M-H, Fixed, 95% CI)	9.84 [0.56, 173.64]
11 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.83, 1.91]
12 leflunomide vs. methotrexate, at 24 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.76, 1.90]
13 leflunomide vs. anti-TNF+MTX, at 24 weeks	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.50, 1.03]
14 Lef vs. CsA, at 12 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.75, 2.30]
15 Lef vs. Lef+CsA, at 12 months	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.43, 0.96]
16 Lef+ADA vs. ADA, at 12 weeks	1	357	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.83, 1.73]
17 Weekly Lef vs. daily Lef, at 6 months	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.83, 3.67]
18 Weekly Lef vs. daily Lef, at 12 months	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.59, 1.29]

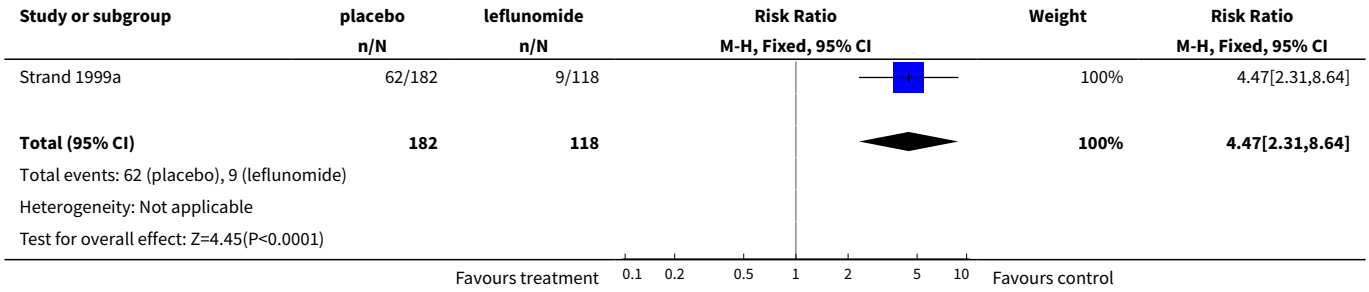
Analysis 19.1. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 1 leflunomide vs. placebo, at 6 months.

Study or subgroup	placebo n/N	leflunomide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Smolen 1999	43/130	13/91		100%	2.32[1.32,4.05]
Total (95% CI)	**130**	**91**		**100%**	**2.32[1.32,4.05]**
Total events: 43 (placebo), 13 (leflunomide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.94(P=0)					

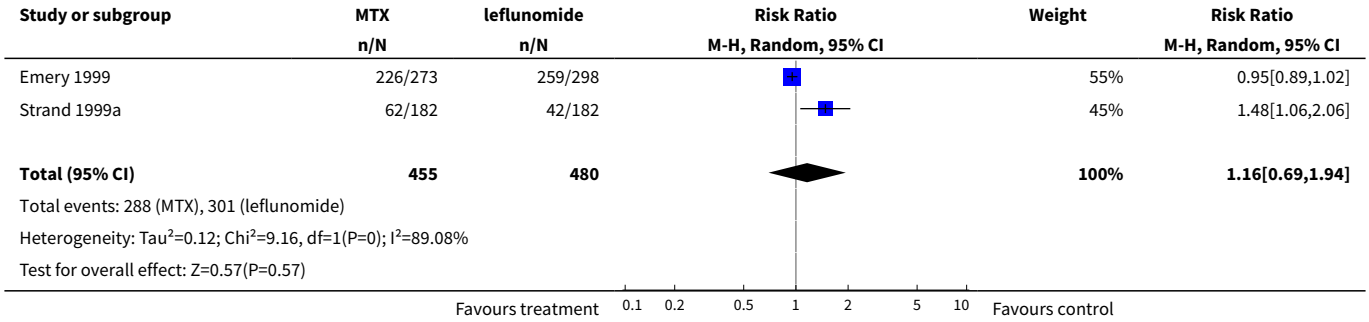


Favours treatment — Favours control

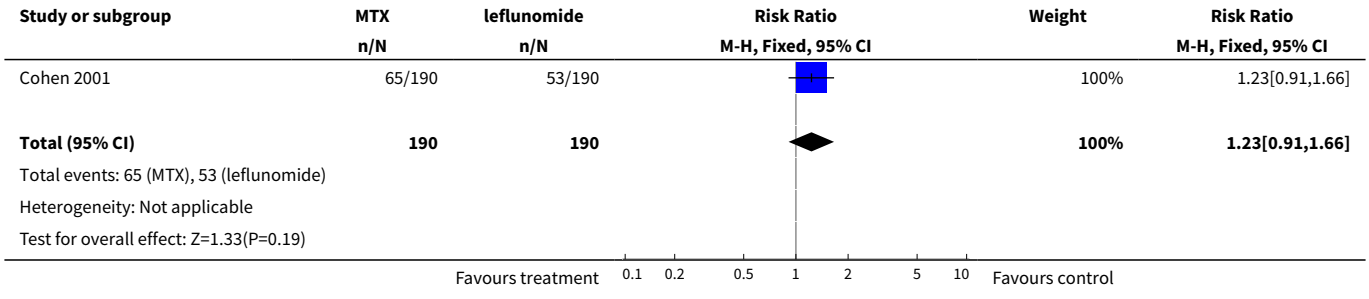
Analysis 19.2. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 2 leflunomide vs. placebo, at 12 months.



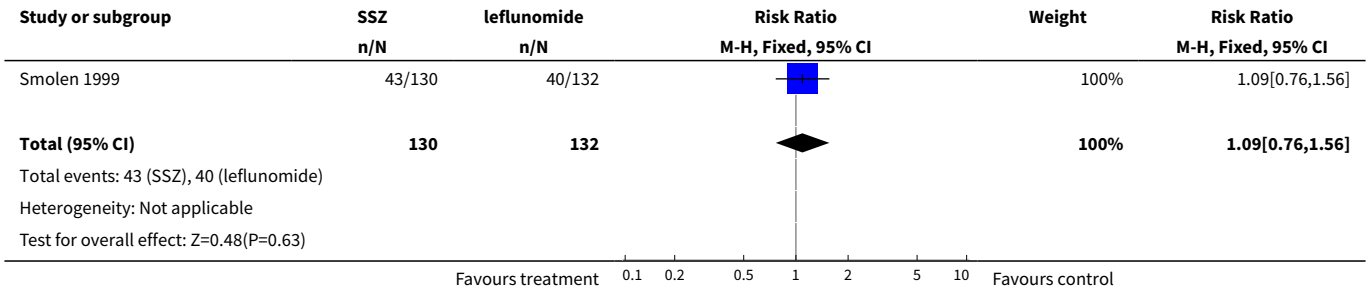
Analysis 19.3. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 3 leflunomide vs. methotrexate, at 12 months.



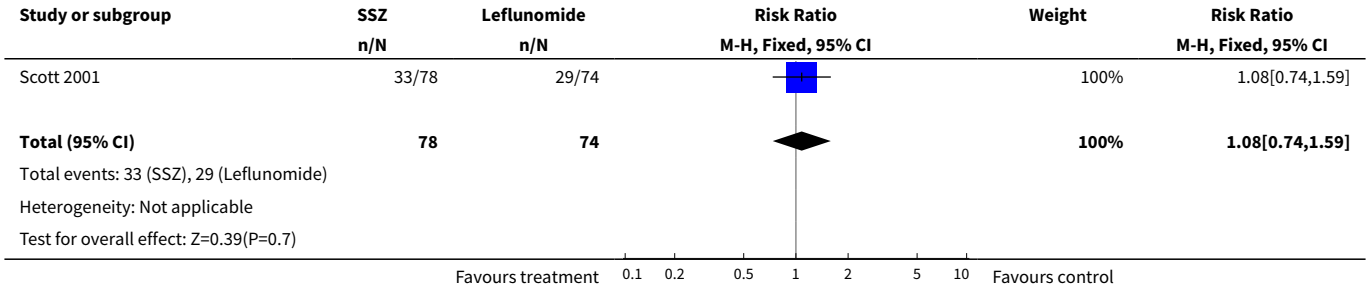
Analysis 19.4. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 4 leflunomide vs. methotrexate, at 2 years.



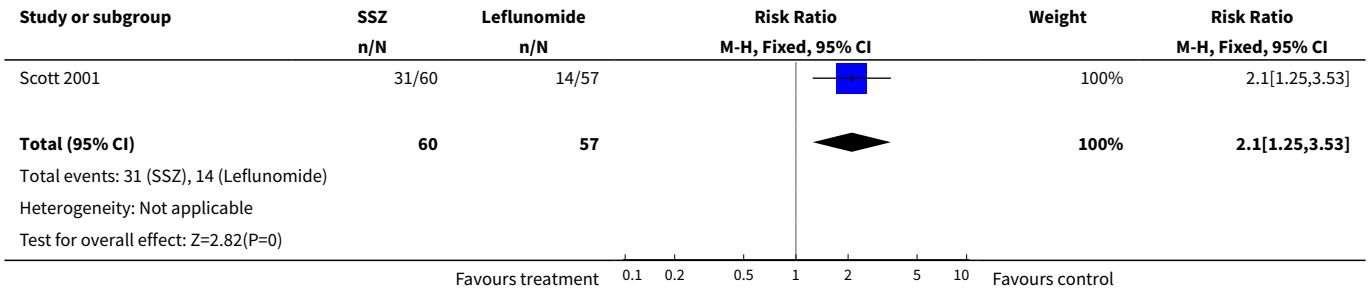
Analysis 19.5. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 5 leflunomide vs. sulfasalazine, at 6 months.



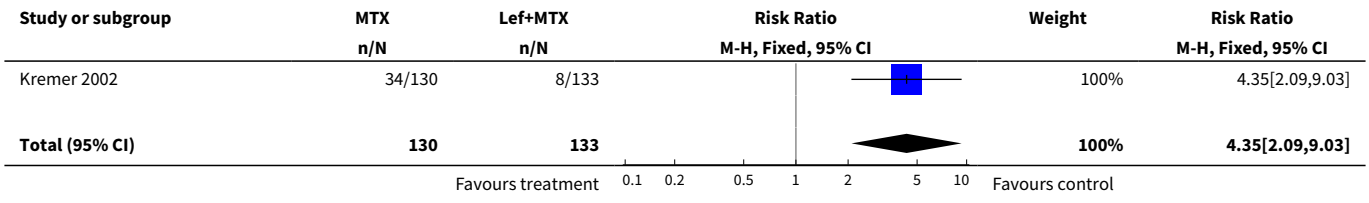
Analysis 19.6. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 6 leflunomide vs. sulfasalazine, at 12 months.

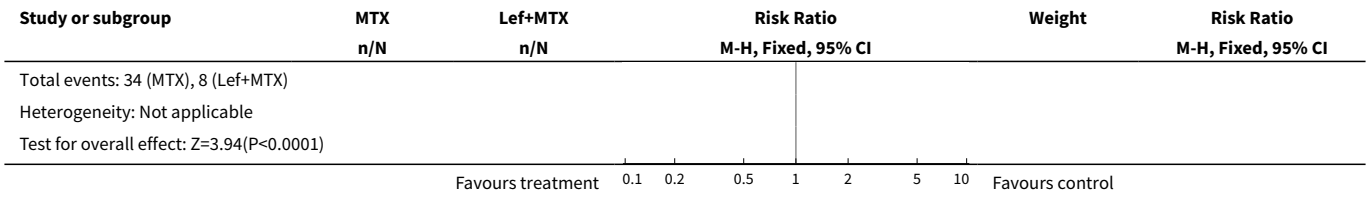


Analysis 19.7. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 7 leflunomide vs. sulfasalazine, at 24 months.

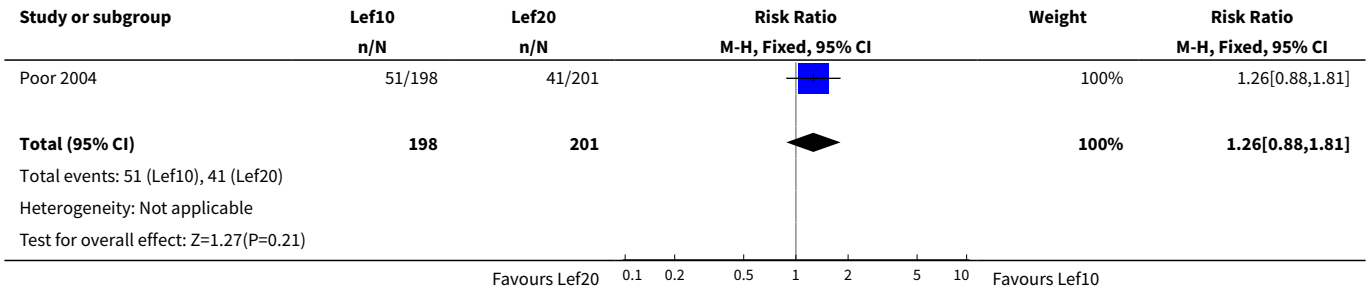


Analysis 19.8. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 8 leflunomide+MTX vs MTX, at 24 weeks.

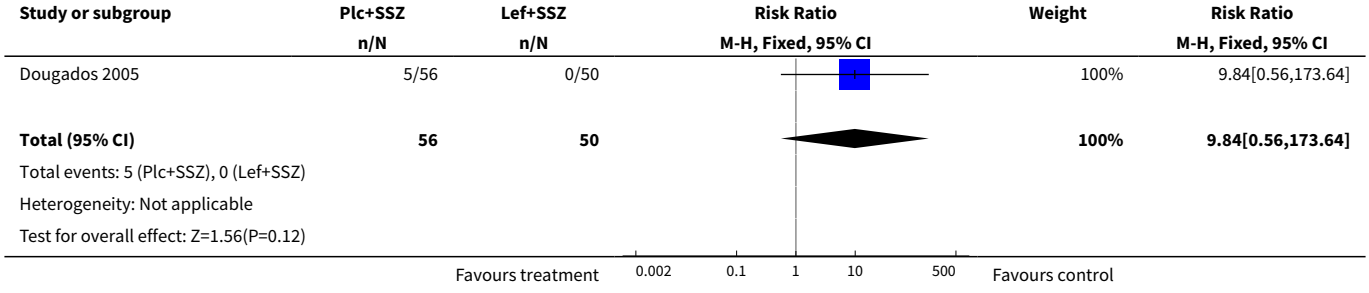




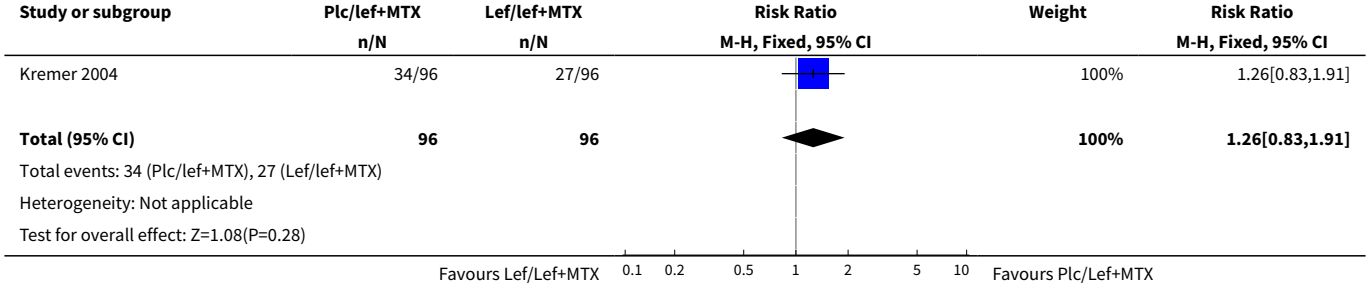
Analysis 19.9. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 9 leflunomide10mg vs leflunomide 20 mg, at 24 weeks.



Analysis 19.10. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 10 leflunomide+SSZ vs. placebo+SSZ, at 24 weeks.



Analysis 19.11. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 11 Lef/lef+MTX vs Plc/lef+MTX, at 48 weeks.



Analysis 19.12. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 12 leflunomide vs. methotrexate, at 24 weeks.

Study or subgroup	MTX n/N	Lef n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Wislowska 2007	18/30	15/30		100%	1.2[0.76,1.9]
Total (95% CI)	**30**	**30**		**100%**	**1.2[0.76,1.9]**
Total events: 18 (MTX), 15 (Lef)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					

Analysis 19.13. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 13 leflunomide vs. anti-TNF+MTX, at 24 weeks.

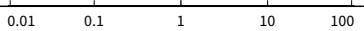
Study or subgroup	anti-TNF+MTX n/N	Lef n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Wislowska 2007	18/30	15/18		100%	0.72[0.5,1.03]
Total (95% CI)	**30**	**18**		**100%**	**0.72[0.5,1.03]**
Total events: 18 (anti-TNF+MTX), 15 (Lef)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.8(P=0.07)					

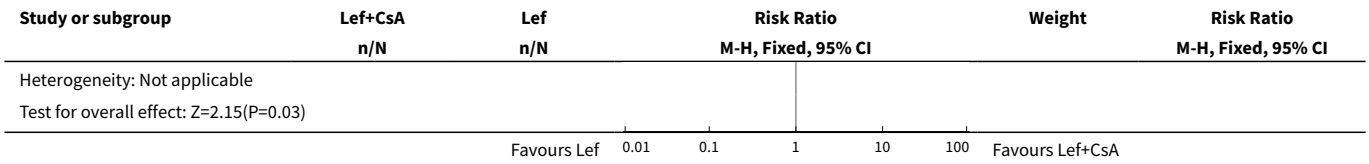
Analysis 19.14. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 14 Lef vs. CsA, at 12 months.

Study or subgroup	CsA n/N	Lef n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Karanikolas 2006	14/27	13/33		100%	1.32[0.75,2.3]
Total (95% CI)	**27**	**33**		**100%**	**1.32[0.75,2.3]**
Total events: 14 (CsA), 13 (Lef)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					

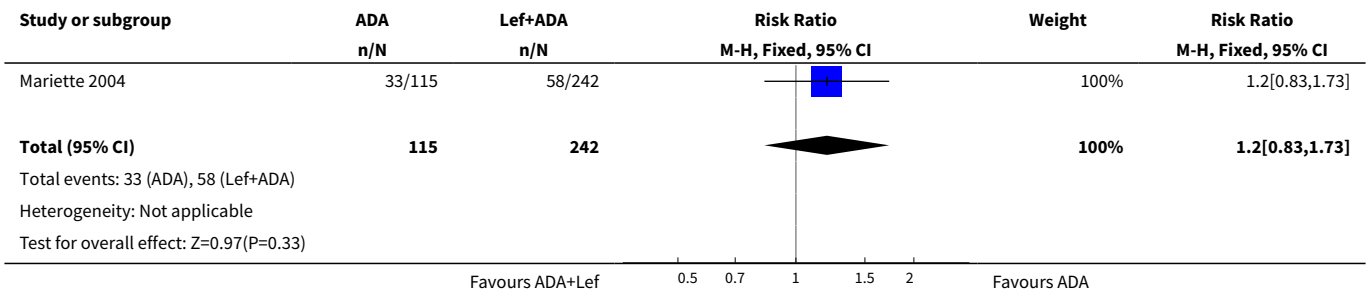
Analysis 19.15. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 15 Lef vs. Lef+CsA, at 12 months.

Study or subgroup	Lef+CsA n/N	Lef n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Karanikolas 2006	14/27	25/31		100%	0.64[0.43,0.96]
Total (95% CI)	**27**	**31**		**100%**	**0.64[0.43,0.96]**
Total events: 14 (Lef+CsA), 25 (Lef)					

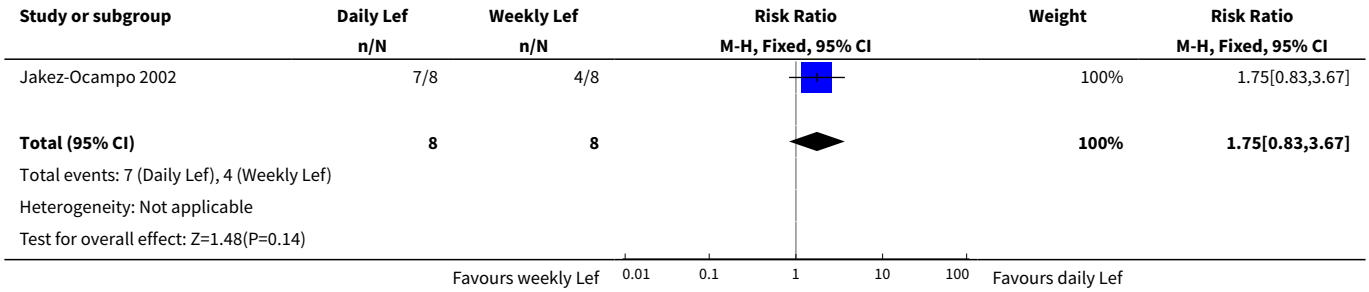




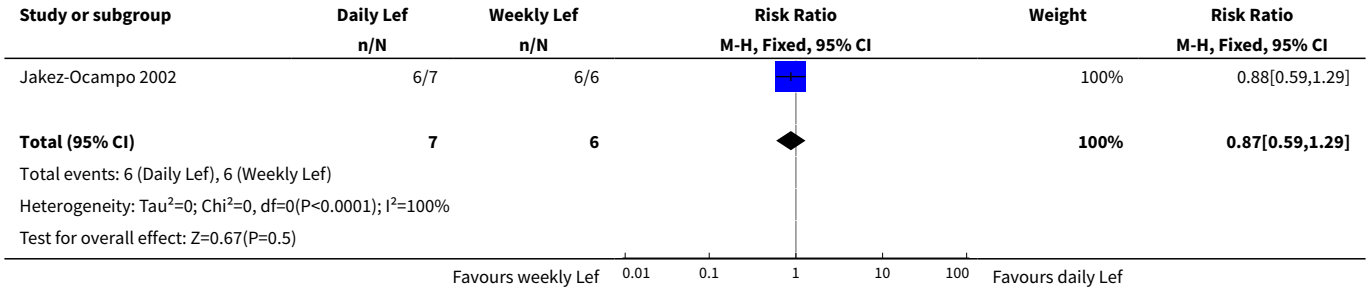
Analysis 19.16. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 16 Lef+ADA vs. ADA, at 12 weeks.



Analysis 19.17. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 17 Weekly Lef vs. daily Lef, at 6 months.



Analysis 19.18. Comparison 19 Treatment responder - ACR50 for SoF, Outcome 18 Weekly Lef vs. daily Lef, at 12 months.



Comparison 20. Adverse events-for SoF

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals due to adverse events in leflunomide vs. placebo	3	727	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.67, 4.47]
2 Withdrawals due to adverse events in leflunomide vs. SSZ, at 6 months	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.45, 1.33]
3 Withdrawals due to adverse events in leflunomide vs. MTX, at 12 months	2	1363	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.13, 1.83]
4 Withdrawals due to adverse events in leflunomide vs. MTX, at 2 years	1	612	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.77, 2.47]
5 Withdrawals due to adverse events in leflunomide vs. SSZ, at 12 months	1	156	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.90]
6 Withdrawals due to adverse events in leflunomide vs. SSZ, at 24 months	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.76]
7 Withdrawals due to adverse events in leflunomide vs. MTX, at 6 months	4	724	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.57]
8 Withdrawals due to adverse events in leflunomide+MTX vs. MTX, at 24 weeks	1	263	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.83, 3.97]
9 Withdrawals due to adverse events in leflunomide10mg vs. leflunomide20mg, at 24 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.78, 2.10]
10 Withdrawals due to adverse events in Lef +SSZ vs. Plc+SSZ, at 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Overall	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.77, 2.34]
11 Withdrawals due to adverse events, Lef/Lef+MTX vs. Plc/Lef+MTX, at 48 weeks	1	192	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.83]
12 Withdrawals due to adverse events, Lef vs. CsA, at 12 months	1	71	Risk Ratio (M-H, Fixed, 95% CI)	8.76 [0.49, 156.85]
13 Withdrawals due to adverse events, Lef vs. Lef+CsA, at 12 months	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.63]
14 Withdrawals due to adverse events, Lef vs. Lef+MTX, at 3 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.03, 8.03]
15 Withdrawals due to adverse events, Lef +MTX vs. MTX, at 36 months	1	466	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.41, 1.81]
16 Withdrawals due to adverse events, weekly Lef vs. daily Lef	1	16	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.28, 90.18]
17 Withdrawals due to adverse events, Lef +MTX vs. MTX, at 24 months	1	166	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.46, 4.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Withdrawals due to adverse events, weekly Lef200 vs. weekly Lef100, at 6 months	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 4.93]

Analysis 20.1. Comparison 20 Adverse events-for SoF, Outcome 1 Withdrawals due to adverse events in leflunomide vs. placebo.

Study or subgroup	leflunomide n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mladenovic 1995	11/104	2/102		9.52%	5.39[1.23,23.74]
Smolen 1999	19/130	6/91		33.28%	2.22[0.92,5.33]
Strand 1999a	40/182	10/118		57.2%	2.59[1.35,4.98]
Total (95% CI)	**416**	**311**		**100%**	**2.73[1.67,4.47]**
Total events: 70 (leflunomide), 18 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.05, df=2(P=0.59); I^2=0%					
Test for overall effect: Z=4.02(P<0.0001)					

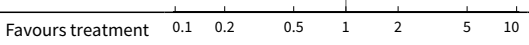
Analysis 20.2. Comparison 20 Adverse events-for SoF, Outcome 2 Withdrawals due to adverse events in leflunomide vs. SSZ, at 6 months.

Study or subgroup	leflunomide n/N	SSZ n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Smolen 1999	19/130	25/132		100%	0.77[0.45,1.33]
Total (95% CI)	**130**	**132**		**100%**	**0.77[0.45,1.33]**
Total events: 19 (leflunomide), 25 (SSZ)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.93(P=0.35)					

Analysis 20.3. Comparison 20 Adverse events-for SoF, Outcome 3 Withdrawals due to adverse events in leflunomide vs. MTX, at 12 months.

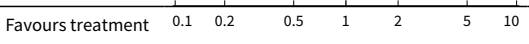
Study or subgroup	leflunomide n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Emery 1999	94/501	74/498		79.62%	1.26[0.96,1.67]
Strand 1999a	40/182	19/182		20.38%	2.11[1.27,3.49]
Total (95% CI)	**683**	**680**		**100%**	**1.43[1.13,1.83]**
Total events: 134 (leflunomide), 93 (MTX)					
Heterogeneity: Tau^2=0; Chi^2=3.02, df=1(P=0.08); I^2=66.85%					

Study or subgroup	leflunomide n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=2.92(P=0)					



Analysis 20.4. Comparison 20 Adverse events-for SoF, Outcome 4 Withdrawals due to adverse events in leflunomide vs. MTX, at 2 years.

Study or subgroup	leflunomide n/N	MTX n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Emery 1999	24/292	19/320		100%	1.38[0.77,2.47]
Total (95% CI)	**292**	**320**		**100%**	**1.38[0.77,2.47]**
Total events: 24 (leflunomide), 19 (MTX)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.1(P=0.27)					

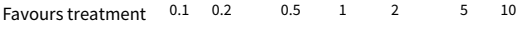


Analysis 20.5. Comparison 20 Adverse events-for SoF, Outcome 5 Withdrawals due to adverse events in leflunomide vs. SSZ, at 12 months.

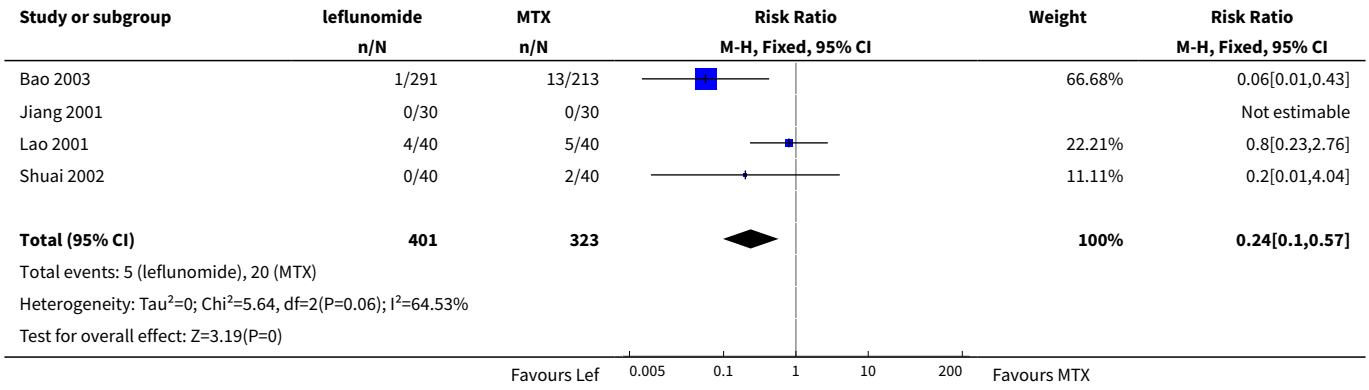
Study or subgroup	leflunomide n/N	SSZ n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	2/80	5/76		100%	0.38[0.08,1.9]
Total (95% CI)	**80**	**76**		**100%**	**0.38[0.08,1.9]**
Total events: 2 (leflunomide), 5 (SSZ)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.18(P=0.24)					

Analysis 20.6. Comparison 20 Adverse events-for SoF, Outcome 6 Withdrawals due to adverse events in leflunomide vs. SSZ, at 24 months.

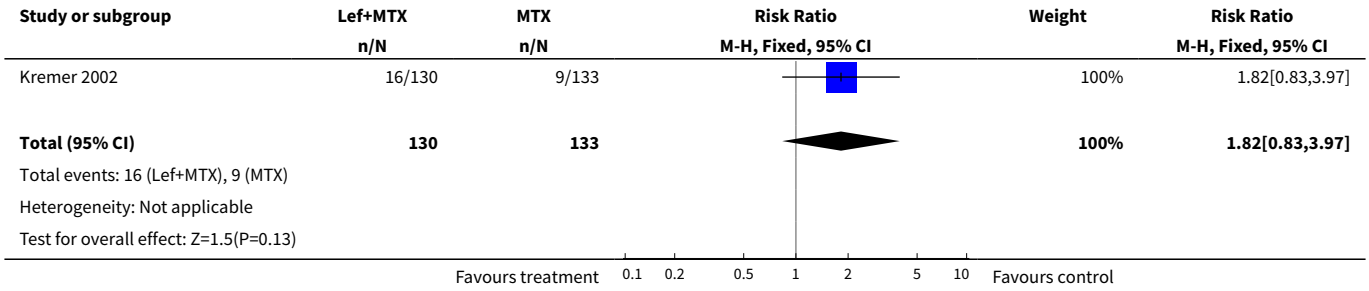
Study or subgroup	leflunomide n/N	SSZ n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Scott 2001	6/60	9/60		100%	0.67[0.25,1.76]
Total (95% CI)	**60**	**60**		**100%**	**0.67[0.25,1.76]**
Total events: 6 (leflunomide), 9 (SSZ)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					



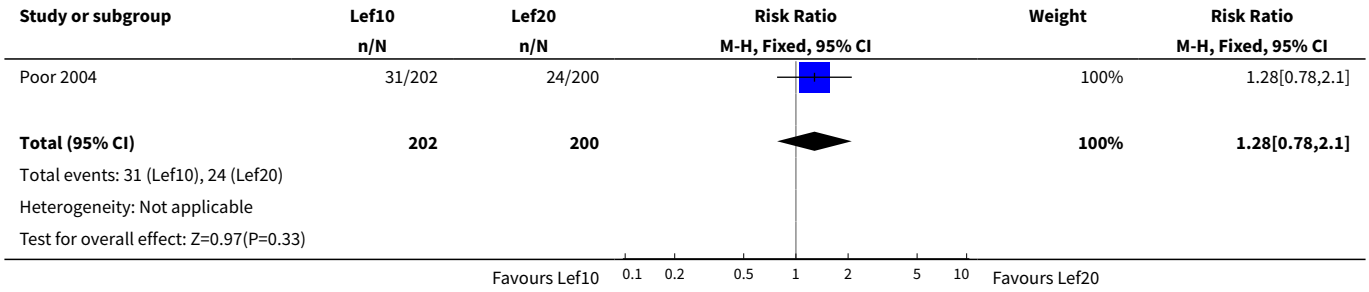
Analysis 20.7. Comparison 20 Adverse events-for SoF, Outcome 7 Withdrawals due to adverse events in leflunomide vs. MTX, at 6 months.



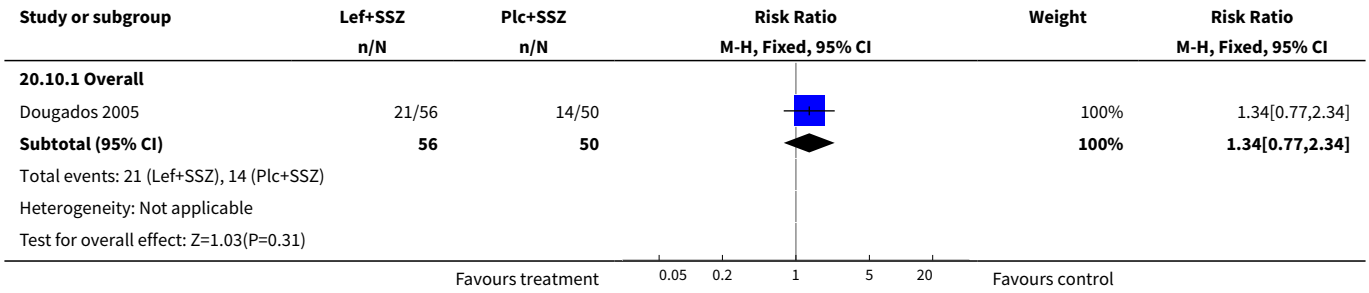
Analysis 20.8. Comparison 20 Adverse events-for SoF, Outcome 8 Withdrawals due to adverse events in leflunomide+MTX vs. MTX, at 24 weeks.



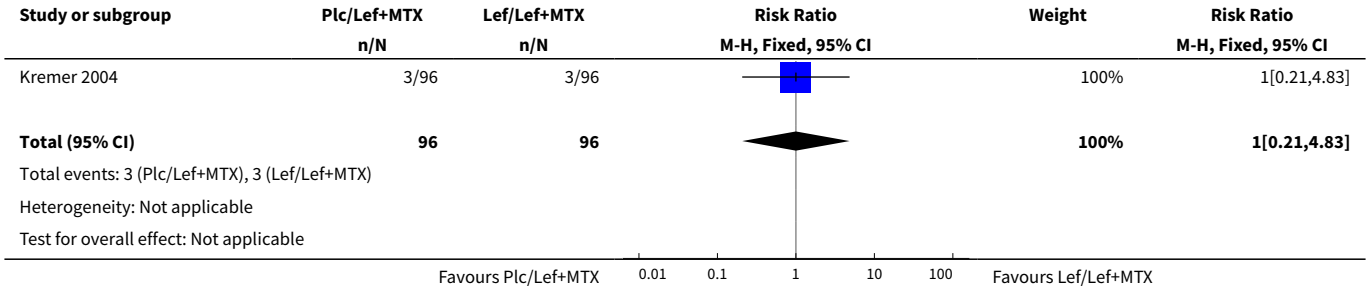
Analysis 20.9. Comparison 20 Adverse events-for SoF, Outcome 9 Withdrawals due to adverse events in leflunomide10mg vs. leflunomide20mg, at 24 weeks.



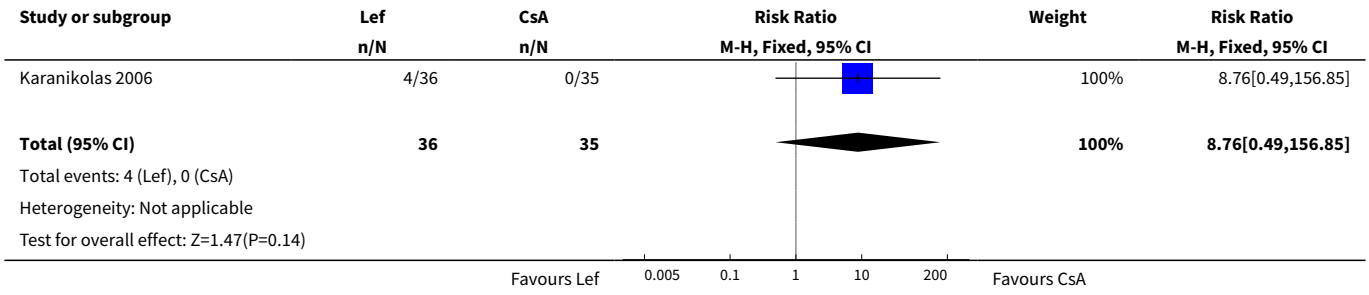
Analysis 20.10. Comparison 20 Adverse events-for SoF, Outcome 10 Withdrawals due to adverse events in Lef+SSZ vs. Plc+SSZ, at 24 weeks.



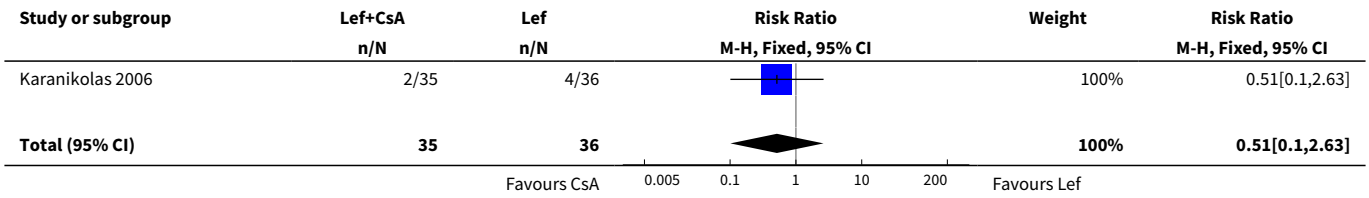
Analysis 20.11. Comparison 20 Adverse events-for SoF, Outcome 11 Withdrawals due to adverse events, Lef/Lef+MTX vs. Plc/Lef+MTX, at 48 weeks.

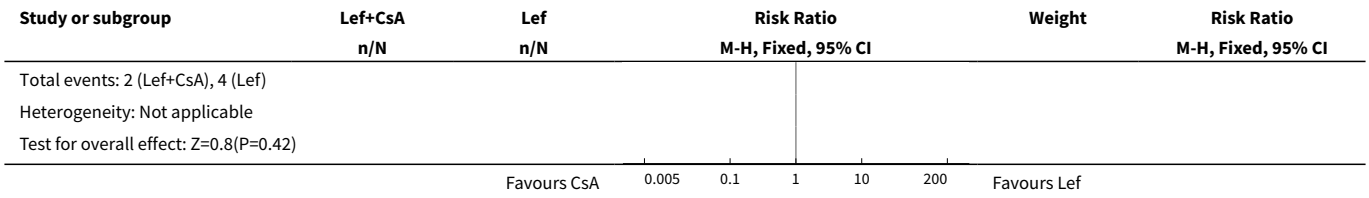


Analysis 20.12. Comparison 20 Adverse events-for SoF, Outcome 12 Withdrawals due to adverse events, Lef vs. CsA, at 12 months.

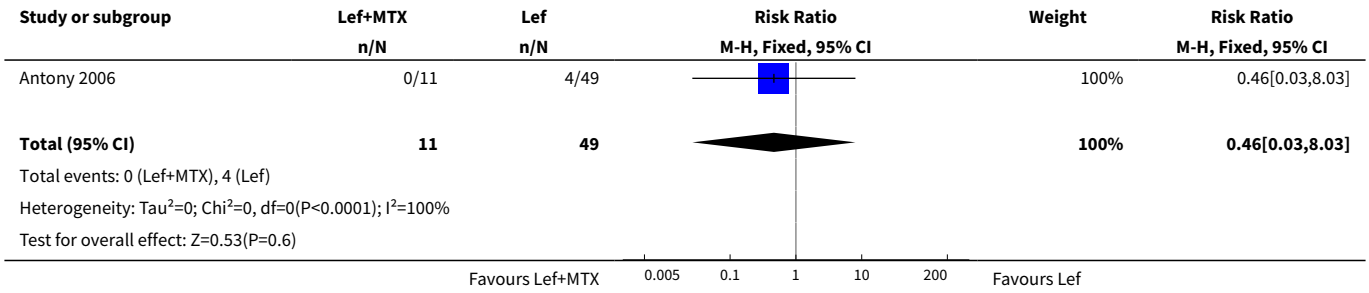


Analysis 20.13. Comparison 20 Adverse events-for SoF, Outcome 13 Withdrawals due to adverse events, Lef vs. Lef+CsA, at 12 months.

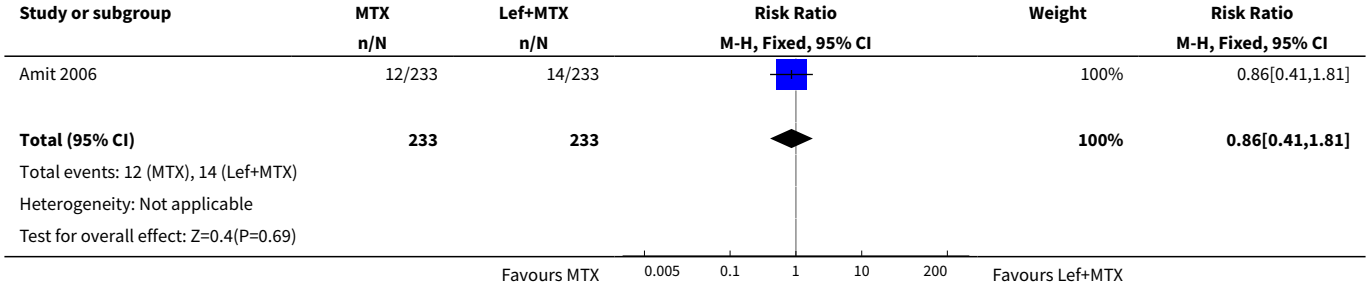




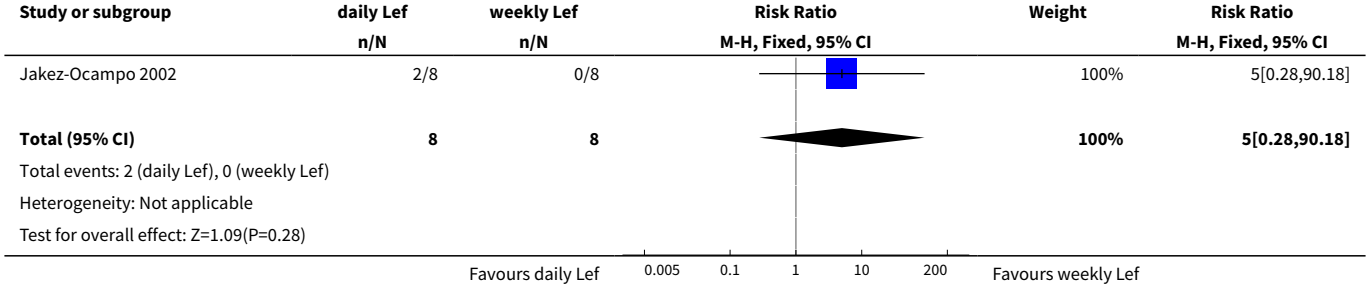
Analysis 20.14. Comparison 20 Adverse events-for SoF, Outcome 14 Withdrawals due to adverse events, Lef vs. Lef+MTX, at 3 months.



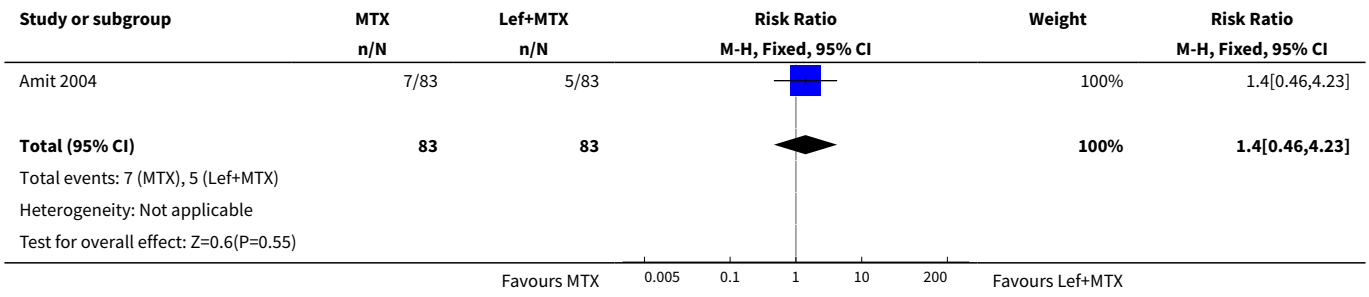
Analysis 20.15. Comparison 20 Adverse events-for SoF, Outcome 15 Withdrawals due to adverse events, Lef+MTX vs. MTX, at 36 months.



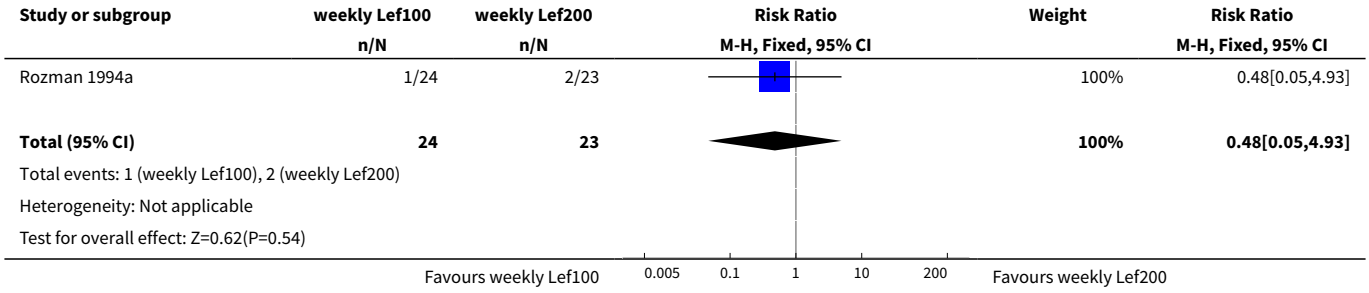
Analysis 20.16. Comparison 20 Adverse events-for SoF, Outcome 16 Withdrawals due to adverse events, weekly Lef vs. daily Lef.



Analysis 20.17. Comparison 20 Adverse events-for SoF, Outcome 17 Withdrawals due to adverse events, Lef+MTX vs. MTX, at 24 months.



Analysis 20.18. Comparison 20 Adverse events-for SoF, Outcome 18 Withdrawals due to adverse events, weekly Lef200 vs. weekly Lef100, at 6 months.



ADDITIONAL TABLES

Table 1. Absolute and relative benefit table of ACR core set outcomes: leflunomide versus placebo

Outcome	Time point	Scale	Absolute benefit	Absolute 95% CI
Tender joint count	6 months	28 joints	5.0 joints	3.7 to 6.3 joints
Tender joint count	12 months	28 joints	4.7 joints	2.8 to 6.6 joints
Swollen joint count	6 months	28 joints	3.3 joints	2.3 to 4.4 joints
Swollen joint count	12 months	28 joints	8.6 joints	7.2 to 10.1 joints
Patient global	6 months	5-point scale and 100 mm VAS	0.64 (SMD)	0.49 to 0.79
Patient global	12 months	100 mm VAS	22.0 mm	15.6 to 28.4 mm
Physician global	6 months	5 point scale and 100 mm VAS	0.67 (SMD)	0.52 to 0.82
Physician global	6 months	100 mm VAS	18.0 mm	11.9 to 24.1 mm

Table 1. Absolute and relative benefit table of ACR core set outcomes: leflunomide versus placebo *(Continued)*

Pain	6 months	100 mm VAS	13.8 mm	11.7 to 15.9 mm
Pain	12 months	100 mm VAS	18.0 mm	12.0 to 24.0 mm
ESR	6 months	mm/hr	7.9 mm/hr	4.9 to 11.0 mm
ESR	12 months	mm/hr	8.9 mm/hr	4.1 to 13.7 mm/hr
HAQ	6 month	0-3 scale	0.43	0.33 to 0.52
HAQ	12 months	0-3 scale	0.48	0.36 to 0.6
SF-36 physical	12 months		6.6	4.3 to 8.9
PET	12 months		6.24	4.0 to 8.5

Table 2. Responder criteria, number needed to treat: leflunomide versus placebo

Criteria	Time point	Comparator	Absolute risk diff	NNT
ACR 20	6 months	Placebo	28% (21 to 35%)	3.6 (2.9 to 4.8)
ACR 20	12 months	Placebo	26% (15 to 37%)	3.9 (2.7 to 6.7)
ACR 20	6 months	SSZ	1% (-13 to 11%)	100 (cannot calculate 95% CI)
ACR20	12 months	MTX	5% (-15 to 25%)	20 (cannot calculate 95% CI)
ACR50	6 months	Placebo	19% (8 to 30%)	5.3 (3.3 to 12.5)
ACR50	12 months	Placebo	26% (18 to 35%)	3.85 (2.9 to 5.6)
ACR50	6 months	SSZ	3% (-8 to 14%)	33 (cannot calculate 95% CI)
ACR 50	12 months	MTX	3% (-12 to 18%)	33 (cannot calculate 95% CI)
ACR 70	12 months	Placebo	16% (9 to 22%)	6.3 (4.5 to 11.1)
ACR70	6 months	SSZ	3% (-3 to 10%)	33 (cannot calculate 95% CI)
ACR70	12 months	MTX	11% (4 to 18%)	9.1 (5.6 to 25)

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp "rheumatoid arthritis"/
2. (rheumat$ arthriti$).tw.
3. 1 or 2
4. exp "isoxazole"/
5. isoxazole$.tw.
6. isoxazole$.rw.

7. leflunomide$.tw.
8. leflunomide$.rn.
9. or/4-8
10. 3 and 9
11. clinical trial.pt.
12. randomized controlled trial.pt.
13. dt.fs.
14. tu.fs.
15. random$.tw.
16. (double adj blind$).tw.
17. placebo$.tw.
18. or/11-17
19. 10 and 18
20. limit 19 to human

WHAT'S NEW

Date	Event	Description
15 May 2008	Amended	CMSG ID C048-R

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 1, 2003

Date	Event	Description
22 July 2009	New search has been performed	New search with 27 new studies. Conclusions not changed.
15 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MO designed the protocol, searched the literature, extracted data and is responsible for content and updates.

BS extracted data and contributed editorial comments.

VW contributed analysis for additional tables.

VS contributed editorial comments.

GW and PT contributed methodological and statistical guidance.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Medicine, Ottawa General Hospital and the University of Ottawa, Canada.

External sources

- The Arthritis Society of Canada (Metro A. Ogryzlo Fellowship), Canada.
- Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Isoxazoles [*therapeutic use]; Leflunomide; Methotrexate [therapeutic use]; Randomized Controlled Trials as Topic; Sulfasalazine [therapeutic use]

MeSH check words

Humans