Rituximab for rheumatoid arthritis (Review)

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[Intervention Review]

Rituximab for rheumatoid arthritis

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ABSTRACT

Background

Rituximab is a selective, B-cell depleting, biologic agent for treating refractory rheumatoid arthritis (RA). It is a chimeric monoclonal antibody targeted against CD 20 that is promoted as therapy for patients who fail to respond to other biologics. There is evidence to suggest that rituximab is effective and well tolerated when used in combination with methotrexate for RA.

Objectives

To evaluate the benefits and harms of rituximab for the treatment of RA.

Search methods

We conducted a search (until January 2014) in electronic databases (*The Cochrane Library*, MEDLINE, EMBASE, CINAHL, Web of Science), clinical trials registries, and websites of regulatory agencies. Reference lists from comprehensive reviews were also screened.

Selection criteria

All controlled trials comparing treatment with rituximab as monotherapy or in combination with any disease modifying anti-rheumatic drug (DMARD) (traditional or biologic) versus placebo or other DMARD (traditional or biologic) in adult patients with active RA.

Data collection and analysis

Two review authors independently assessed the risk of bias and abstracted data from each study.

Main results

We included eight studies with 2720 patients. For six studies selection bias could not be evaluated and two studies were considered to have low risk of bias. The level of evidence ranged from low to high, but was rated as moderate for most outcomes. We have prioritised reporting of rituximab (two 1000 mg doses) in combination with methotrexate since this is the approved dose and most commonly used combination. We also reported data on other combinations and doses as supplementary information in the results section of the review.

American College of Rheumatology (ACR) 50 response rates were statistically significantly improved with rituximab (two 1000 mg doses) in combination with methotrexate compared with methotrexate alone at 24 to 104 weeks. The RR for achieving an ACR 50 at

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24 weeks was 3.3 (95% CI 2.3 to 4.6); 29% of patients receiving rituximab (two 1000 mg doses) in combination with methotrexate achieved the ACR 50 compared to 9% of controls. The absolute treatment benefit (ATB) was 21% (95% CI 16% to 25%) with a number needed to treat (NNT) of 6 (95% CI 4 to 9).

At 52 weeks, the RR for achieving clinical remission (Disease Activity Score (DAS) 28 joints < 2.6) with rituximab (two 1000 mg doses) in combination with methotrexate compared with methotrexate monotherapy was 2.4 (95% CI 1.7 to 3.5); 22% of patients receiving rituximab (two 1000 mg doses) in combination with methotrexate achieved clinical remission compared to 11% of controls. The ATB was 11% (95% CI 2% to 20%) with a NNT of 7 (95% CI 4 to 13).

At 24 weeks, the RR for achieving a clinically meaningful improvement (CMI) in the Health Assessment Questionnaire (HAQ) (> 0.22) for patients receiving rituximab combined with methotrexate compared to patients on methotrexate alone was 1.6 (95% CI 1.2 to 2.1). The ATB was 24% (95% CI 12% to 36%) with an NNT of 5 (95% CI 3 to 13). At 104 weeks, the RR for achieving a CMI in HAQ (> 0.22) was 1.4 (95% CI 1.3 to 1.6). The ATB was 24% (95% CI 16% to 31%) with a NNT of 5 (95% CI 3 to 7).

At 24 weeks, the RR for preventing radiographic progression in patients receiving rituximab (two 1000 mg doses) in combination with methotrexate was 1.2 (95% CI 1.0 to 1.4) compared to methotrexate alone; 70% of patients receiving rituximab (two 1000 mg doses) in combination with methotrexate had no radiographic progression compared to 59% of controls. The ATB was 11% (95% CI 2% to 19%) and the NNT was 10 (95% CI 5 to 57). Similar benefits were observed at 52 to 56 weeks and 104 weeks.

Statistically significantly more patients achieved a CMI on the physical and mental components of the quality of life, measured by the Short Form (SF)-36, in the rituximab (two 1000 mg doses) in combination with methotrexate-treated group compared with methotrexate alone at 24 to 52 weeks (RR 2.0, 95% CI 1.1 to 3.4; NNT 4, 95% CI 3 to 8 and RR 1.4, 95% CI 1.1 to 1.9; NNT 8, 95% CI 5 to 19, respectively); 34 and 13 more patients out of 100 showed an improvement in the physical component of the quality of life measure compared to methotrexate alone (95% CI 5% to 84%; 95% CI 7% to 8%, respectively).

There was no evidence of a statistically significant difference in the rates of withdrawals because of adverse events or for other reasons (that is, withdrawal of consent, violation, administrative, failure to return) in either group. However, statistically significantly more people receiving the control drug withdrew from the study compared to those receiving rituximab (two 1000 mg doses) in combination with methotrexate at all times (RR 0.40, 95% CI 0.32 to 0.50; RR 0.61, 95% CI 0.40 to 0.91; RR 0.48, 95% CI 0.28 to 0.82; RR 0.58, 95% CI 0.45 to 0.75, respectively). At 104 weeks, 37% withdrew from the control group and 20% withdrew from the rituximab (two 1000 mg doses) in combination with methotrexate group. The absolute risk difference (ARD) was -20% (95% CI -34% to -5%) with a number needed to harm (NNH) of 7 (95% CI 5 to 11).

A greater proportion of patients receiving rituximab (two 1000 mg doses) in combination with methotrexate developed adverse events after their first infusion compared to those receiving methotrexate monotherapy and placebo infusions (RR 1.6, 95% CI 1.3 to 1.9); 26% of those taking rituximab plus methotrexate reported more events associated with their first infusion compared to 16% of those on the control regimen with an ARD of 9% (95% CI 5% to 13%) and a NNH of 11 (95% CI 21 to 8). However, no statistically significant differences were noted in the rates of serious adverse events.

Authors' conclusions

Evidence from eight studies suggests that rituximab (two 1000 mg doses) in combination with methotrexate is significantly more efficacious than methotrexate alone for improving the symptoms of RA and preventing disease progression.

PLAIN LANGUAGE SUMMARY

Rituximab for rheumatoid arthritis

We examined research published up to January 2014 on the effect of rituximab for people with rheumatoid arthritis. From eight studies evaluating 2720 people with rheumatoid arthritis, we found that rituximab probably:

- improved pain, function and other symptoms;

- reduced disease activity;

- reduced joint damage as seen on the x-ray.

We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Possible side effects are infusion reactions, vascular disorders, and infections.

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What is rheumatoid arthritis and what is rituximab?

When you have rheumatoid arthritis, your immune system, which normally fights infection, attacks the lining of your joints. This makes your joints swollen, stiff, and painful. There is no cure for rheumatoid arthritis at present, so the treatments aim to relieve pain and improve your ability to move.

Rituximab works by depleting the levels of B-cells, a type of immune cell in the body that causes swelling and joint damage in people who have rheumatoid arthritis. Rituximab is given intravenously. Rituximab is of great interest to rheumatoid arthritis patients based on improvements in symptoms and radiographic progression, and the low rate of short-term side effects.

What happens to people with rheumatoid arthritis who are given rituximab plus methotrexate?

ACR 50 (number of tender or swollen joints, pain, and disability)

- 21 more people out of 100 experienced improvement in their symptoms after 6 months with rituximab plus methotrexate compared to methotrexate alone (21% absolute improvement)*.

- 29 people out of 100 experienced improvement with rituximab plus methotrexate compared to 9 out of 100 who took methotrexate alone.

Disease activity

- 11 more people out of 100 achieved remission of their rheumatoid arthritis after 1 year with rituximab plus methotrexate compared to methotrexate alone (11% absolute improvement).

- 22 people out of 100 on rituximab plus methotrexate achieved remission compared to 11 out of 100 who took methotrexate alone.

Physical function

- 24 more people out of 100 achieved a meaningful improvement in their physical function after 2 years with rituximab plus methotrexate compared to methotrexate alone (24% absolute improvement).

- 85 people out of 100 on rituximab plus methotrexate achieved a meaningful improvement in their physical function compared to 61 out of 100 who took methotrexate alone.

X-rays of the joints

- 19 more people out of 100 had no damage to their joints after 2 years with rituximab plus methotrexate compared to methotrexate alone (19% absolute improvement)*.

- 57 people out of 100 on rituximab plus methotrexate had no damage to their joints compared to 39 out of 100 who took methotrexate alone.

Quality of life - physical component (general health, pain, and ability to perform physical activities)

- 34 more people out of 100 perceived their general health, pain, and ability to perform physical activities better after 6 to 12 months with rituximab plus methotrexate compared to methotrexate alone (34% absolute improvement)*.

- 70 people out of 100 who took rituximab plus methotrexate perceived their general health, pain, and ability to perform physical activities to be better compared to 36 out of 100 who took methotrexate alone.

Quality of life - mental component

- 13 more people out of 100 perceived their mental well-being better after 6 to 12 months with rituximab plus methotrexate compared to methotrexate alone (13% absolute improvement).

- 48 people out of 100 who took rituximab plus methotrexate perceived their mental well-being to be better compared to 35 out of 100 who took methotrexate alone.

Discontinuations due to adverse events

- 2 less people out of 100 discontinued rituximab plus methotrexate due to side effects after 2 years compared to methotrexate alone (-2% absolute withdrawals).

- 3 people out of 100 who took rituximab plus methotrexate discontinued methotrexate due to side effects compared to 5 out of 100 who took a placebo.

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Serious adverse events

- 4 less people out of 100 experienced serious side effects after 2 years with rituximab plus methotrexate compared to methotrexate alone (-4% absolute harms).

- 13 people out of 100 who took rituximab plus methotrexate had side effects compared to 17 out of 100 who took methotrexate alone.

*1% unit difference due to rounding.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Rituximab (2 x 1000 mg) plus methotrexate compared to methotrexate monotherapy for rheumatoid arthritis

Patient or population: patients with rheumatoid arthritis
Settings: rheumatology clinics
Intervention: rituximab (two 1000 mg doses) plus methotrexate
Comparison: methotrexate monotherapy

Outcomes	Follow-up (weeks)	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Methotrexate monotherapy	Rituximab (2 x 1000 mg) plus methotrexate				
Clinical improvement American College of Rheumatology 50% improvement criteria Analysis 1.2	**24**	**88 per 1000**	**286 per 1000** (203 to 402)	**RR 3.3** (2.3 to 4.6)	1165 (4 studies)	⊕⊕⊕◯ **moderate**[1]	Absolute treatment benefit 21% (95% CI 16% to 25%) ; Relative per cent change 225% (95% CI 131% to 358%); NNTB 6 (95% CI 9 to 4)
	48 to 56	**331 per 1000**	**742 per 1000** (418 to 1000)	**RR 2.2** (1.3 to 4.0)	852 (4 studies)	⊕⊕⊕◯ **moderate**[1]	Absolute treatment benefit 24% (95% CI 18% to 30%) ; Relative per cent change 124% (95% CI 26% to 295%); NNTB 4 (95% CI 6 to 3)

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	104	**377 per 1000**	**562 per 1000** (471 to 668)	**RR 1.5** (1.3 to 1.8)	579 (2 studies)	⊕⊕⊕◯ **moderate**[1]	Absolute treatment benefit 17% (95% CI 8% to 27%); Relative per cent change 149% (95% CI 25% to 77%); NNTB 6 (95% CI 11 to 4)
Clinical remission (Disease Activity Score-28 joint count < 2.6) (Scale from 2 to 10) Analysis 1.7	**24**	**11 per 1000**	**99 per 1000** (8 to 1000)	**RR 9.1** (0.76 to 108.2)	834 (2 studies)	⊕⊕⊕◯ **moderate**[2]	Not statistically significant. Absolute treatment benefit 8% (95% CI 6% to 11%); Relative per cent change 809% (95% CI -24% to 1072%); NNTB N/A
	48 to 52	**112 per 1000**	**221 per 1000** (190 to 387)	**RR 2.4** (1.7 to 3.5)	772 (3 studies)	⊕⊕⊕◯ **moderate**[2]	Absolute treatment benefit 11% (95% CI 2% to 20%); Relative per cent change 142% (95% CI 70% to 246%); NNTB 7 (95% 13 CI to 4)
	104	**129 per 1000**	**320 per 1000** (221 to 464)	**RR 2.5** (1.7 to 3.6)	499 (1 study)	⊕⊕⊕◯ **moderate**[2]	Absolute treatment benefit 19% (95% CI 12% to 26%) ; Relative per cent change 149% (95% CI 72% to 261%); NNTB 6 (95% 11 CI to 3)

Physical function (HAQ-DI MCID = -0.22) Analysis 1.10	**24**	**387 per 1000**	**623 per 1000** (472 to 821)	**RR 1.6** (1.2 to 2.1)	1161 (4 studies)	⊕⊕⊕⊕ **high**	Absolute treatment benefit 24% (95% CI 12% to 36%) ; Relative per cent change 61% (95% CI 22% to 112%); NNTB 5 (95% CI 13 to 3)
	48 to 56	**726 per 1000**	**1000 per 1000** (516 to 1000)	**RR 1.6** (0.71 to 3.4)	562 (2 studies)	⊕⊕⊕⊕ **high**	Absolute treatment benefit 24% (95% CI -5% to 52%) ; Relative per cent change 57% (95% CI -29% to 244%); NNTB N/A
	72	**200 per 1000**	**464 per 1000** (156 to 1000)	**RR 2.3** (0.78 to 6.89)	43 (1 study)	⊕⊕⊕⊕ **high**	Absolute treatment benefit 26% (95% CI -1% to 54%) ; Relative per cent change 132% (95% CI -22% to 589%); NNTB N/A
	104	**608 per 1000**	**845 per 1000** (760 to 942)	**RR 1.4** (1.3 to 1.6)	523 (2 studies)	⊕⊕⊕⊕ **high**	Absolute treatment benefit 24% (95% CI 16% to 31%) ; Relative per cent change 39% (95% CI 25% to 55%); NNTB 5 (95% CI 7 to 3)

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No radiographic progression in total Genant-modified Sharp score (range 0 to 290) Analysis 1.21		**24**	**591 per 1000**	**697 per 1000** (608 to 797)	**RR 1.2** (1.0 to 1.4)	476 (1 study)	⊕⊕⊕○ **moderate**[1]	Absolute treatment benefit 11% (95% CI 2% to 19%) ; Relative per cent change 18% (95%CI 3% to 35%) ; NNTB 10 (95% CI 57 to 5)
		56	**500 per 1000**	**625 per 1000** (555 to 700)	**RR 1.3** (1.11 to 1.4)	940 (2 studies)	⊕⊕⊕○ **moderate**	Absolute treatment benefit 12% (95% CI 6% to 19%) ; Relative per cent change 25% (95%CI 11% to 40%); NNTB 8 (95% CI 19 to 5)
		104	**379 per 1000**	**568 per 1000** (492 to 655)	**RR 1.5** (1.3 to 1.7)	945 (2 studies)	⊕⊕⊕○ **moderate**[1]	Absolute treatment benefit 19% (95% CI 13% to 25%) ; Relative per cent change 50% (95%CI 30% to 73%); NNTB 6 (95% CI 9 to 4)
Health-related quality of life	SF-36 PCS MCID = -5 or 5.42 Analysis 1.12	**24 to 52**	**355 per 1000**	**697 per 1000** (405 to 1000)	**RR 2.0** (1.1 to 3.4)	1,526 (4 studies)	⊕⊕⊕⊕ **high**	Absolute treatment benefit 34% (95% CI 5% to 84%) ; Relative per-cent change 96% (95%CI 14% to 226%); NNTB 4 (95% CI 8 to 3)

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	SF-36 MCS MCID = -5 or 6.33 Analysis 1.14	**24 to 52**	**345 per 1000**	**475 per 1000** (352 to 638)	**RR 1.4** (1.1 to 1.9)	1282 (3 studies)	⊕⊕⊕⊕ **high**	Absolute treatment benefit 13% (95% CI 7% to 18%); Relative per cent change 43% (95% CI 6% to 92%); NNTB 8 (95% CI 19 to 5)
Discontinuations due to adverse events Analysis 6.3		**24**	**10 per 1000**	**21 per 1000** (9 to 48)	**RR 2.1** (0.88 to 4.9)	1385 (5 studies)	⊕⊕⊕◯ **moderate**[2]	Not statistically significant; Absolute risk difference 1% (95% CI 0% to 3%) ; Relative per cent change 107% (95% CI -12% to 388%); NNTH N/A
		48-52	**24 per 1000**	**24 per 1000** (10 to 54)	**RR 1.0** (0.44 to 2.3)	927 (3 studies)	⊕⊕⊕⊕ **high**	Not statistically significant; Absolute risk difference 0% (95% CI -2% to 2%) ; Relative per cent change 0% (95% CI -56% to 129%); NNTH N/A
		72	**75 per 1000**	**25 per 1000** (3 to 230)	**RR 0.33** (0.04 to 3.1)	80 (1 study)	⊕⊕⊕◯ **moderate**[1]	Not statistically significant; Absolute risk difference -5% (95% CI -14% to 4%); Relative per cent change -67% (95% CI -96% to 207%); NNTH N/A

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	104	**55 per 1000**	**31 per 1000** (14 to 69)	**RR 0.56** (0.25 to 1.3)	579 (2 studies)	⊕⊕⊕⊕ **high**	Not statistically significant; Absolute risk difference -2% (95% CI -6% to 1%) ; Relative per cent change -44% (95% CI -45% to 25%); NNTH N/A
Serious adverse events Analysis 11.2	**24**	**75 per 1000**	**75 per 1000** (51 to 108)	**RR 1** (0.69 to 1.5)	1280 (4 studies)	⊕⊕⊕◯ **moderate**[2]	Not statistically significant; Absolute risk difference 0% (95% CI -3% to 3%) ; Relative per cent change 0% (95% CI -32% to 45%); NNTH N/A
	48 to 56	**103 per 1000**	**97 per 1000** (59 to 158)	**RR 0.94** (0.57 to 1.5)	579 (2 studies)	⊕⊕⊕⊕ **high**	Not statistically significant; Absolute risk difference -1% (95% CI -6% to 4%) ; Relative per cent change -6% (95% CI -43% to 53%); NNTH N/A
	104	**169 per 1000**	**132 per 1000** (86 to 201)	**RR 0.78** (0.51 to 1.2)	499 (1 study)	⊕⊕⊕◯ **moderate**[1]	Not statistically significant; Absolute risk difference -4% (95% CI -10% to 3%); Relative per cent change -22% (95% CI -49% to 19%); NNTH N/A

*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).

DAS28: Disease Activity Score - 28 joints; **CI:** Confidence interval; **HAQ-DI:** Health Assessment Questionnaire - Disability Index; **MCID:** Minimal clinically important difference in HAQ-DI reflecting a meaningful improvement in physical function (a decrease of $\geq$ 0.22) in SF-36 represents the minimal difference in scores of the PCS or MCS that is perceived by patients as beneficial; **NNTB** and **NNTH**: Number of patients needed to be treated for one additional patient to benefit or be harmed; **RR:** Risk ratio; **SF-36 PCS and MCS:** Medical Outcomes Survey SF-36 items physical component score or mental component score

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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: We are very uncertain about the estimate.

[1] Only one study was graded as having low risk of bias

[2] One of the studies was judged with potential to attrition bias

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BACKGROUND

Description of the condition

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis that causes significant morbidity and can lead to considerable loss of function (Grassi 1998; Wolfe 1996). Early intervention can control joint pain and swelling, and reduce the risk of disability and permanent joint damage. Disease modifying anti-rheumatic drugs (DMARDs) remain the preferred initial treatment for RA; they have been shown to reduce disease activity, retard joint erosions, and improve patients' quality of life (Fries 1996; Lopez-Olivo 2014). Unfortunately, many patients either fail to respond adequately or need to stop treatment because of side effects. Biologic drugs have shown effectiveness in patients who do not respond to DMARDs (Breedveld 2006; Lethaby 2013; Lipsky 2000; Maxwell 2009; Navarro-Sarabia 2005; Singh 2009; Singh 2010; Singh 2010a).

Description of the intervention

Rituximab (MabThera or Rituxan) is a genetically engineered chimeric monoclonal antibody targeting CD20 (Dörner 2003; Olsen 2004). In 2006, rituximab was approved for use in patients with RA. Each course encompasses two 1000 mg intravenous infusions at day 0 and 15. Courses are administered at intervals of at least four months. The cost of rituximab varies across healthcare settings.

How the intervention might work

Rituximab is a selective, CD20 B-cell depleting, biologic agent used for the treatment of adult patients with active RA who fail to respond to other biologic DMARDs (Cohen 2006; Higashida 2005). B-cells play a critical role in the pathogenesis of RA. They have been associated with auto-antibodies (rheumatoid factor (RF) and anti-citrullinated protein antibodies (anti-CCP)) and have been found in the inflamed synovium where they can lead to bone and cartilage damage in the joints (Boumas 2009). Most infusion reactions of rituximab are mild to moderate and occur during the first infusion (Mohrbacher 2005). Rituximab-induced infusion reactions and infections are the most common adverse events. Acetaminophen, antihistamine agents, and glucocorticoids can be administered before each infusion to reduce the incidence and severity of infusion reactions. Medical management must be available during administration of rituximab to address severe infusion reactions.

Why it is important to do this review

There is evidence to suggest that rituximab is effective and well tolerated when used used in combination with methotrexate to manage RA (Edwards 2001; Edwards 2004). This review synthesizes the most current evidence on the use of rituximab for RA, and informs clinicians, consumers, and policy makers about its efficacy and safety when used alone or combined with other DMARDs.

OBJECTIVES

To evaluate the benefits and harms of rituximab for the treatment of RA.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing rituximab in combination with any DMARD or rituximab alone versus placebo, other DMARDs, or any biologic agent for a minimum trial duration of four months. RCTs with patients on concomitant therapy including stable doses of corticosteroids or non-steroidal anti-inflammatory drugs were accepted.

Types of participants

Patients at least 18 years of age meeting the American College of Rheumatology (ACR) 1987 revised criteria (Arnett 1988) for RA and active disease as described by authors in relation to the outcome measures.

Types of interventions

Studies reporting on the efficacy or safety of rituximab as monotherapy or in combination with any DMARDs (traditional or biologic) versus placebo or other DMARDs (traditional or biologic) were eligible for inclusion. We have prioritised reporting of rituximab (two 1000 mg doses) in combination with methotrexate since this is the most commonly use combination and approved dose. We also reported additional data in the results section of the review as supplementary information on: (i) rituximab monotherapy versus methotrexate monotherapy, (ii) rituximab (two 500 mg doses) in combination with methotrexate versus methotrexate, (iii) rituximab (two 1000 mg doses) in combination with cyclophosphamide versus rituximab monotherapy, and (iv) rituximab

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in combination with methotrexate and a tumour necrosis factor (TNF) inhibitor versus methotrexate in combination with a TNF inhibitor.

Types of outcome measures

The primary efficacy outcomes included in this review were the response of RA to treatment with rituximab as defined by the ACR (Felson 1995), the World Health Organization (WHO), and the International League of Associations for Rheumatology (ILAR) core set of disease activity measures (Furst 1994).

Major outcomes

1. Improvement criteria. Measured by the ACR 50 response which represent a 50% improvement in tender and swollen joints counts plus a 50% improvement in three of the five core components (Felson 1995)
2. Disease remission. Measured by Disease Activity Scores (DAS) < 2.6 (Prevoo 1995)
3. Functional status. Measured by the Health Assessment Questionnaire (HAQ) (Fries 1982)
4. Radiographic progression for studies with a minimum of six months duration, including the Sharp/Genant, Sharp/van der Heijde, and Larsen scores (Genant 1998; Larsen 1973; van der Heijde 1999)
5. Health-related quality of life. Measured by the Medical Outcomes Study Short-Form Health Survey (SF-36)
6. Withdrawals due to adverse events
7. Serious adverse events

Secondary outcomes

1. ACR 20 and ACR 70 responses, which represent a 20% or 70% improvement in tender and swollen joints counts plus a 20%, 50%, or 70% improvement in three of the five core components (Felson 1995)
2. The European League Against Rheumatism (EULAR) response criteria, which include not only change in disease activity but also current disease activity. Per EULAR, patients are classified as responders if a significant change in DAS and low current disease activity is observed. It includes three categories: good, moderate, and non-responders (Van Gestel 1996)
3. Individual ACR core set components: tender joint count (TJC), swollen joint count (SJC), patient's assessment of pain using a 10 cm visual analogue scale or Likert scale, patient global assessment of disease activity, physician global assessment of disease activity using a 10 cm visual analogue scale or Likert scale, HAQ, or acute phase reactants such as Westergren erythrocyte sedimentation rate or C-reactive protein (Felson 1995)
4. Patient-reported outcome measures such as the fatigue scale of the functional assessment of chronic illness therapy (FACIT-F)
5. Withdrawals (total, due to lack of efficacy, and due to other reasons)
6. Adverse events (total, infections, serious infections, deaths, acute infusion reactions, cardiovascular, and malignancies)

Search methods for identification of studies

We followed the Cochrane Musculoskeletal Group methods used in previous reviews.

Electronic searches

From inception to January 2014, we conducted a search in the following electronic databases: *The Cochrane Library* (Wiley), MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), Web of Science (Thomson-Reutors). Our search was not restricted by language, year, or type of publication. The specific search strategy for the databases is shown in Appendix 1.

Searching other resources

Reference lists from comprehensive reviews and identified clinical trials were searched for possible references not otherwise found. Clinical trials registries were also searched, including clinical trials.gov and the World Health Organization (WHO) Clinical Trials Registry Platform. For safety assessments, we searched the websites of the regulatory agencies: US Food and Drug Administration MedWatch (http://www.fda.gov/Safety/MedWatch/default.htm), European Medicines Evaluation Agency (http://www.ema.europa.eu), Australian Adverse Drug Reactions Bulletin (http://www.tga.gov.au/safety/ews-monitoring.htm), and UK Medicines and Healthcare products Regulatory Agency (MHRA) pharmacovigilance and drug safety updates (http://www.mhra.gov.uk/Safetyinformation/index.htm) using the keyword(s) 'rituximab' AND 'rheumatoid arthritis' (March 2014).

Data collection and analysis

Selection of studies

Two review authors independently determined if each study met the inclusion criteria for the review (MLO-MAU). The review authors' differences regarding inclusion were resolved by discussion and consensus.

Data extraction and management

Two review authors independently abstracted data from each study (MLO, NP), and abstraction forms were cross-checked by two additional review authors (SP, SKM). Discrepancies were resolved by consensus. The extraction of data included study design, demographics, concomitant treatment, and outcome measures.

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Assessment of risk of bias in included studies

The risk of bias of the included studies was assessed by two independent review authors (SP, SKM). As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the following methodological domains were assessed:
I: sequence generation;
II: allocation concealment;
III: blinding of participants, personnel, and outcome assessors;
IV: incomplete outcome data;
V: selective outcome reporting;
VI: other potential threats to validity (funding, relevant use of co-interventions).
Each of these criteria were explicitly judged using: low risk of bias; high risk of bias; or unclear (either lack of information or uncertainty over the potential for bias).

Measures of treatment effect

When possible, we analysed data using an intention-to-treat model. We pooled continuous data as mean differences (MD) and dichotomous data as risk ratios (RR), Peto odds ratios (Peto OR) in the case of rare events (< 10%), or risk differences (RD) in the case of studies with zero events in both groups; 95% confidence intervals (CI) were calculated for all measures of treatment effect.

Unit of analysis issues

Treatment groups were analysed separately (for trials comparing more than two dosages of rituximab). Analysis of outcomes was performed at 24, 48 to 56, 72, and 104 weeks.

Dealing with missing data

We used the mean and standard deviation when available. When only median and interquartile ranges were reported, we followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the median was used as the mean and the standard deviation was calculated from the interquartile range. When no standard deviation was given at the end of the study, the baseline standard deviation was used at the end as well; for studies with no standard deviation reported either at the end of the study or at baseline we used the standard deviation reported by the most representative study. Values were extracted from graphs when numerical data were not reported.

Assessment of heterogeneity

To test the heterogeneity of the data, we performed Chi^2 tests using n - 1 degrees of freedom and a P value of less than or equal to 1.0. Overall effects were only estimated for groups of trials using the same intervention and where several individual meta-analyses were performed. We used fixed-effect models to estimate the overall effects. We used the I^2 statistic to describe the percentage of the variability in effect estimates that was due to heterogeneity rather than chance. A value greater than 40% was considered substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

We evaluated potential publication bias with inverted funnel plot techniques.

Data synthesis

Fixed-effect models were used throughout. Random-effects models were used when heterogeneity existed.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses to indirectly compare the effects of disease duration (more or less than four years), previous treatment (methotrexate-naive, prior DMARD failure, or prior DMARD and TNF inhibitor failure), or study quality (low or high risk of bias) on the response to rituximab. In addition, we summarized the evidence on whether RF or anti-CCP status predicted the response to treatment.

Sensitivity analysis

We directly compared the efficacy of two rituximab dosages (1000 mg versus 500 mg) and the use of different concomitant treatments (methotrexate, cyclophosphamide, or none that is rituximab monotherapy).

Summary of findings table

A 'Summary of findings' table was created using the following outcomes: 1) ACR 50 response, 2) disease remission, 3) functional status, 4) health-related quality of life, 5) radiographic progression, 6) discontinuations due to adverse events, 7) serious adverse events. We calculated the absolute and relative magnitude of effect and the number needed to treat (NNT). We calculated the NNT to provide an indication for each outcome, reflecting the number of patients required to treat to obtain a beneficial outcome with the intervention.The NNT was calculated from the control group event rate and the RR using the Visual Rx NNT calculator (Cates 2003). For continuous outcomes, the NNT was calculated using the Wells calculator software available at the Cochrane Musculoskeletal Group (CMSG) editorial office. The minimal clinically important difference (MCID) for each outcome was determined for input into the calculator. In addition, we used the GRADE working group grades of evidence to provide an overall grading of the quality of the evidence.

RESULTS

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Description of studies

Results of the search

Our search resulted in 5099 records; 2100 citations were selected for a further review based on their title or abstract. After review of the abstracts, 28 full text articles were retrieved. Twelve articles were excluded after reviewing the full publication (see Characteristics of excluded studies for further details). A total of 16 publications (8 studies) met the inclusion criteria. See Figure 1 for a flow diagram of the search results.

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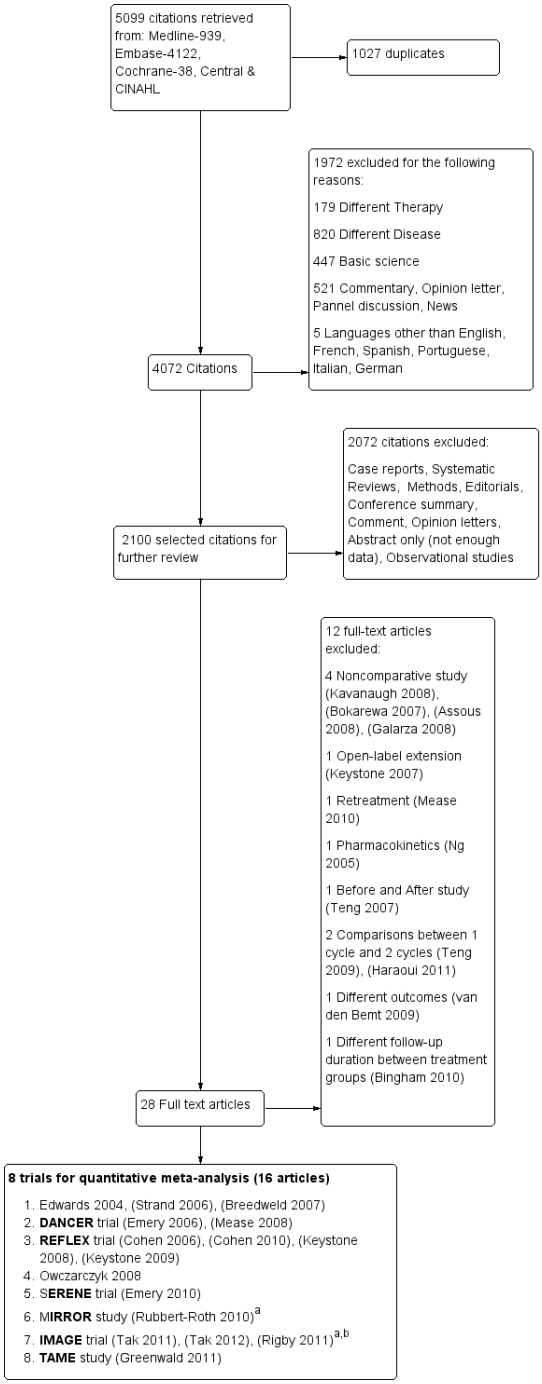
Figure 1. Flow diagram of included studies.aStudy reported results on cycle 1 and cycle 2 (re-treatment)bRe-treatment was permitted at 24 weeks for patients not responding at least 20%



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Included studies

Please refer to the table Characteristics of included studies for an overview of the included studies.

Design

Seven studies were randomised, double-blind, placebo-controlled trials (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Greenwald 2011 (TAME); Rubbert-Roth2010 (MIRROR); Tak 2010 (IMAGE)) and one was randomised but unblinded (Owczarczyk 2008). The randomisation ratios ranged between 1:1:1 and 3:2 for treatment to control.

Sample sizes

Sample sizes ranged from 161 in Edwards 2004 (WA16291) to 748 in the Tak 2010 (IMAGE) study.

Setting

Seven trials were multicentre studies including centres across the US, Canada, Israel, Australia, Brazil, Mexico, New Zealand, and several European countries (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Greenwald 2011 (TAME); Rubbert-Roth2010 (MIRROR); Tak 2010 (IMAGE).

Participants

Eight trials with 2720 patients were included in this review: 837 patients were randomised to a traditional DMARD (methotrexate or cyclophosphamide), 60 patients to rituximab monotherapy, 1791 to rituximab (either 500 or 1000 mg) combined with a traditional DMARD, and 32 to rituximab in combination with methotrexate and a TNF inhibitor. Only one trial did not report on gender (Owczarczyk 2008), but for the remaining studies the majority of included patients were women (2268) with percentages ranging from 73% to 94%. The average age of the participants in all of the trials was 51.1 ± 13 years. The average disease duration ranged between 0.91 and 12 years. Five studies enrolled patients with a disease duration greater than six months (Cohen 2006 (REFLEX); Emery 2006 (DANCER); Emery 2010 (SERENE); Greenwald 2011 (TAME); Rubbert-Roth2010 (MIRROR); another study enrolled patients that had a disease duration ≥ one year (Owczarczyk 2008); one study did not specify disease duration in their enrolment criteria, but the disease duration range was 9 to 12 years Edwards 2004 (WA16291). Only one study included patients with a disease duration of ≥ 8 weeks and ≤ 4 years (Tak 2010 (IMAGE)).

All studies, except Tak 2010 (IMAGE), included patients receiving ongoing treatment with methotrexate at a dosage of 10 to 25 mg/week for at least 12 to 16 weeks prior to study enrolment. In Tak 2010 (IMAGE) all patients were methotrexate-naive and 69% to 72% of the patients were DMARDs-naive. Table 1 summarizes the inclusion and exclusion criteria for each trial and reported mean of previous DMARDs (range between 1.1 and 2.6), per cent of patients with prior anti-TNF inhibitor treatment (range between 25% and 100%) and mean methotrexate dose per group (range between 12.5 and 17.5).

Interventions

Table 1 lists the treatment groups per trial.

- Seven trials included an arm of two courses of rituximab 1000 mg in addition to methotrexate (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Owczarczyk 2008; Rubbert-Roth2010 (MIRROR); Tak 2010 (IMAGE).
- One trial included a treatment group of rituximab in combination with an intravenous infusion of cyclophosphamide 750 mg on days 3 and 17 (Edwards 2004 (WA16291).
- Two trials included one treatment arm where patients received rituximab alone (Edwards 2004 (WA16291); Owczarczyk 2008).
- Five trials included an arm of two courses of rituximab 500 mg (Emery 2006 (DANCER); Emery 2010 (SERENE); Greenwald 2011 (TAME); Rubbert-Roth2010 (MIRROR); Tak 2010 (IMAGE)).
- Five trials included one control group (placebo plus methotrexate) (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Tak 2010 (IMAGE).
- Greenwald 2011 (TAME) compared combined rituximab plus methotrexate plus TNF inhibitor (adalimumab or etanercept) with methotrexate plus TNF inhibitor.

The dosing schedule in all trials included one course of two intravenous injections applied on days 1 and 15. In four trials re-treatment was permitted (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2010 (SERENE); Tak 2010 (IMAGE)). Rubbert-Roth2010 (MIRROR) randomised patient to three rituximab re-treatment regimes: i) two courses of 500 mg followed by two courses of 500 mg; ii) two courses of 500 mg followed by an increased dose (two 1000 mg doses); or iii) two courses of 1000 mg followed by two courses of 1000 mg. Data from this study were included only for the dose comparison of this review

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(rituximab 500 mg versus rituximab 1000 mg) at 24 weeks, before re-treatment occurred.

In all trials administration of rituximab was accompanied with intravenous methylprednisolone (100 mg injected 30 min before each infusion). Concomitant treatment included folate (≥ 5 mg/wk), oral prednisone (60 mg on days 2 to 7; 30 mg on days 8 to 14; after that ≤ 10 mg/day), and NSAIDs in stable doses. In Emery 2006 (DANCER) each treatment group was divided into three subgroups: i) without glucocorticoids, ii) methylprednisolone 100 mg given intravenously 30 to 60 min before, iii) methylprednisolone 100 mg given intravenously + oral prednisone 60 mg on day 27 and 30 mg on days 8 to 14.

Outcomes

The major outcome measured in five trials was the proportion of patients meeting the ACR response criteria. Cohen 2006 (REFLEX), Emery 2006 (DANCER), Emery 2010 (SERENE), and Rubbert-Roth2010 (MIRROR) defined the response as at least 20% improvement from baseline values in the individual ACR core set variables. Edwards 2004 (WA16291) used ACR 50 as the primary endpoint. Owczarczyk 2008 used the Disease Activity Score in 28 joints (DAS28) and Greenwald 2011 (TAME) the proportion of patients developing at least one serious infection. Only one study used radiographic changes as the primary endpoint (Tak 2010 (IMAGE)).

Minor outcomes included ACR 50, ACR 70, individual ACR criteria components, DAS28, EULAR responses, patient-reported outcomes (health-related quality of life, disability score, fatigue). To evaluate safety, studies included occurrence of adverse events, serious adverse events, presence of human anti-chimeric antibodies, and discontinuations due to lack of efficacy, adverse events, other reasons (for example, withdrawal of consent, protocol violation), and death.

Duration

The duration of trials ranged from 24 weeks to 104 weeks (Edwards 2004 (WA16291); Tak 2010 (IMAGE)). Most trials reported the timing of the primary outcome at 24 weeks. Findings were reported at 12, 16, 24 to 36, 48 to 56, 72, and 104 weeks.

Funding

Seven trials were sponsored by Genetech, Hoffman-La Roche, or Biogen Idec. One study did not disclose the source of funding (Owczarczyk 2008) but reported no conflict of interest.

Excluded studies

The Characteristics of excluded studies table and Figure 1 list the studies excluded. Twelve studies were excluded: four were excluded because they were non-comparative studies (Assous 2008; Bokarewa 2007; Galarza 2008; Kavanaugh 2008 (ARISE)); one reported data only on pharmacokinetics (Ng 2005); one was an open-label extension (Keystone 2007); one reported results after re-treatment (both groups, control and intervention, were exposed to rituximab before randomisation) (Mease 2010 (SUNRISE)); one was a before and after study (Teng 2007); two studies were comparisons between patients who received one cycle versus patients who received two cycles of rituximab (Haraoui 2011 (RESET); Teng 2009); one study did not reported clinical outcomes (van den Bemt 2009); and one reported safety data but the follow-up duration of the treatment groups was different and results could not be compared (Bingham 2010 (SIERRA)).

Risk of bias in included studies

The ratings for the risk of bias items for each included study are shown in Figure 2, and the ratings for each risk of bias item presented as percentages across all included studies are shown in Figure 3.

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

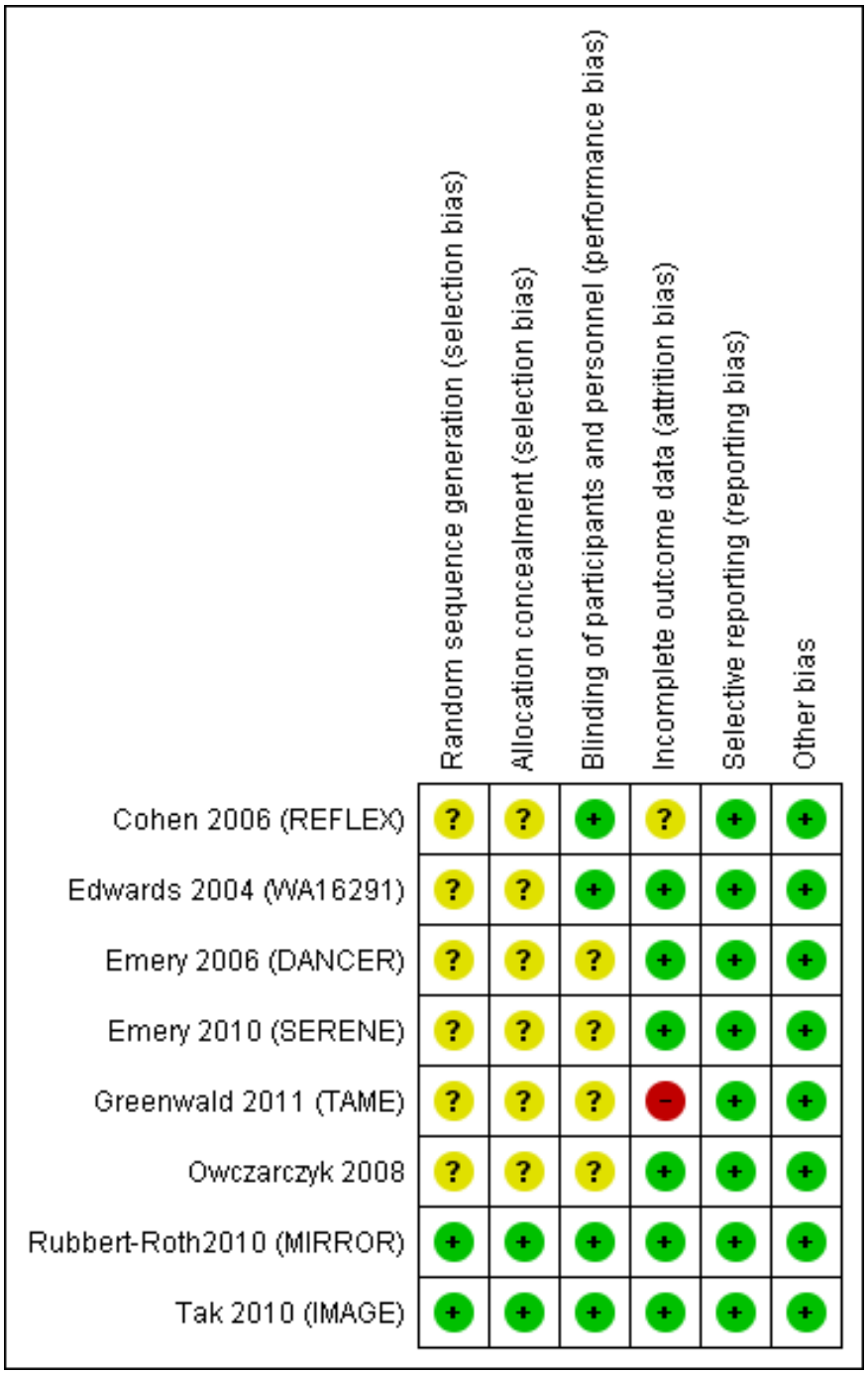

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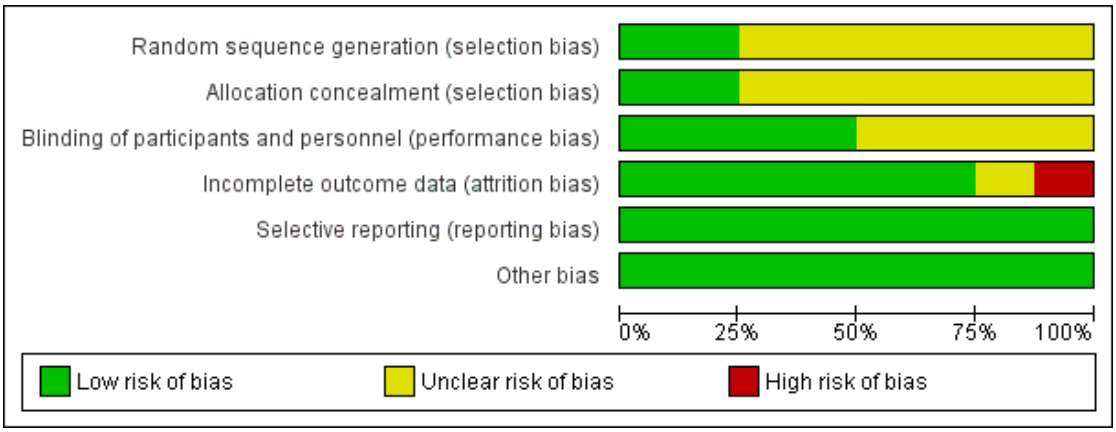
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Seven studies were reported as randomised studies (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Greenwald 2011 (TAME); Rubbert-Roth2010 (MIRROR); Tak 2010 (IMAGE)). However, five of these trials did not report their method of randomisation or allocation concealment in the published article and additional information was not available (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Greenwald 2011 (TAME)). Only two studies were judged to provide sufficient details on this item (Rubbert-Roth2010 (MIRROR); Tak 2010 (IMAGE)). Sequence generation was through an interactive voice response system and the allocation was concealed for the sponsor, investigators, and patients until data analysis was performed.

Blinding

One trial was open-label (Owczarczyk 2008). Three studies were reported as double-blind trials with no further details reported (Emery 2006 (DANCER); Emery 2010 (SERENE); Greenwald 2011 (TAME)). In Cohen 2006 (REFLEX), Edwards 2004 (WA16291), Rubbert-Roth2010 (MIRROR), and Tak 2010 (IMAGE) the method of blinding was not described but it was mentioned that patients, study sponsor, and investigators were unaware of the treatment assignment of each patient.

Incomplete outcome data

In Owczarczyk 2008 all analyses were based on the 40 patients originally enrolled. Cohen 2006 (REFLEX), Emery 2010 (SERENE), Greenwald 2011 (TAME), and Tak 2010 (IMAGE) performed a modified intention-to-treat (ITT) analysis; that is, only those participants who received at least one infusion of study medication were accounted for. Emery 2006 (DANCER) reported an ITT analysis only for categorical variables. Only two studies reported an ITT analysis (where all patients who were randomised were accounted for) for all outcome measures (Edwards 2004 (WA16291); Rubbert-Roth2010 (MIRROR)).

Missing data were imputed using last observation carried forward (LOCF) in Edwards 2004 (WA16291). In three studies, for patients who withdrew prematurely from the study or who started rescue therapy missing categorical endpoints were imputed as non-responders and continuous variables as the LOCF (Emery 2006 (DANCER); Emery 2010 (SERENE); Rubbert-Roth2010 (MIRROR)). In Tak 2010 (IMAGE) missing data were imputed by linear extrapolation. In one study missing data were not imputed (Greenwald 2011 (TAME)).

Fewer patients in the placebo plus methotrexate group completed the studies compared to the rituximab arms. The most common reason for withdrawal in this group was lack of efficacy.

Selective reporting

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All trials reported outcome measures as recommended by the Outcome Measures in Rheumatology (OMERACT) group (Tugwell 1992).

Other potential sources of bias

Seven studies were supported by the manufacturer of the drug. In some cases the authors of the publications were staff of the pharmaceutical company that provided funding. One study (Owczarczyk 2008) did not disclose the source of funding but no conflicts of interest were reported. There was no evidence of other biases that had the potential to affect the results in the clinical trials.

Effects of interventions

See: **Summary of findings for the main comparison** Rituximab (2 x 1000 mg) plus methotrexate versus methotrexate monotherapy for rheumatoid arthritis

We included the following comparison groups: (i) rituximab monotherapy (two 1000 mg doses) versus methotrexate monotherapy; (ii) rituximab (two 500 mg doses) in combination with methotrexate versus methotrexate; (iii) rituximab (two 1000 mg doses) in combination with methotrexate versus methotrexate; (iv) rituximab (two 1000 mg doses) in combination with cyclophosphamide versus methotrexate; and (v) rituximab (two 500 mg courses) in combination with methotrexate and TNF inhibitor versus methotrexate in combination with TNF inhibitor. We have prioritised reporting of rituximab (two 1000 mg doses) in combination with methotrexate since this is the most commonly used combination and approved dose.

Eight trials with 2720 patients were included in this study; 119 patients from the Rubbert-Roth2010 (MIRROR) who received rituximab (two 500 mg doses) and had a dose increase (two 1000 mg doses) were excluded from our analysis. Of the 2720 participants, 675 were randomised to rituximab (two 500 mg doses), 1075 to rituximab (two 1000 mg doses), 60 to rituximab monotherapy, 41 to rituximab + cyclophosphamide, 32 to rituximab plus TNF inhibitor, and 837 to control. Results for efficacy, withdrawals, and toxicity are shown separately.

A. Efficacy

See 'Types of outcomes' in methods section for description of measures presented below.

Rituximab (two 1000 mg doses) + methotrexate versus methotrexate

Five studies (1664 patients) compared rituximab (two 1000 mg doses) plus methotrexate to methotrexate alone (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Tak 2010 (IMAGE)).

ACR response

For rituximab (two 1000 mg doses) with methotrexate compared to methotrexate monotherapy, the RR for achieving an ACR 20 at 24 weeks was 2.2 (95% CI 1.9 to 2.7); 53% of those receiving combined rituximab and methotrexate achieved an ACR 20 response (compared to 23% of controls) with an absolute treatment benefit (ATB) of 30% (95% CI 25% to 35%) and a number needed to treat (NNT) of 4 people (95% CI 6 to 3). This statistically significant difference was also observed at 52 weeks but not at 104 weeks (Analysis 1.1).

ACR 50, 70, and 90 response rates were significantly improved with rituximab (two 1000 mg doses) when compared with control at 24, 48 to 56, and 104 weeks (Analysis 1.2; Analysis 1.3; Analysis 1.4).

The RR for achieving an ACR 50 with rituximab (two 1000 mg doses) in addition to methotrexate at 24 weeks was 3.3 (95% CI 2.3 to 4.6); 29% of those receiving rituximab plus methotrexate achieved an ACR 50 response compared to 9% of controls, with an ATB of 21% (95% CI 16% to 25%) and a NNT of 6 people (95% CI 9 to 4) (Figure 4; Summary of findings for the main comparison).

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Figure 4. Twenty-nine out of every 100 rituximab plus methotrexate recipients experience a clinical improvement of 50% versus 9 methotrexate recipients.

The RR for achieving an ACR 70 with rituximab plus methotrexate at 24 weeks was 3.9 (95% CI 1.8 to 8.3); 14% of those in the rituximab plus methotrexate group achieved an ACR 70 response compared to 4% of controls, with an ATB of 11% (95% CI 6% to 15%) and a NNT of 10 people (95% CI 34 to 4).

Only one study reported ACR 90. The RR for achieving an ACR 90 with rituximab in addition to methotrexate at 52 weeks was 1.8 (95% CI 1.1 to 3.0); 16% of those in the rituximab plus methotrexate group achieved an ACR 90 response compared to 9% of controls, with an ATB of 7% (95% CI 1% to 13%) and a NNT of 14 people (95% CI 51 to 7).

Disease activity

A significant mean reduction from baseline in DAS28 scores between rituximab and the control group was observed at 24, 48 to 56, and 104 weeks (MD -1.2, 95% CI -1.5 to -0.92; MD -1.2, 95% CI -1.4 to -0.93; MD -1.6, 95% CI -1.8 to -1.4, respectively) (Analysis 1.5).

Compared to patients receiving methotrexate monotherapy, patients receiving rituximab plus methotrexate were significantly more likely to have a low DAS (DAS28 $\leq$ 3.2) at 24, 52, and 104 weeks or be in clinical remission (DAS28 $\leq$ 2.6) at 52 and 104 weeks (Analysis 1.6; Analysis 1.7). The RR for achieving clinical remission with rituximab (two 1000 mg doses) in addition to methotrexate at 52 weeks was 2.4 (95% CI 1.7 to 3.5); 22% of those in the rituximab plus methotrexate group achieved clinical remission compared to 11% of controls, with an ATB of 11% (95% CI 2% to 20%) and a NNT of 7 people (95% CI 13 to 4).

Patients in the rituximab group were more likely to have a moderate or good EULAR response than those patients in the control group at 24, 48, and 104 weeks (RR 1.9, 95% CI 1.6 to 2.4; RR 2.3, 95% CI 1.7 to 3.1; RR 2.1, 95% CI 1.6 to 2.6, respectively) (Analysis 1.8). At 24 weeks, 55% of those in the rituximab plus methotrexate group achieved a moderate or good EULAR response (compared to 27% of controls) with an ATB of 29% (95% CI 14% to 43%) and a NNT of 4 people (95% CI 7 to 3).

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Patient-reported outcomes

There was significant improvement noted in function scores with rituximab combined with methotrexate when compared with methotrexate monotherapy at 24, 48 to 52, and 104 weeks (MD -0.24, 95% CI -0.30 to -0.18; MD -0.29, 95% CI -0.38 to -0.20; MD -0.44, 95% CI -0.54 to -0.34, respectively) (Analysis 1.9). At 24 weeks, the pooled RR for clinically meaningful improvement in HAQ (> 0.22) was 1.6 (95% CI 1.2 to 2.1) with an ATB of 24% (95% CI 12% to 36%) and a NNT of 5 people (95% CI 13 to 3). At 104 weeks, the pooled RR for clinically meaningful improvement in HAQ (> 0.22) was 1.4 (95% CI 1.3 to 1.6) with an ATB of 24% (95% CI 16% to 31%) and a NNT of 5 people (95% CI 7 to 3). No statistically significant differences were found at 48 to 56 and 72 weeks (Analysis 1.10).

There was significant improvement in the physical component score of the quality of life measurement (SF-36) with rituximab plus methotrexate when compared with methotrexate monotherapy at 24 to 52 weeks (MD -4.1, 95% CI -4.5 to -3.3) (Analysis 1.11). At 24 to 52 weeks, the pooled RR for clinically meaningful improvement in the physical component score (PCS) (SF-36 PCS $\geq$ 5) was 2.0 (95% CI 1.1 to 3.4) with an ATB of 34% (95% CI 5% to 84%) and a NNT of 4 people (95% CI 83 to 3) (Analysis 1.12).

There was significant improvement in the mental component score (MCS) of the quality of life measurement (SF-36) with rituximab plus methotrexate when compared with methotrexate monotherapy at 24 to 52 weeks (MD -2.22, 95% CI -3.52 to -0.92) (Analysis 1.13). At 24 to 52 weeks, the pooled RR for a clinically meaningful improvement in the mental component score (SF-36 MCS $\geq$ 5) was 1.4 (95% CI 1.1 to 1.9) with an ATB of 13% (95% CI 7% to 18%) and a NNT of 8 people (95% CI 51 to 4) (Analysis 1.14).

There was a significant reduction in the fatigue score (FACIT-F) with rituximab plus methotrexate when compared with methotrexate monotherapy at 24 to 52 weeks (MD -5.22, 95% CI -7.71 to -2.74) (Analysis 1.15). At 24 to 52 weeks, the pooled RR for clinically meaningful improvement in the fatigue score (FACIT $\geq$ 4) was 1.6 (95% CI 1.0 to 2.5) with an ATB of 24% (95% CI 6% to 41%) and a NNT of 4 people (95% CI 17 to 2) (Analysis 1.16). There was a statistically significant difference in the pain score reduction from baseline with rituximab plus methotrexate when compared with methotrexate monotherapy at 24 to 52 weeks (MD -13.89, 95% CI -21.31 to -6.48) (Analysis 1.17).

Radiographic scores

Two studies reported results on structural joint changes (Cohen 2006 (REFLEX); Tak 2010 (IMAGE)) using the Genant-modified Sharp score (range 0 to 290) (Genant 1998). There was evidence of a statistically significant difference from baseline in the radiographic scores (total Sharp score (TSS), erosion score (ES), and joint space narrowing score (JSNS)) with rituximab plus methotrexate compared to methotrexate alone at 24, 52 to 56, and 104 weeks (Analysis 1.18; Analysis 1.19; Analysis 1.20). The RR for no radiographic progression at 24 weeks was 1.2 (95% CI 1.0 to 1.4); 70% of those on rituximab plus methotrexate had no radiographic progression compared to 59% of controls, with an ATB of 11% (95% CI 2% to 19%) and a NNT of 10 people (95% CI 57 to 5). Similar benefits were observed at 52 to 56 and 104 weeks (Analysis 1.21). The RR for no worsening of erosions at 52 weeks was 1.3 (95% CI 1.1 to 1.5); 70% of those on rituximab plus methotrexate achieved clinical remission compared to 51% of controls, with an ATB of 19% (95% CI 12% to 25%) and a NNT of 7 people (95% CI 22 to 4). Similar benefits were observed at 104 weeks (RR 1.5, 95% CI 1.3 to 1.7) but no statistically significant differences were observed at 24 weeks (Analysis 1.22).

Other comparisons

Rituximab (two 1000 mg doses) monotherapy versus methotrexate monotherapy

Only one study (80 patients) compared the use of rituximab monotherapy to methotrexate monotherapy (Edwards 2004 (WA16291)).

ACR response

At 24 weeks, ACR 20 response rates were significantly improved with 1000 mg of rituximab (on days 1 and 15) alone compared to methotrexate alone (RR 1.7, 95% CI 1.1 to 2.8) (Analysis 2.1), with an ATB of 28% (95% CI 6% to 49%) and a NNT of 4 people (95% CI 17 to 2).

Similarly, the RR for achieving an ACR 50 response at 24 weeks was 2.6 (95% CI 1.0 to 6.6); 33% of those in the rituximab alone group achieved an ACR 50 response compared to 13% of those in the methotrexate alone group (Analysis 2.2). These statistically significant differences disappeared at 48 weeks and 104 weeks. In addition, no statistically significant differences between groups were observed on the ACR 70 response rates at 24, 48, and 104 weeks (Analysis 2.3).

Disease activity

There was evidence of a significant reduction from baseline in the DAS28 at 24 weeks between rituximab alone and the methotrexate alone group (MD -0.90, 95% CI -1.47 to -0.33) (Analysis 2.4). Patients treated with rituximab alone (1000 mg on days 1 and 15) were also 1.7 times more likely to have a moderate or good

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EULAR response than those patients in the methotrexate alone group (RR 1.70, 95% CI 1.21 to 2.38) (Analysis 2.5).

Patient-reported outcomes

For the functional scale, there was a statistically significant improvement noted in HAQ scores with rituximab alone compared to methotrexate alone. HAQ scores were statistically significantly better with rituximab alone, with a MD of -0.40 (95% CI -0.65 to -0.15) at 24 weeks, but the statistically significant difference disappeared at 48 and 72 weeks (Analysis 2.6). A clinically meaningful improvement in physical function was defined as decreases from baseline on the HAQ of at least 0.25. Patients on rituximab alone were more likely to achieve the minimal clinically important difference (MCID) in the HAQ Disability Index (HAQ-DI) compared with patients receiving methotrexate at 24 weeks only (Analysis 2.7).

Rituximab (two 500 mg doses) + methotrexate versus methotrexate

Three studies (1082 patients) compared rituximab (two doses of 500 mg) plus methotrexate to methotrexate alone (Emery 2006 (DANCER); Emery 2010 (SERENE); Tak 2010 (IMAGE)).

ACR response

For rituximab (two 500 mg doses) plus methotrexate compared to methotrexate monotherapy, the RR for achieving an ACR 20 was 2.2 (95% CI 1.7 to 2.7) at 24 weeks; 55% of those in the rituximab group achieved an ACR 20 response compared to 25% of controls with an ATB of 30% (95% CI 22% to 37%) and a NNT of 4 people (95% CI 6 to 3) (Analysis 3.1).

For achieving an ACR 50, the RR was 2.7 at 24 weeks (95% CI 1.9 to 3.9); 29% achieved an ACR 50 compared to 10% of controls with an ATB of 18% (95% CI 12% to 25%) and a NNT of 6 people (95% CI 12 to 4). This statistically significant difference was maintained at 48 to 52 and 104 weeks (Analysis 3.2).

The RR for achieving an ACR 70 was 2.1 at 24 weeks (95% CI 1.1 to 3.8); 10% of those in the rituximab group achieved an ACR 70 response compared to 5% of controls with an ATB of 5% (95% CI 1% to 10%) and a NNT of 19 people (95% CI 143 to 8). At 104 weeks, patients in the rituximab (two 500 mg doses) plus methotrexate group were also more likely to achieve an ACR 70 response compared with patients in the methotrexate monotherapy group (RR 1.7, 95% CI 1.3 to 2.2) (Analysis 3.3).

The RR for achieving an ACR 90 was 2.2 at 52 weeks (95% CI 1.3 to 3.6) (Analysis 3.4).

Disease activity

There was a statistically significant reduction from baseline in the DAS28 in favour of rituximab in addition to methotrexate at 24, 52, and 104 weeks (MD -0.96, 95% CI -1.1 to -0.81; MD -0.99, 95% CI -1.2 to -0.77; MD -1.6; 95% CI -1.8 to -1.4, respectively) (Analysis 3.5). The RR for achieving low disease activity (DAS28 $\leq$ 3.2) at 24 weeks was 3.7 (95% CI 1.8 to 7.9) for combined rituximab (two 500 mg doses) plus methotrexate compared to methotrexate alone. Similar statistically significant differences were observed at 48 to 52 weeks and 104 weeks (Analysis 3.6). Clinical remission (DAS28 < 2.6) was more likely to be achieved by patients in the rituximab group compared to controls at 24, 52, and 104 weeks (RR 4.0, 95% CI 1.4 to 11.8; RR 2.0, 95% CI 1.4 to 3.0; RR 2.7, 95% CI 1.8 to 3.8, respectively) (Analysis 3.7).

The RR for a moderate or good EULAR response at 24 weeks was 1.9 (95% CI 1.6 to 2.2) (Analysis 3.8); 49% of those in the rituximab group achieved a moderate or good EULAR response compared to 27% of controls with an ATB of 23% (95% CI 17% to 28%) and a NNT of 5 people (95% CI 7 to 4). This statistically significant difference was also observed at 52 and 104 weeks (Analysis 3.8).

Patient-reported outcomes

For rituximab plus methotrexate there was a significant improvement in function scores (HAQ) when compared with methotrexate monotherapy at 24, 52, and 104 weeks (MD -0.22, 95% CI -0.30 to -0.14; MD -0.28, 95% CI -0.37 to -0.18; MD -0.34, 95% CI -0.44 to -0.24, respectively) (Analysis 3.9). The RR for a clinically meaningful improvement in HAQ for rituximab plus methotrexate compared with methotrexate alone was 1.6 (95% CI 1.2 to 2.1) at 24 weeks. The ATB for HAQ $\geq$ 0.22 was 23% (95% CI 13% to 34%). The NNT in order to achieve a HAQ $\geq$ 0.22 was 5 people (95% CI 14 to 3). Similar statistically significant differences were observed at 52 and 104 weeks (Analysis 3.10).

There was a statistically significant reduction in the PCS of the quality of life measurement (SF-36) in favour of rituximab in addition to methotrexate at 24 to 52 weeks (MD -3.5, 95% CI -4.5 to -2.6) (Analysis 3.11). The RR for a clinically meaningful improvement in SF-36 PCS ($\geq$ 5) for rituximab plus methotrexate compared with methotrexate alone was 1.8 (95% CI 1.2 to 2.8) at 24 weeks but this statistically significant difference was not observed at 52 weeks (Analysis 3.12).

There was a statistically significant reduction in the MCS of the quality of life measurement (SF-36) in favour of rituximab in addition to methotrexate at 24 to 52 weeks (MD -1.8, 95% CI -3.3 to -0.36) (Analysis 3.13). However, the RR for a clinically meaningful improvement in SF-36 MCS ($\geq$ 6.33) was similar between groups (Analysis 3.14).

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There was a statistically significant reduction in the fatigue score (FACIT-F) in favour of rituximab in addition to methotrexate at 24 to 52 weeks (MD -3.1, 95% CI -4.4 to -1.8) (Analysis 3.15). The RR for a clinically meaningful improvement in FACIT-F (MCID of ≥ 3.5) for rituximab plus methotrexate compared with methotrexate alone was 1.6 (95% CI 1.2 to 2.1) at 24 weeks (Analysis 3.16). In addition, there was a statistically significant reduction in the visual analogue scale of pain in favour of rituximab in addition to methotrexate at 24 to 52 weeks (MD -8.3, 95% CI -12.3 to -4.4) (Analysis 3.17).

Radiographic scores

For this comparison the only study that reported results for structural joint changes was the Tak 2010 (IMAGE) study. There was evidence of a statistically significant difference from baseline in the radiographic scores (TSS, ES and JSNS) between rituximab (two 500 mg doses) plus methotrexate compared to control only at 104 weeks (Analysis 3.18; Analysis 3.19; Analysis 3.20). Also, there were more patients in the rituximab plus methotrexate group with no radiographic progression or no worsening of erosion compared with the methotrexate monotherapy group at 24 weeks (RR 1.3, 95% CI 1.1 to 1.6; RR 1.4, 95% CI 1.1 to 1.7, respectively) (Analysis 3.21; Analysis 3.22).

Rituximab (two 1000 mg doses) + cyclophosphamide versus methotrexate

One study (80 patients) compared rituximab (two 1000 mg doses) plus cyclophosphamide (two 750 mg doses intravenously) with methotrexate (Edwards 2004 (WA16291)).

ACR response

For rituximab plus cyclophosphamide compared to methotrexate monotherapy, the RR for achieving an ACR 20 at 24 and 48 weeks was 2.0 (95% CI 1.3 to 3.1) and 2.4 (95% CI 1.2 to 4.9), respectively (Analysis 4.1). The RR for achieving an ACR 50 at 24 and 48 weeks was 3.3 (95% CI 1.4 to 8.1) and 4.9 (95% CI 1.1 to 20.9), respectively. The ACR 20 and ACR 50 at 104 weeks, and ACR 70 at 24, 48, and 104 weeks were not different between groups (Analysis 4.3).

Disease activity

A statistically significant reduction in DAS28 score from baseline (MD -1.30, 95% CI -1.89 to -0.71) favoured rituximab plus cyclophosphamide in comparison with methotrexate alone (Analysis 4.4). The RR for achieving a moderate or good EULAR response was 1.71 (95% CI 1.22 to 2.39) (Analysis 4.5); 85% on rituximab plus cyclophosphamide achieved a moderate or good response compared to 50% of controls with an ATB of 35% (95% CI 16% to 54%) and a NNT of 3 people (95% CI 6 to 2).

Patient-reported outcomes

No statistically significant differences were found for functional scores (HAQ) and rates of clinically meaningful improvements in functional scores (HAQ ≤ 0.22) (Analysis 4.6; Analysis 4.7).

Rituximab + methotrexate + TNF inhibitor versus methotrexate + TNF inhibitor

One study (51 patients) compared rituximab (two 500 mg doses) plus methotrexate plus a TNF inhibitor (adalimumab or etanercept) to methotrexate plus TNF inhibitor (Greenwald 2011 (TAME)); 100% of the patients in the rituximab group had previously been exposed to TNF inhibitor (at least 12 weeks prior to study enrolment) compared to 97% of the patients in the control group. The mean duration of prior TNF inhibitor use was 2.1 years in the rituximab group versus 2.4 years in the control group.

ACR response

No statistically significant differences were noted in the ACR response rates (20 and 50) between patients receiving combined rituximab plus methotrexate plus a TNF inhibitor and methotrexate plus a TNF inhibitor (Analysis 5.1; Analysis 5.2).

Disease activity

No statistically significant differences were noted between groups in the rates of patients achieving low disease activity (DAS28 ≤ 3.2) or clinical remission (DAS28 < 2.6) (Analysis 5.3; Analysis 5.4).

Patient-reported outcomes

Patients in the combined rituximab plus methotrexate plus TNF inhibitor group were more likely to achieve a clinically meaningful improvement in functional score (HAQ ≤ 0.22) compared with patients in the methotrexate plus TNF inhibitor group at 28 weeks (RR 3.8, 95% CI 1.6 to 9.2); 84% achieved a clinically meaningful improvement in functional score in the group with rituximab compared to 22% of controls with an ATB of 63% (95% CI 40% to 85%) and a NNT of 2 people (95% CI 3 to 1) (Analysis 5.5).

B. Safety

Study withdrawals

Withdrawals were reported as: total withdrawals, withdrawal because of lack of efficacy, withdrawal because of adverse events, and withdrawal because of other reasons.

Rituximab (two 1000 mg doses) + methotrexate versus methotrexate

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Total withdrawals

Statistically significantly more people withdrew from the control group than from the rituximab group at 24, 48 to 52, 72, and 104 weeks (RR 0.40, 95% CI 0.32 to 0.50; RR 0.61, 95% CI 0.40 to 0.91; RR 0.48, 95% CI 0.28 to 0.82; RR 0.58, 95% CI 0.45 to 0.75, respectively). At 24 weeks, 28% withdrew from the control group and 12% withdrew from the combined rituximab group with an absolute risk difference (ARD) of -14% (95% CI -26% to -1%) and a number needed to harm (NNH) of 6 people (95% CI 6 to 8). At 48 to 52 weeks, 38% withdrew from the control group and 30% withdrew from the combined rituximab group with an ARD of -16% (95% CI -28% to -3%) and a NNH of 7 people (95% CI 5 to 30). At 72 weeks, 62% withdrew from the control group and 30% withdrew from the combined rituximab group with an ARD of -33% (95% CI -53% to -12%) and a NNH of 4 people (95% CI 3 to 9). At 104 weeks, 37% withdrew from the control group and 20% withdrew from the combined rituximab group with an ARD of -20% (95% CI -34% to -5%) and a NNH of 7 people (95% CI 5 to 11) (Analysis 6.1).

Lack of efficacy

Withdrawal rates were reduced in the rituximab group compared to the control group at 24, 48 to 52, and 104 weeks (RR 0.30, 95% CI 0.23 to 0.39; RR 0.15, 95% CI 0.06 to 0.36; RR 0.24, 95% CI 0.09 to 0.64, respectively) (Analysis 6.2).

Adverse events and other reasons

There was no evidence of a statistically significant difference in the rates of withdrawals because of adverse events or other reasons (that is, withdrawal of consent, violation, administrative, failure to return) in either group (Analysis 6.3; Analysis 6.4).

Other comparisons

Rituximab (two 1000 mg doses) monotherapy versus methotrexate monotherapy

Total withdrawals and adverse events

There were no statistically significant differences between groups in the rates of total withdrawals (Analysis 7.1) or withdrawals due to adverse events (Analysis 7.3).

Lack of efficacy

Withdrawals due to lack of efficacy were reduced in the rituximab monotherapy compared with the methotrexate monotherapy at 104 weeks (RR 0.29, 95% CI 0.12 to 0.72). No other statistically significant differences were observed at 24, 48, or 72 weeks (Analysis 7.2).

Other reasons

Patients in the rituximab group were twice as likely to discontinue treatment for other reasons (that is, withdrawal of consent, unknown reasons) compared to patients in the methotrexate group at 104 weeks (95% CI 1.2 to 3.3) (Analysis 7.3; Analysis 7.4).

Rituximab (two 500 mg doses) + methotrexate versus methotrexate

Total withdrawals

The total discontinuation rates were lower in the rituximab plus methotrexate group compared with the methotrexate monotherapy group at 24, 48 to 52, and 104 weeks (RR 0.30, 95% CI 0.18 to 0.50; RR 0.64, 95% CI 0.43 to 0.94; RR 0.51, 95% CI 0.36 to 0.73, respectively) (Analysis 8.1).

Lack of efficacy

Withdrawals rates were reduced in the rituximab group compared to the methotrexate controls at 24 and 48 to 52 weeks (RR 0.20, 95% CI 0.10 to 0.39; RR 0.37, 95% CI 0.19 to 0.73, respectively). At 24 weeks, 3% withdrew from the combined rituximab plus methotrexate group and 17% withdrew from the methotrexate monotherapy group with an ARD of -13% (95% CI -17% to -9%) and a NNH of 8 people (95% CI 7 to 10) (Analysis 8.2).

Adverse events and other reasons

There was no evidence of a statistically significant difference in the rates of withdrawals because of adverse events or other reasons (that is, withdrawal of consent, violation, administrative, failure to return) in either group (Analysis 8.4).

Rituximab (two 1000 mg doses) + cyclophosphamide versus methotrexate

Total withdrawals

There was no evidence of a statistically significant difference in the rates of total withdrawals between groups (Analysis 9.1).

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Lack of efficacy

Statistically significantly more people withdrew from the methotrexate monotherapy group than from the combined rituximab plus cyclophosphamide group at 104 weeks (RR 0.23, 95% CI 0.08 to 0.62). By the second year, 43% had withdrawn from the monotherapy group and 10% had withdrawn from the combined group with an ARD of -33% (95% CI -51% to -15%) and a NNH of 4 people (95% CI 3 to 7) (Analysis 9.2).

Adverse events

There was no evidence of a statistically significant difference between groups in the rates of withdrawals due to adverse events (Analysis 9.3).

Other reasons

Withdrawals due to reasons other than lack of efficacy and adverse events (that is, withdrawal of consent, unknown reasons) were significantly increased in the combination group compared to the methotrexate alone group at 104 weeks (RR 1.9, 95% CI 1.1 to 3.1); 61% withdrew in the rituximab plus cyclophosphamide group compared to 33% of the methotrexate monotherapy group with an ARD of 28% (95% CI 8% to 49%) and a NNH of 4 people (95% CI 13 to 2) (Analysis 9.4).

Rituximab + methotrexate + TNF inhibitor versus methotrexate + TNF inhibitor

Total withdrawals and adverse events

There was no evidence of statistically significant differences between groups in the rates of total withdrawals or withdrawals because of adverse events (Analysis 10.1; Analysis 10.2).

Adverse events

Rituximab (two 1000 mg doses) + methotrexate versus methotrexate

A greater proportion of patients receiving combined rituximab plus methotrexate developed adverse events after their first infusion than those taking methotrexate monotherapy (RR 1.6, 95% CI 1.3 to 2.0); 28% of those taking rituximab plus methotrexate reported more events associated with their first infusion compared to 18% of controls with an ARD of 9% (95% CI 5% to 13%) and a NNH of 11 people (95% CI 21 to 8) (Analysis 11.16). Similarly, vascular disorders (as reported in Emery 2010 (SERENE); Tak 2010 (IMAGE)) plus hypertension events as reported in Edwards 2004 (WA16291) and Emery 2006 (DANCER) were more commonly reported in the combination group compared to the methotrexate monotherapy group (RR 1.54, 95% CI 1.00 to 2.38) (Analysis 11.29). In addition, at 24 weeks, there was a trend toward higher rates of hypertension in patients receiving combined rituximab plus methotrexate compared to patients receiving methotrexate monotherapy (RR 1.6, 95% CI 0.96 to 2.6) (Analysis 11.15). At two years, a trend toward higher rates of infections (serious or not) in patients receiving combined rituximab plus methotrexate compared to patients receiving methotrexate monotherapy was observed (RR 1.1, 95% CI 0.95 to 1.3) (Analysis 11.3). No other statistically significant differences were noted (Analysis 11.1; Analysis 11.2; Analysis 11.4; Analysis 11.5; Analysis 11.6; Analysis 11.7; Analysis 11.8; Analysis 11.9; Analysis 11.10; Analysis 11.11; Analysis 11.12; Analysis 11.13; Analysis 11.14; Analysis 11.17; Analysis 11.18; Analysis 11.19; Analysis 11.20; Analysis 11.21; Analysis 11.22; Analysis 11.23; Analysis 11.24; Analysis 11.25; Analysis 11.26; Analysis 11.27; Analysis 11.28).

Other comparisons

Rituximab (two 1000 mg doses) monotherapy versus methotrexate monotherapy

There was no evidence of statistically significant differences in the rates of adverse events between groups (Analysis 12.1; Analysis 12.2; Analysis 12.3; Analysis 12.4; Analysis 12.5; Analysis 12.6; Analysis 12.7; Analysis 12.9; Analysis 12.11; Analysis 12.12; Analysis 12.13; Analysis 12.14; Analysis 12.15) except for cough and disease exacerbation at 24 weeks (Analysis 12.8; Analysis 12.10). Patients in the rituximab monotherapy group had greater odds of increased cough compared with patients in the methotrexate monotherapy group (Peto OR 8.22, 95% CI 1.36 to 49.69). Exacerbation of rheumatoid arthritis was decreased in the rituximab monotherapy group compared with the methotrexate monotherapy group (RR 0.38, 95% CI 0.16 to 0.86).

Rituximab (two 500 mg doses) + methotrexate versus methotrexate

A greater proportion of patients in the combined rituximab 500 mg plus methotrexate group developed infusion-related reactions during the second infusion of their first course compared with patients in the methotrexate monotherapy group at 24 weeks (RR 1.51, 95% CI 1.10 to 2.09) (Analysis 13.16). No other statistically significant differences in the rates of adverse events were observed between groups (Analysis 13.1; Analysis 13.2; Analysis 13.3; Analysis 13.4; Analysis 13.5; Analysis 13.6; Analysis 13.7; Analysis 13.8; Analysis 13.9; Analysis 13.10; Analysis 13.11; Analysis 13.12; Analysis 13.13; Analysis 13.14; Analysis 13.15; Analysis 13.17; Analysis 13.18; Analysis 13.19; Analysis 13.20;

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Analysis 13.21; Analysis 13.22; Analysis 13.23; Analysis 13.24; Analysis 13.25; Analysis 13.26).

Rituximab (two 1000 mg doses) + cyclophosphamide versus methotrexate

No statistically significant differences in the rates of adverse events were observed between groups (Analysis 14.1; Analysis 14.2; Analysis 14.3; Analysis 14.4; Analysis 14.5; Analysis 14.6; Analysis 14.7; Analysis 14.8; Analysis 14.9; Analysis 14.10; Analysis 14.11; Analysis 14.12; Analysis 14.13; Analysis 14.14; Analysis 14.15; Analysis 14.16).

Rituximab + methotrexate + TNF inhibitor versus methotrexate + TNF inhibitor

No statistically significant differences in the rates of adverse events were observed between groups (Analysis 15.1; Analysis 15.2; Analysis 15.3; Analysis 15.4; Analysis 15.5; Analysis 15.6; Analysis 15.7; Analysis 15.8; Analysis 15.9; Analysis 15.10; Analysis 15.11; Analysis 15.12; Analysis 15.13; Analysis 15.14; Analysis 15.15; Analysis 15.16; Analysis 15.17; Analysis 15.18; Analysis 15.19; Analysis 15.20; Analysis 15.21; Analysis 15.22; Analysis 15.23; Analysis 15.24; Analysis 15.25; Analysis 15.26; Analysis 15.27).

C. Subgroup and sensitivity analyses

Subgroup and sensitivity analyses were performed comparing rituximab 1000 mg plus methotrexate versus methotrexate at 24 to 52 weeks for ACR 50 responses on disease duration (≤ 4 years versus > 4 years), previous treatment (methotrexate-naive versus DMARDs failure versus DMARD and TNF inhibitor failure), and study quality (low versus high risk of bias). In addition, we conducted subgroup analyses to compare different dosages (500 mg versus 1000 mg), use of concomitant treatment (methotrexate versus cyclophosphamide), and RF or anti-CCP (positive versus negative).

Disease duration

Five studies (1664) patients) were used for this comparison (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Tak 2010 (IMAGE)). Only one study included participants with a disease duration of ≤ four years (Tak 2010 (IMAGE)). The RR for achieving an ACR 50 response was greater for patients with longer disease duration (> 4 years) compared with patients at ≤ 4 years of being diagnosed (RR 3.4, 95% CI 2.5 to 4.6; RR 1.6; 95% CI 1.3 to 1.8, respectively) (Analysis 16.1). For those patients with longer disease duration, 29% of those in the rituximab plus methotrexate groups achieved an ACR 50 response compared to 9% of controls; while for those patients with shorter disease duration 65% of those in the rituximab plus methotrexate groups achieved an ACR 50 response compared to 42% of controls.

Previous treatment

We grouped the studies (1664 patients) according to whether enrolled patients were methotrexate-naive (Tak 2010 (IMAGE)), had an inadequate response to methotrexate or other traditional DMARDs without prior exposure to TNF inhibitors (Edwards 2004 (WA16291); Emery 2010 (SERENE)), or had failed TNF inhibitors (Cohen 2006 (REFLEX); Emery 2006 (DANCER); Greenwald 2011 (TAME); Owczarczyk 2008; Rubbert-Roth2010 (MIRROR)). A greater RR for the ACR 50 was observed in the studies including patients with prior exposure to TNF inhibitors and traditional DMARDs or failure with traditional DMARDs compared to the studies including only methotrexate-naive patients (RR 1.6, 95% CI 1.3 to 1.8; RR 2.9; 95% CI 1.9 to 4.6; RR 3.8, 95% CI 2.5 to 5.7, respectively) (Analysis 17.1).

Study quality

Two studies (579 patients) were judged to have a lower risk of bias (Edwards 2004 (WA16291); Tak 2010 (IMAGE)) and three studies (1085 patients) did not report on at least three domains of the risk of bias tool (Cohen 2006 (REFLEX); Emery 2006 (DANCER); Emery 2010 (SERENE)). From the ACR 50 responses, the RRs were 2.0 (95% CI 0.96 to 4.26) and 3.27 (95% CI 2.1 to 5.1) for the low versus high risk studies, respectively.

Dosage

Four trials (1308 patients) provided data for this comparison (Emery 2006 (DANCER); Emery 2010 (SERENE); Rubbert-Roth2010 (MIRROR); Tak 2010 (IMAGE)). The effect of the use of two rituximab 500 mg doses was directly compared with two rituximab 1000 mg doses. No statistically significant differences were observed for ACR responses and numerous other outcomes (Analysis 19.1; Analysis 19.2; Analysis 19.3; Analysis 19.4; Analysis 19.5; Analysis 19.6; Analysis 19.7; Analysis 19.8; Analysis 19.9; Analysis 19.10; Analysis 19.11; Analysis 19.13; Analysis 19.15; Analysis 19.17; Analysis 19.19; Analysis 19.21; Analysis 19.22; Analysis 19.23; Analysis 19.24; Analysis 19.25; Analysis 19.26; Analysis 19.28; Analysis 19.29; Analysis 19.30; Analysis 19.31; Analysis 19.32; Analysis 19.33; Analysis 19.34; Analysis 19.35; Analysis 19.36; Analysis 19.37; Analysis 19.38; Analysis 19.39; Analysis 19.41; Analysis 19.42; Analysis 19.44; Analysis 19.45; Analysis 19.46; Analysis 19.47; Analysis 19.48; Analysis 19.49; Analysis 19.50). However, at 24 to 48 weeks, a greater proportion of patients on rituximab 1000 mg achieved a clinically meaningful improvement in the fatigue score (FACIT-F ≥ 3.5)

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compared with the patients on rituximab 500 mg (RR 1.2, 95% CI 1.0 to 1.4) with an ATB of 11% (95% CI 2% to 20%) and a NNT of 9 people (95% CI 50 to 5) (Analysis 19.16). Also, although not statistically significant, higher rates were observed with the rituximab 1000 mg dose compared with the 500 mg dose in the clinically meaningful improvements in the physical and mental component scores of the quality of life measure (SF-36 ≤ 5) (Analysis 19.12; Analysis 19.14). There was a significant reduction from baseline in the total radiographic score for those who received rituximab 1000 mg plus methotrexate (mean score -0.41) compared to those who received rituximab 500 mg plus methotrexate (mean score -0.76) at 104 weeks (MD 0.35, 95% CI 0.01 to 0.69) (Analysis 19.18). The difference from baseline in the erosion scores was also statistically significantly less in those who received the combination of rituximab 1000 mg and methotrexate (mean score -0.11) compared to those who received combined rituximab 500 mg plus methotrexate (mean score -0.18) at 104 weeks (MD 0.27, 95% CI 0.04 to 0.50) (Analysis 19.20). Rates of total adverse events were similar in patients receiving combined rituximab 1000 mg plus methotrexate compared to patients receiving rituximab 500 mg plus methotrexate at 24, 48 to 52, and 104 weeks (RR 1.0, 95% CI 0.95 to 1.1; RR 1.0, 95% CI 0.95 to 1.1; RR 1.1, 95% CI 0.97 to 1.1, respectively) (Analysis 19.27). Higher rates of adverse events after the first infusion of rituximab were observed in patients receiving 1000 mg compared with patients receiving 500 mg with borderline significance at 24 weeks (RR 1.4, 95% CI 1.0 to 1.8) (Analysis 19.40). Similarly, a non-significant tendency toward higher rates of adverse events was observed in patients receiving a third course of 1000 mg rituximab compared to patients receiving 500 mg at 52 weeks (RR 4.5, 95% CI 0.98 to 20.6) (Analysis 19.43).

Concomitant treatment

Data were retrieved from one study (81 patients) (Edwards 2004 (WA16291)). The use of methotrexate as a concomitant treatment versus using cyclophosphamide with rituximab 1000 mg was evaluated. No statistically significant differences were observed in ACR responses or DAS (Analysis 20.1; Analysis 20.2; Analysis 20.3 Analysis 20.4; Analysis 20.5). However, for rituximab (two 1000 mg doses) combined with cyclophosphamide there was a significant improvement in functional scores (HAQ) when compared with combined rituximab plus methotrexate at 72 and 104 weeks (MD 0.30, 95% CI 0.01 to 0.59; MD 0.50; 95% CI 0.15 to 0.85, respectively); no statistically significant differences were observed at 24 weeks (Analysis 20.6). Patients in the combined rituximab plus cyclophosphamide group were less likely to achieve a clinically meaningful improvement in functional score (HAQ ≤ 0.22) compared with patients in the rituximab plus methotrexate group at 48 weeks (RR 0.56, 95% CI 0.35 to 0.90). Only 38% achieved a clinically meaningful improvement in functional score compared to 68% of patients receiving rituximab plus methotrexate with an ARD of 30% (95% CI 52% to 8%). No statistically significant differences were observed at 24, 72, and 104 weeks (Analysis 20.7). Statistically significantly more people withdrew from the combined rituximab plus cyclophosphamide group than from the combined rituximab plus methotrexate group at 104 weeks (RR 1.4, 95% CI 1.0 to 2.0). By the second year, 78% from the rituximab plus cyclophosphamide group had withdrawn and 55% had withdrawn from the combined rituximab plus methotrexate group with an ARD of 23% (95% CI 3% to 43%) and a NNH of 4 people (95% CI 33 to 2) Analysis 20.8). No statistically significant differences were observed in safety outcomes (Analysis 20.9; Analysis 20.10; Analysis 20.11; Analysis 20.12; Analysis 20.13; Analysis 20.14; Analysis 20.15; Analysis 20.16; Analysis 20.17; Analysis 20.18; Analysis 20.19; Analysis 20.20; Analysis 20.21; Analysis 20.22; Analysis 20.23; Analysis 20.24; Analysis 20.25; Analysis 20.26; Analysis 20.27).

We also compared rituximab combined with either methotrexate or cyclophosphamide versus rituximab monotherapy (no concomitant treatment). Data were retrieved from one study (121 patients) (Edwards 2004 (WA16291)). The ACR 20 response rates were significantly improved with rituximab 1000 mg combined with methotrexate compared to rituximab monotherapy at 48 and 104 weeks (RR 2.0, 95% CI 1.2 to 3.3; RR 4.3, 95% CI 1.3 to 14.1, respectively) (Analysis 21.1). The pooled RR for achieving an ACR 50 with rituximab 1000 mg plus methotrexate compared with rituximab monotherapy at 48 weeks was RR 2.3 (95% CI 1.0 to 5.5) (Analysis 21.2). There was a statistically significant reduction in the DAS28 in favour of combined rituximab 1000 mg and methotrexate compared to rituximab monotherapy at 24 weeks (MD -1.1, 95% CI -1.8 to -0.36) (Analysis 21.4). The RR for achieving a moderate or good EULAR response at 104 weeks was 3.3 (95% CI 1.2 to 9.1) (Analysis 21.5); 33% of those in the rituximab combined with methotrexate group achieved a moderate or good EULAR response compared to 10% of patients receiving rituximab alone, with an ATB of 23% (95% CI 5% to 40%) and a NNT of 5 people (95% CI 84 to 2). There was a higher percentage of patients achieving a clinically meaningful improvement in physical function (HAQ ≤ 0.22) in the rituximab combined with methotrexate group compared with the rituximab monotherapy group only at 48 weeks (RR 1.63, 95% CI 1.02 to 2.60) (Analysis 21.7). The ATB was 26% (95% CI 4 to 49) with a NNT of 4 people (95% CI 250 to 2). Significantly more people withdrew from the rituximab monotherapy group than from the combined rituximab 1000 mg plus methotrexate group at 48 to 52, 72, and 104 weeks (RR 0.22, 95% CI 0.05 to 0.96; RR 0.52, 95% CI 0.30 to 0.90; RR 0.61, 95% CI 0.45 to 0.82, respectively). By the second year, 90% from the control group had withdrawn and 55% had withdrawn from the combined rituximab plus methotrexate group with an ARD of -35% (95% CI -53% to -17%) and a NNH of 3 people (95% CI 3 to 7) (Analysis 21.8). No other statistically significant differences were noted (Analysis 21.3; Analysis 21.6; Analysis 21.9; Analysis 21.10; Analysis 21.11;

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Analysis 21.12; Analysis 21.13; Analysis 21.14; Analysis 21.15; Analysis 21.16; Analysis 21.17; Analysis 21.18; Analysis 21.19; Analysis 21.20; Analysis 21.21; Analysis 21.22; Analysis 21.23; Analysis 21.24; Analysis 21.25; Analysis 21.26; Analysis 21.27). No statistically significant differences were noted between patients receiving combined rituximab plus cyclophosphamide and rituximab monotherapy (Analysis 22.1; Analysis 22.2; Analysis 22.3; Analysis 22.4; Analysis 22.5 Analysis 22.6; Analysis 22.7; Analysis 22.8; Analysis 22.9; Analysis 22.10; Analysis 22.11; Analysis 22.12; Analysis 22.13; Analysis 22.14; Analysis 22.15; Analysis 22.16; Analysis 22.17; Analysis 22.18; Analysis 22.19; Analysis 22.20; Analysis 22.21; Analysis 22.22; Analysis 22.23; Analysis 22.24; Analysis 22.25; Analysis 22.26).

Anti-CCP and rheumatoid factor (RF)

Four studies provided data on whether RF or anti-CCP status predicted the response to treatment (Cohen 2006 (REFLEX); Emery 2006 (DANCER); Owczarczyk 2008; Tak 2010 (IMAGE). However, data could not be pooled because the numbers were not reported for all groups for the same outcomes. Owczarczyk 2008 did not find a statistically significant difference in the DAS28 at week 24 between patients with RF positive and RF negative disease (1.57 versus 1.55, respectively). In Cohen 2006 (REFLEX) fewer RF negative patients achieved an ACR20 response at week 24 compared with RF positive patients. Rates in the placebo group were 12% for RF negative patients versus 19% for the RF positive patients, and in the rituximab group rates were 41% versus 54%, respectively. The differences observed in the ACR 20 response rates between groups were statistically significant for both subgroups (RF positive P value < 0.0001; RF negative P value < 0.0009) and no statistically significant interaction was found between ACR 20 response and baseline RF status (P = 0.9). Emery 2006 (DANCER) observed a mean decrease in RF levels in the active rituximab groups ranging from 11.5% to 47.9% and a mean increase in RF levels in the placebo groups ranging from 7.1% to 37.4%. The ACR 20 improved in the RF positive subgroup treated with rituximab 1000 mg compared to methotrexate (RR 1.9, 95% CI 1.4 to 2.7). However, when analyses were performed in both subpopulations (RF positive and RF negative) 52% of the rituximab (two 1000 mg doses) group achieved an ACR 20 response at week 24 compared with 32% of the methotrexate group. In an exploratory analysis including only RF negative patients the ACR 20 response at 24 weeks was achieved by 48% in the rituximab group versus 52% in the methotrexate group. Tak 2010 (IMAGE) also reported higher ACR 50 responses and no radiographic progression rates for RF and anti-CCP positive patients compared with RF and anti-CCP negative patients. The OR of no radiographic progression for patients on rituximab 1000 mg plus methotrexate compared to methotrexate alone in the RF or anti-CCP positive subpopulation was 2.2 (95% CI 1.5 to 3.2) and for the RF or anti-CCP negative subpopulation the OR was 1.8 (95% CI 0.56 to 6.0).

Publication bias

Publication bias was assessed using a funnel plot of the ACR 50 response for the comparison of combined rituximab 1000 mg plus methotrexate versus methotrexate alone at 24 to 104 weeks (Analysis 1.2). Figure 5 shows the resulting funnel plot. Only five trials were included in the assessment and no clear symmetry could be observed in the plot. Five trials (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER); Emery 2010 (SERENE); Tak 2010 (IMAGE)) including a total of 1664 patients were included in this review. Although the funnel plot shape may suggest the presence of publication bias, a detailed or quantitative evaluation was not possible due to the small number of studies.

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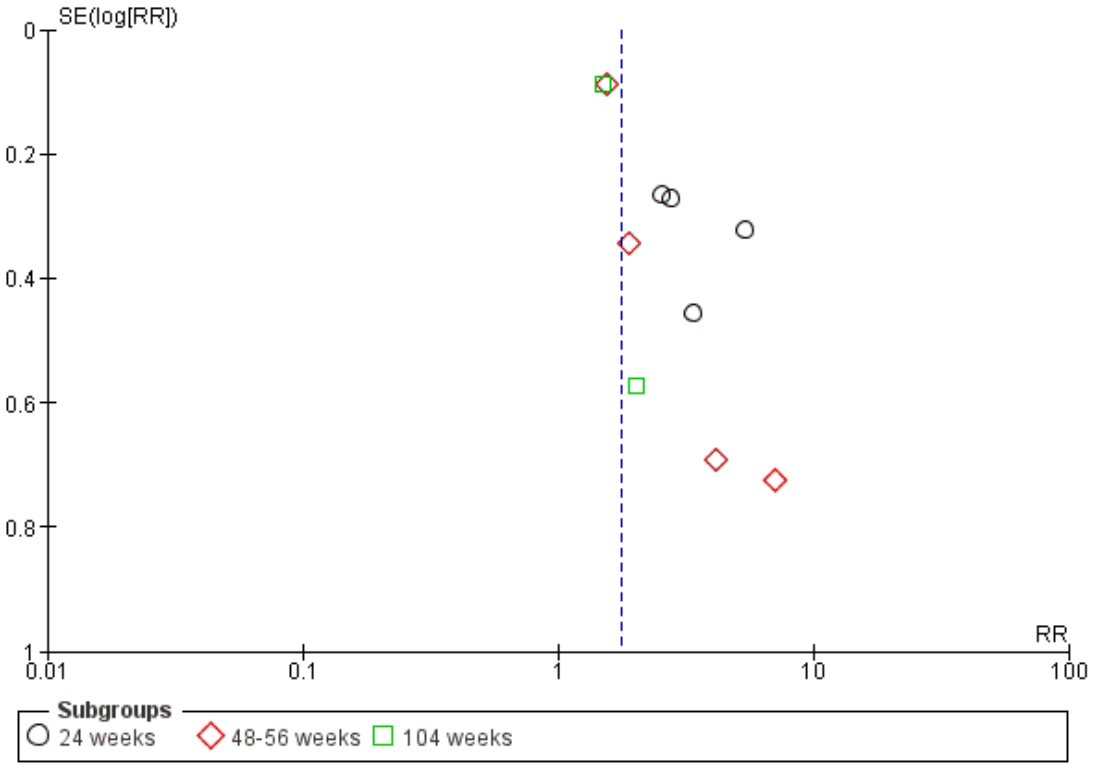
Figure 5. Funnel plot of comparison: 1 Benefits - RTX (2*1000 mg) + MTX versus MTX, outcome: 1.2 ACR 50.



DISCUSSION

Summary of main results

The purpose of this systematic review was to evaluate the efficacy and toxicity of rituximab for the treatment of patients with rheumatoid arthritis (RA). There is evidence to suggest that rituximab (500 mg or 1000 mg) in combination with methotrexate is more efficacious than methotrexate alone for the management of RA (Summary of findings for the main comparison). Rituximab plus methotrexate showed a statistically significant difference when compared with controls for most of the outcome measures (Summary of findings for the main comparison). Regarding the other comparisons also evaluated in this review, only one study compared rituximab monotherapy versus methotrexate monotherapy and the ACR 50 response rates were higher for rituximab monotherapy at 24 weeks. Except for rituximab in combination with cyclophosphamide, the total number of withdrawals and withdrawals due to lack of efficacy were greater in the control groups, in support of the beneficial effect of rituximab. Two trials assessed radiological progression and statistically significant differences were observed between rituximab and control (in favour of rituximab). Overall, in the short term, the review found no significant adverse effects other than in the rates of infusion reactions, vascular events including hypertension, and cough that were increased with rituximab compared to the control group. Further studies are needed to assess long-term safety. From the subgroup analyses we observed better ACR 50 responses for patients receiving combination treatment (1000 mg); in those participants with inadequate response to TNF inhibitors and traditional DMARDs compared with methotrexate-naive patients, those with methotrexate as concomitant treatment compared with those using cyclophosphamide or no concomitant treatment (rituximab monotherapy), and RF or anti-CCP positive patients compared with seronegative patients. Although we also observed better ACR 50 responses for patients receiving rituximab plus methotrexate in patients with late compared to early disease, the absolute risks

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suggests that the RR might be larger in patients with late disease because the control responses were much lower. From the sensitivity analysis, there was no clear evidence to support that two 1000 mg doses of rituximab were more efficacious than two 500 mg doses.

Overall completeness and applicability of evidence

Eight trials addressed the use of rituximab for RA. Some of the characteristics of patients included in these trials may not be typical of patients seen in daily clinical practice, such as the high disease activity state. Only one trial enrolled patients with early disease. Participants in the majority of the included studies had moderate to severe RA of at least nine years duration and few major comorbidities. In all the studies patients with significant systemic involvement or functional class status IV were excluded.

All trials included the recommended standard dosage of rituximab (two 1000 mg doses) per cycle. Four trials also evaluated a lower dosage (500 mg) in combination with methotrexate, which also proved efficacious compared to methotrexate monotherapy. Appropriate outcomes based on OMERACT recommendations were assessed to establish short-term efficacy. However, data to establish long-term efficacy and safety were found in one study only. Further studies are needed to assess long-term efficacy and safety. The effect sizes for ACR responses that were observed in our review are similar to those observed in other reviews of different biologic DMARDs. ACR 50 response rates were statistically significantly improved with abatacept, adalimumab, etanercept, golimumab, and tocilizumab plus DMARD treatment when compared with a DMARD at 6 to 24 months, with similar rates of response (Lethaby 2013; Maxwell 2009; Navarro-Sarabia 2005; Singh 2010; Singh 2010a). A network meta-analysis of all biologics which included only three of the rituximab trials in this report found no statistically significant differences between rituximab and other biologic agents.

Quality of the evidence

The level of evidence ranged from low to high. Using the GRADE system, for most outcomes the level of evidence was rated as moderate. The quality of the evidence was downgraded because of study limitations (see Summary of findings for the main comparison). There is little risk of bias due to selective reporting in these trials. For this review, we have assumed that the definitions provided for the serious adverse events were similar enough to warrant combining. Only two of the studies described their method for sequence generation or allocation concealment but we believe it is likely that there was adequate allocation concealment in those trials without detailed information on this item given that all trials were sponsored and managed by a pharmaceutical company and normally these companies are expected to use a central randomisation system. Three trials did not provided detailed descriptions of the blinding methods used. Given that the outcome established in all trials was a subjective measure (ACR composite criteria of improvement) the method of blinding of participants and assessors is imperative to ensure there are no systematic biases that compromise the study results. Effect estimates were derived from data provided by one to five studies, therefore the risk of publication bias cannot be discarded and results should be interpreted with caution.

Potential biases in the review process

All analyses were performed according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Seven trials did not provide enough details to adequately assess risk of bias for two to three outcomes, and some variance measures necessary for meta-analysis were also not provided. To avoid excluding these trials, in some instances we estimated missing data with approximate values derived from the trial or, when this was not possible, from results of the other trials. This could have created some bias but the overall impact on the estimation of statistically significant differences between groups is probably small.

Four of the studies allowed re-treatment with rituximab but only one of these studies switched patients initially assigned to placebo to rituximab. The exclusion of this study from the analysis did not change the magnitude or direction of the main results. We decided to use these data because the patients had not previously been treated with rituximab. However, there is evidence that rituximab re-treatment can be effective. An open pilot study evaluated nine patients with RA that responded inadequately to TNF inhibitors. Patients were previously treated with rituximab (two 1000 mg doses) at least 24 weeks prior to the inclusion. Patients were re-treated with rituximab (one 1000 mg dose) when the DAS28 score was $\geq$ 2.6 and they were followed for up to 48 weeks with bimonthly assessments of DAS28 score and x-rays of the hands and feet at 48 weeks were compared to baseline using the Sharp/van der Heijde scoring method. The mean DAS28 during the 48 weeks of follow-up reached clinical remission and the mean change in the radiographic score after 1 year was -1.5 ± 2.8 without progression of structural damage after the first re-treatment (Boumas 2009).

Agreements and disagreements with other studies or reviews

Our results are concordant with other studies (Bagust 2009; Bredemeier 2013; Hernandez-Cruz 2011; Isaacs 2013; Lee 2011; Maneiro 2013; Moots 2012; Orme 2012; Salliot 2009; Schoels 2012; Shetty 2013; Singh 2009; Volkmann 2010). An overview of reviews of the other biologics have demonstrated the clinical efficacy of rituximab in patients with RA (Singh 2009). Another review of biologics for the treatment of RA summarized and analysed the efficacy of rituximab and other biologics with a different

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statistical method but had similar findings (Venkateshan 2009). Salliot 2009 performed a meta-analysis of RCTs to investigate the risk of serious infections with rituximab, anakinra, and abatacept for RA. Singh 2011 conducted a network meta-analysis to evaluate the adverse events of the biologics used in autoimmune disorders. The inclusion of other conditions besides RA did not modify the findings reported by other studies. The rates of total adverse events, withdrawals due to adverse events, serious infections, and serious adverse events in patients assigned to combined rituximab 1000 mg plus methotrexate were not statistically significantly different from methotrexate alone (Singh 2011). Similarly to our review, they found no statistically significant increase in risk of serious infections with the use of rituximab. All these systematic reviews have only included three of the eight trials included in this review (Cohen 2006 (REFLEX); Edwards 2004 (WA16291); Emery 2006 (DANCER)), and some used different statistical approaches; however, no major differences were observed in the interpretation of the results and conclusions. Furthermore, the SUNDIAL II study, a non-comparative open-label study that was not included in this review, examined the use of rituximab with other biologic DMARDS (etanercept, adalimumab, infliximab, or abatacept) and found that the rate of serious adverse events in patients treated with this combination was 9.1% (16/176) after 24 weeks (Rigby 2013). Finally, Hernandez-Cruz 2011 also evaluated the efficacy of rituximab in a meta-analysis where the preferred method for pooling estimates was ORs. The study included results for six efficacy and four safety outcome measures with treatment estimates that reflect our results for the same outcomes. In addition, the study included a subanalysis by dose (500 mg and 1000 mg) and the use of concomitant treatment (combination versus monotherapy). However, none of these studies have presented a detailed analysis of six different comparisons and four subgroup analyses as in the present review. Regarding our subgroups analyses, data from the Swiss Clinical Quality Management in RA (SCQM-RA) (Finckh 2010) observed similar results to our study, suggesting that those patients with inadequate responses to TNF inhibitors may benefit from switching to rituximab compared to switching to an alternative treatment. In the SCQM-RA, the observed DAS28 score reduction was -1.3 for the patients receiving rituximab (two 1000 mg doses) compared with patients receiving a TNF inhibitor (95% CI -1.5 to -1.2). This result can vary based on the type of TNF inhibitor used according to a recent analysis from the Stockholm Tumor Necrosis Factor-α Follow-up Registry (STURE) (Chatzidionysiou 2013). After switching to rituximab, DAS28 scores at six months were significantly lower for patients who had an inadequate response to etanercept compared to patients with an inadequate response to monoclonal antibodies (P = 0.01).

AUTHORS' CONCLUSIONS

Implications for practice

Rituximab (two 1000 mg doses) in combination with methotrexate is efficacious for the management of rheumatoid arthritis. Its overall effect appears to be moderate to large for treating those patients with chronic and active disease who have failed either methotrexate or TNF-α antagonists. Furthermore, our findings from a sensitivity analysis suggest that rituximab (two 500 mg doses) in combination with methotrexate has similar efficacy as rituximab (two 1000 mg doses). We also found in our additional comparisons that rituximab monotherapy (two 1000 mg doses) appears to have an overall mild to moderate effect when compared with methotrexate monotherapy for treating these patients.

Implications for research

Long-term data on the efficacy and toxicity of rituximab are limited. Post-marketing surveillance studies are needed to better inform patients and physicians about its effectiveness and safety, especially regarding the risk for hepatitis B reactivation, progressive multifocal leukoencephalopathy, and its use in the setting of previous cancer. Studies comparing rituximab to other biologics may also be helpful to inform physicians about the relative efficacies of these agents for treatment of RA. Controlled studies are also needed to evaluate the use of rituximab (i) in combination with traditional DMARDs other than methotrexate or cyclophosphamide, (ii) in different re-treatment schedules, and using (iii) clinical determinants for re-treatment.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Cohen 2006 (REFLEX)

Methods	**Design:** Randomised, double blind, placebo-controlled phase III trial **Sample Size:** 520 patients randomised **Setting:** 114 rheumatology centres (US, Europe, Canada, and Israel) **Follow-up:** 24 weeks
Participants	**Inclusion criteria:** 1. at least 6 months with RA 2. ≥ 8 SJC and ≥ TJC (66 and 68 assessed); and at least two of the following: CRP level ≥ 1.5 mg/dl or ESR ≥ mm/hr 3. Radiographic evidence of at least 1 joint with definite erosion 4. Appropriate vaccinations/boosters at least 4 weeks prior enrolment 5. intolerant to at least 1 TNF inhibitor **Exclusion criteria:** 1. significant systemic involvement secondary to RA 2. ACR functional class IV 3. Other rheumatic autoimmune diseases
Interventions	**Control:** Methotrexate (n = 209) **Group 1:** Rituximab 1000 mg + methotrexate (n = 308) **Concomitant treatment:** Prednisone (10 mg/day or equivalent) NSAIDs **Retreatment:** rescue therapy between weeks 16 and 24 (placebo group received rituximab and for rituximab received standard of care)
Outcomes	**Primary endpoint:** ACR 20 **Secondary endpoints:** ACR 50, 70; HAQ; FACIT-F; EULAR response; AEs; DAS28; Immunogenicity; Genant/Sharp score; SF-36; Individual ACR core set measures **Safety:** Withdrawals, infusion-related reactions, severe AEs, infections, serious AEs, HACA antibodies
Notes	**Funding:** Supported by Hoffmann-La Roche, Biogen Idec and Genentech. **Objectives:** "i) to determine the efficacy and safety of treatment with rituximab plus methotrexate in patients with active rheumatoid arthritis who had an inadequate response to anti-tumour necrosis factor therapies and ii) to explore the pharmacokinetics and pharmacodynamics of rituximab in this population"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not reported

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Cohen 2006 (REFLEX) (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Method of blinding was not described, but it is mentioned that patients, study sponsor, and investigators were unaware of the treatment assignment of each patient
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing data reported/ reporting of discontinuations not clear **Power calculation:** Yes, 91% **Patients randomised:** 520 **Patients analysed:** 499 for efficacy outcomes and 517 for safety outcomes **ITT analysis:** No (modified ITT), but sensitivity analyses were conducted including all patients
Selective reporting (reporting bias)	Low risk	No study protocol, but article includes all the pre-specified and expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias. The sponsor was a pharmaceutical company and was responsible for the data collection, and the statistical analyses

Edwards 2004 (WA16291)

Methods	**Design:** Randomised, double-blind, controlled study **Sample Size:** 161 patients randomised **Setting:** 26 rheumatology centres **Follow-up:** 48 weeks, 104 weeks
Participants	**Inclusion criteria:** 1. > 21 years of age 2. ≥ 8 SJC and ≥ 8 TJC and at least two of the following: CRP level ≥ 15 mg/l or ESR ≥ 28 mm/hr, or morning stiffness > 45 min, RF ≥ 20 IU/ml 3. Inadequate response to methotrexate **Exclusion criteria:** 1. concomitant treatment with any DMARD or any anti-TNF 2. American Rheumatism Association functional class IV disease 3. active rheumatoid vasculitis 4. a history of systemic diseases associated with arthritis 5. chronic fatigue syndrome 6. Autoimmune disease other than rheumatoid arthritis (except concurrent Sjögren's syndrome) 7. serious and uncontrolled coexisting diseases 8. primary or secondary immunodeficiency 9. a history of cancer (except basal-cell carcinoma of the skin that had been excised)

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Edwards 2004 (WA16291) (*Continued*)

	10. active infection 11. a history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms
Interventions	**Control:** Methotrexate (n = 40) **Group 1:** Rituximab1000 mg (n = 40) **Group 2:** Rituximab 1000 mg + cyclophosphamide (n = 41) **Group 3:** Rituximab 1000 mg + methotrexate (n = 40) **Concomitant treatment:** Prednisone (10 mg/day or equivalent) **Re-treatment:** a repeat course of rituximab or alternative therapy was was allowed after 24 weeks
Outcomes	**Primary endpoint:** ACR 50 **Secondary endpoints:** ACR 20, 70; DAS28; EULAR responses; individual ACR core set measures, DAS28, HAQ, CD19 + B-cells, CD3 +, CD4 +, CD8 + T-cells, IgG, IgA, and IgM, RF levels, anti-tetanus antibody titres **Safety:** Withdrawals, Infusion related reactions, Infections, Serious AEs, human anti-chimeric antibodies against rituximab
Notes	**Funding:** Supported by Roche **Objective:** "To evaluate the effect of rituximab in patients with active rheumatoid arthritis in a multicenter, randomised, double-blind, controlled study"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinding reported. Personnel at all sites remained blinded to treatment during the follow-up
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons documented for dropouts. For patients who withdrew before week 24, a last observation carried forward method of imputation was applied **Power calculation:** Yes, 82% **Patients randomised:** 161 **Patients analysed:** 161 **ITT analysis:** Yes
Selective reporting (reporting bias)	Low risk	No protocol for study identified but wide range of outcomes assessed

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Other bias	Low risk	The study appears to be free of other sources of bias. The sponsor was a pharmaceutical company and was responsible for the data collection, and the statistical analyses

Emery 2006 (DANCER)

Methods	**Design:** Phase IIb, randomised, double-blind, double-dummy, placebo-controlled, dose-ranging multifactorial trial **Sample Size:** 465 patients were randomised **Setting:** 99 centres (Australia, Brazil, Canada, Czech Republic, Finland, Germany, Italy, Mexico, New Zealand, Poland, Spain, Sweden, UK, US) **Follow-up:** 24 weeks
Participants	**Inclusion criteria:** 1. Outpatients 2. 18 and 80 years of age 3. RA diagnosis > 6 months prior to randomisation 4. ≥ 8 SJC and ≥ 8 TCJ and at least two of the following: CRP level ≥ 15 mg/l or ESR ≥ 28 mm/hr 5. Inadequate response to methotrexate for >12 weeks, or > 1 but not more than 5 DMARDs/BRMs **Exclusion criteria:** 1. Concomitant treatment with any DMARD (other than methotrexate), anti-TNF, or other biologic therapy 2. Significant systemic involvement secondary to RA 3. evidence of significant or laboratory abnormalities 4. a history of severe allergic reaction to humanized or murine monoclonal antibodies 5. previous treatment with RTX or any lymphocyte-depleting therapies 6. history of recurrent significant infection
Interventions	**Control:** Methotrexate (n = 149) **Group 1:** Rituximab + methotrexate 500 mg (n = 124) **Group 2:** Rituxiimab + methotrexate 1000 mg (n = 192) **Concomitant treatment:** Prednisone (10 mg/day or equivalent) NSAIDs **Re-treatment:** Not allowed
Outcomes	**Primary endpoint:** ACR 20 **Secondary endpoints:** ACR 50, 70; DAS28; EULAR responses; FACIT-F; Individual parameters of the ACR improvement criteria; HAQ **Safety:** Withdrawals, incidence of adverse events (CTC); CD19; Ig levels; protective antibody titers; human anti-chimeric antibodies against rituximab levels

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Emery 2006 (DANCER) (*Continued*)

Notes	**Funding:** Supported by Genetech, Biogen Idec, and Hoffmann-La Roche. **Objective:** "To examine the efficacy and safety of different rituximab doses plus methotrexate with or without glucocorticoids, in patients with active rheumatoid arthritis resistant to disease-modifying antirheumatic drugs, including biologic agents"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data reported/ clear reporting of discontinuations **Power calculation:** Yes, 80% **Patients randomised:** 465 **Patients analysed:** 465 for safety, 367 for efficacy **ITT analysis:** Only for categorical variables
Selective reporting (reporting bias)	Low risk	No study protocol, but article includes all the pre-specified and expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias, but the sponsor was a pharmaceutical company and was responsible for the data collection, and the statistical analyses

Emery 2010 (SERENE)

Methods	**Design:** Randomised, placebo-controlled, double-blind, parallel group study **Sample Size:** 511 patients were randomised **Setting:** 102 centres (US, Canada, LatinAmerica and European countries) **Follow-up:** 48 weeks
Participants	**Inclusion criteria:** 1. 18 to 80 years 2. RA diagnosis $\geq$ 6 months 3. SJC and TJC both $\geq$ 8, and either CRP $\geq$ 0.6 mg/dl or ESR $\geq$ 28 mm/h 4. absolute neutrophil count $\geq$ 1500 cells/μl, a HB level $\geq$ 8 g/dl and IgM and IgG

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Emery 2010 (SERENE) (*Continued*)

	levels of ≥ 40 and ≥ 500 mg/dl 5. Prior treatment with methotrexate (10 to 25 mg/week for at least 12 weeks) **Exclusion criteria:** 1. Previously treated with biologics
Interventions	**Control:** Methotrexate (n = 172) **Group 1:** Rituximab 500 mg + methotrexate (n = 168) **Group 2:** Rituximab 1000 mg + methotrexate (n = 172) **Concomitant treatment:** Prednisone (10 mg/day or equivalent) NSAIDs **Re-treatment:** rescue therapy was allowed with one non-biological DMARD between week 16 and 23. After week 24 repeat courses of open-label rituximab were allowed
Outcomes	**Primary endpoint:** ACR 20 **Secondary endpoints:** ACR 50, 70; EULAR responses; DAS28-ESR (mean change, low disease activity and remission); HAQ-DI; SF36; FACIT-F **Safety:** Withdrawals, Infusion related reactions, Infections, Serious AEs, HACA antibodies
Notes	**Funding:** Sponsored by Genentech **Objective:** "To evaluate the safety and efficacy of rituximab 2x500 mg and 2x1000 mg in combination with methotrexate, compared to methotrexate monotherapy, in patients with active rheumatoid arthritis who had inadequate response to methotrexate and in whom no prior biological treatment for RA had been administered"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were imputed using the non-responder method and LOCF, clear reporting of discontinuations **Power calculation:** Yes, 90% **Patients randomised:** 511 **Patients analysed:** 509 **ITT analysis:** No (modified ITT)

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Emery 2010 (SERENE) (*Continued*)

Selective reporting (reporting bias)	Low risk	Study protocol available in clinical trial.gov, article includes all the pre-specified and expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias, but the sponsor was a pharmaceutical company and was responsible for the data collection, and the statistical analyses

Greenwald 2011 (TAME)

Methods	**Design:** Randomised, double-blinded, placebo-controlled study **Sample Size:** 54 patients enrolled **Setting:** 17 sites (US) **Follow-up:** 24 weeks
Participants	**Inclusion criteria:** 1. 18 to 65 years 2. ≥ 6 months with RA 3. SJC and TJC both ≥ 5 4. Methotrexate (10 to 25 mg/week) and either etanercept at 50 mg/week or adalimumab 40 mg every other week for at least 12 weeks **Exclusion criteria:** 1. significant systemic involvement secondary to RA 2. rheumatic disease disorder other than RA 3. congestive heart failure 4. uncontrolled concomitant disease 5. cancer 6. serious or opportunistic infections within 2 years of screening
Interventions	**Control:** Methotrexate + TNFi (n = 18) **Group 1:** Rituximab + methotrexate + TNFi (n = 32) **Concomitant Treatment:** Prednisone (10 mg/day or equivalent) DMARDs other than methotrexate **Re-treatment:** Not allowed
Outcomes	**Primary endpoint:** Proportion of patients developing at least 1 serious infection **Secondary endpoints:** Individual ACR core set measures, ACR 20, 50, 70; EULAR responses, DAS28-ESR **Safety:** Withdrawals, serious infections, total AEs, serious AEs, grade 3 or 4 infections, duration of all infections, immunologic and laboratory assessment
Notes	**Funding:** Biogen Idec, Genetech, and Roche **Objective:** "To preliminary assess the safety of rituximab (dose of 2 X 500 mg) in combination with a TNF inhibitor and methotrexate in patients with active RA"

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Greenwald 2011 (TAME) (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data were no imputed and all analyses were based on available data **Power calculation:** Yes, 78% **Patients randomised:** 54 **Patients analysed:** 51 **ITT analysis:** No (modified ITT)
Selective reporting (reporting bias)	Low risk	No study protocol, but article includes all the pre-specified and expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias, but the sponsor was a pharmaceutical company and was responsible for the data collection, and the statistical analyses

Owczarczyk 2008

Methods	**Design:** Randomised, open-label trial **Sample Size:** 40 participants **Setting:** 2 centres (Germany) **Follow-up:** 24 weeks
Participants	**Inclusion criteria:** 1. Inadequate response to methotrexate 2. Active RA **Exclusion criteria:** 1. Not reported
Interventions	**Control:** RTX alone (n = 20) **Group 1:** RTX + methotrexate (n = 20) **Concomitant treatment:** Not specified **Re-treatment:** Not allowed

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Owczarczyk 2008 (*Continued*)

Outcomes	**Primary endpoint:** DAS28 **Secondary endpoints:** EULAR response, mean absolute CD19 + B-cell counts, incidence of repopulation of CD19 + B-cells, individual **Safety:** acute infusion reactions; infections
Notes	**Funding:** Source of funding was not disclosed, but no conflict of interest were reported **Objective:** "To determine the efficacy, safety and kinetics of B-cell depletion following a single course of RTX as a monotherapy"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for in the analysis **Power calculation:** No **Patients randomised:** 40 **Patients analysed:** 40 **ITT analysis:** Yes
Selective reporting (reporting bias)	Low risk	No study protocol, but article includes all the pre-specified outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Rubbert-Roth2010 (MIRROR)

Methods	**Design:** Randomised, double-blind, phase III trial **Sample Size:** 378 participants were randomised **Setting: 81 centres** (Australia, Belgium, Brazil, Canada, China, Finland, France, Germany, Hungary, Italy, New Zealand, Slovakia, South Africa, Spain, Taiwan, the Netherlands, UK) **Follow-up:** 48 weeks
Participants	**Inclusion criteria:** 1. Diagnosis of RA for $\geq$ 6 months 2. SJC and TJC both $\geq$ 8, and either CRP $\geq$ 6 mg/dl or ESR $\geq$ 28 mm/h 3. Inadequate response to methotrexate (10 to 25 mg/week for at least 12 weeks)

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Rubbert-Roth2010 (MIRROR) (*Continued*)

	Exclusion criteria: 1. Significant systemic involvement secondary to RA 2. Inflammatory joint disease disorder other than RA, systemic autoimmune disorder, significant cardiac or pulmonary disease 3. Previous treatment with more than one biologic 4. Active infection or history of serious recurrent or chronic infection
Interventions	**Group 1:** RTX 2 x 500 mg, then at 24 weeks RTX 2 x 500 mg (n = 134) **Group 2:** RTX 2 x 500 mg, then at 24 weeks RTX 2 x 1000 mg (n = 119) **Group 3:** RTX 2 x 1000 mg, then at 24 weeks RTX 2 x 1000 mg (n = 93) **Concomitant treatment:** Prednisone (10 mg/day or equivalent) Methotrexate (10 to 25 mg/week) NSAIDs **Re-treatment:** At week 24, patients initially on rituximab 2 x 500 mg received a repeat course also of 2 x 500 mg or a dose increase of 2 x 1000 mg. Patients initially on rituximab 2 x 1000 mg received a course also of 2 x 1000 mg
Outcomes	**Primary endpoint:** ACR 20 **Secondary endpoints:** ACR 50, 70, DAS28-ESR, EULAR response, SF-36, FACIT-F, HAQ-DI, MCID in HAQ-DI, pharmacodynamics (B-cell and T-cell counts, Ig concentrations, levels of RF and anti-CCP antibodies) **Safety:** Presence of human anti-chimeric antibodies, adverse events and serious adverse events
Notes	**Funding:** Sponsored by F Hoffmann-La Roche, Biogen Idec and Genetech. Open access publication of the article was paid by F Hoffmann-La Roche **Objective:** "i) to determine if initiating treatment with RTX 2 x 500 mg followed by a repeat course with the same dose at 24 weeks was different from repeat course increasing the dose to 2 x 1000 mg; ii) to compare efficacy and safety of RTX 2 x 500 and 2 x 1000 over 48 weeks with a fixed repeat treatment"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly allocated using an interactive voice response system"
Allocation concealment (selection bias)	Low risk	"The sponsor, investigators and patients were blinded to the treatment allocation up to the Week 48 analysis. Treatment assignments were unblinded to the sponsor at this time for the purpose of the data analysis"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Although all patients were randomly assigned to RTX-containing regimens, allocation to dose and repeat treatment regimen was blinded"

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Rubbert-Roth2010 (MIRROR) (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were imputed using the non-responder method for ACR and EULAR (all patients who withdrew were categorized as non-responders). The last observation carried forward was used for the remaining outcomes **Power calculation:** Yes, 80% **Patients randomised:** 378 **Patients analysed:** 346 for safety, 346 for disease activity measures, 320 to 345 for patient-reported outcomes **ITT analysis:** Yes
Selective reporting (reporting bias)	Low risk	No study protocol, but article includes all the pre-specified and expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias. The sponsor was a pharmaceutical company and was responsible for the data collection, and the statistical analyses

Tak 2010 (IMAGE)

Methods	**Design:** Phase III, double-blind randomised controlled trial **Sample Size:** 755 methotrexate-naive patients randomised **Setting:** 169 centres (US, Latin America, Asia, and Australia) **Follow-up:** 104 weeks
Participants	**Inclusion criteria:** 1. 18 to 80 years 2. RA with disease duration $\geq$ 8 weeks but $\leq$ 4 years 3. SJC (66 joints) and TJC (68 joints) both $\geq$ 8 at screening and baseline, and CRP $\geq$ 1.0 mg/dl 4. radiographic evidence of erosive damage attributable to RA for RF seronegative 5. no previous treatment with methotrexate **Exclusion criteria:** 1. IV or IM glucocorticoids 2. DMARDs or biologics
Interventions	**Control:** Methotrexate (n = 249) **Group 1:** Rituximab 2 x 500 mg + methotrexate (n = 249) **Group 2:** Rituximab 2 x 1000 mg + methotrexate (n = 250) **Concomitant treatment:** Prednisone (10 mg/day or equivalent) NSAIDs **Re-treatment:** Repeat courses of rituximab/placebo were allowed from week 24

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Tak 2010 (IMAGE) (*Continued*)

Outcomes	**Primary endpoint:** Change in Total Modified Sharp Score (TMSS) **Secondary endpoints:** ACR 20, 50, 70, 90; EULAR response; DAS28-ESR; HAQ-DI **Safety:** Withdrawals, AEs
Notes	**Funding:** Sponsored by F Hoffmann-La Roche Ltd, Genentech Inc and Biogen Idec **Objective:** i) To determine the efficacy of rituximab in the prevention of joint damage and its safety in combination with methotrexate in patients initiating treatment with methotrexate; "ii) to investigate the early therapeutic introduction of rituximab in patients with active RA not previously treated with methotrexate"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation schedule was generated by the sponsor and supplied to an Interactive Voice Response System"
Allocation concealment (selection bias)	Low risk	"Patients were assigned unique medication and randomisation numbers via IVRS. The sponsor, investigators and patients were blinded to treatment allocation until week 52"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded and study medications were identical (RTX and PBO)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were imputed by linear extrapolation/ clear reporting of discontinuations **Power calculation:** Yes, > 90% **Patients randomised:** 755 **Patients analysed:** 748 **ITT analysis:** No (modified ITT)
Selective reporting (reporting bias)	Low risk	Study protocol available in clinical trial. gov, article includes all the pre-specified and expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias, but the sponsor was a pharmaceutical company and was responsible for the data collection, and the statistical analyses

ACR - Americn College of Rheumatology

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AE - adverse event
CRP - C-reactive protein
CTC - common toxicity criteria
DAS28 - Disease activity score 28
ESR - erythrocyte sedimentation rate
EULAR - European League Against Rheumatism
FACIT-F - fatigue scale of the functional assessment of chronic illness therapy
HACA antibodies - anti-human chimeric antibodies
HAQ - health assessment questionnaire
RA - rheumatoid arthritis
SJC - swollen joint count
TJC - tender joint count

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

Study	Reason for exclusion
Assous 2008	Retrospective study, 50 patients, 24 months of follow-up
Bingham 2010 (SIERRA)	The SIERRA trial evaluated the effects of rituximab on immune responses in subjects with active rheumatoid arthritis receiving background methotrexate. This was a phase II, randomised, parallel-group, open-label, multicenter study. 103 patients of 26 centres (US) were randomised to RTX 1000 mg + methotrexate (n = 68) or methotrexate (n = 32). Concomitant treatment was prednisone (10 mg/day or equivalent) and antihistamine and/or acetaminophen. Retreatment was not allowed. Patients were followed for 36 weeks. Primary endpoint was the proportion of subjects with a positive response to tetanus toxoid adsorbed vaccine. Secondary endpoints included the proportion of subjects with a 2-fold increase in tetanus antibody titres, or with tetanus antibody titres $\geq$ 0.2 IU/mL; proportion of subjects with positive responses against an individual anti pneumococcal antibody serotype; proportion of subjects with positive responses against at least 50% of the serotypes; levels of anti-tetanus antibody in subjects measured immediately prior to and 4 weeks after a booster vaccine; levels of anti pneumococcal antibody to 12 serotypes in subjects measured immediately prior to and 4 weeks after vaccination; levels of anti-KLH antibody in subjects measured immediately prior to the first administration of KLH and 4 weeks after the first administration of KLH; proportion of subjects who maintain a positive response to *Candida albicans*; pharmacodynamics. Safety outcomes were infusion reactions and serious adverse events. The study was sponsored by Genetech
Bokarewa 2007	Observational study, 46 patients, 12 months of follow-up
Galarza 2008	Observational study, 74 patients (only 21 with RA), 2 to 35 months of follow-up
Haraoui 2011 (RESET)	The RESET trial assessed safety and efficacy of rituximab in patients with RA that were taking stable doses of methotrexate and failed tumour necrosis factor (TNF) inhibitors. This was an open-label; multicentre trial with 120 patients receiving the first course of rituximab (2 x 1000 mg) then from this group, 77 patients received re-treatment with rituximab (2 x 1000 mg) between weeks 24 and 48 with a total of 72 patients that received rituximab re-treatment completing the 24 week second course of treatment period, 112 patients completing the 24 week primary treatment period and 25 patients completing the 48 week primary treatment period. Analysis preformed after 24 weeks showed that 58%, 27% and 7% of patients achieved an ACR 20, 50 and 70 improvements respectively. During the primary

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(*Continued*)

	treatment the amount of patients with a decrease in at least 0.25 in the HAQ-DI score was 56.7% after 24 weeks of the first course of rituximab and 64.9% after 24 weeks of re-treatment. No infections or infusion reactions were found life-threatening during treatment courses
Kavanaugh 2008 (ARISE)	Open-label study, 13 patients, 24 weeks of follow-up
Keystone 2007	An open-label extension analysis, patients of the 3 RCTs included in this review (1039 patients), reported efficacy at 24 weeks
Mease 2010 (SUNRISE)	The SUNRISE trial evaluated the efficacy and safety of rituximab given in 1 course versus 2 courses over 48 weeks in patients with RA that were on a stable dose of methotrexate 10 to 25 mg/week and failed previously treatment with tumour necrosis inhibitors. 559 patients received a first course of rituximab (2 x 1000 mg) in an open-label fashion and then 475 patients were randomised in a double-blind ratio at week 24, of these 318 into a second course of rituximab and 157 into placebo group. It was found at week 48 that efficacy was improved in patients re-treated with rituximab (2 x 1000 mg) comparing to placebo group. American College of Rheumatology (ACR 20) criteria 54% versus 45%, P = 0.02; Mean change in Disease Activity Score-28 (DAS-28) of -1.9 versus -1.5, P = 0.006. Also the amounts of patients experiencing any side effects, or serious adverse events, infections or serious infections were similar in the 2 groups
Ng 2005	Population pharmacokinetics of rituximab, 102 patients
Teng 2007	Observational study, 25 patients, 12 weeks of follow-up. Immunohistochemical analysis
Teng 2009	Comparison between 1 cycle and 2 cycles
van den Bemt 2009	This was a prospective cohort study conducted to assess the proportion of patients with rheumatoid arthritis in which treatment with rituximab resulted in the depletion or anti-infliximab antibodies. 32 participants who had been treated with infliximab in 4 centres (the Netherlands) were included if they met the following criteria: diagnosis of RA, detectable anti-infliximab antibodies and initiated on treatment with rituximab or adalimumab. Patients were assigned to rituximab 2 x 1000 mg (n = 17) or adalimumab 40 mg SC every other week (n = 15) and followed for 24 weeks. At 24 weeks found similar per cent reduction between groups (20% versus 36%, adalimumab versus rituximab, respectively)

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

August III 2008

Trial name or title	A Randomized, Double-Blind, Placebo Controlled, Multi-Centre, Exploratory, Pilot, Phase II Trial of 150mg Atacicept Given Subcutaneously in Combination With Rituximab in Subjects With Rheumatoid Arthritis
Methods	The primary objective of this study is to assess the safety and tolerability of combined treatment with atacicept and rituximab in subjects with active rheumatoid arthritis receiving re-treatment with rituximab
Participants	> 18 years of age; rheumatoid arthritis (American College of Rheumatology criteria); disease history of at least 12 months; active disease defined by > 8 swollen joints (out of 66) > 8 tender joints (out of 68); CRP > 6 mg/LESR > 28 mm/h; previous treatment with rituximab; candidates for re-treatment with rituximab

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Interventions	Rituximab 1000 mg IV infusion, second 1000 mg IV infusion given 2 weeks later, followed 28 days later by atacicept/placebo 150 mg/mL SC once weekly for 25 weeks Atacicept/placebo 150 mg/mL SC once weekly for 25 weeks, given in combination with rituximab 1000 mg IV infusion on study day 10, second 1000 mg IV infusion given 2 weeks later
Outcomes	**Primary outcome measures:** Incidence and severity of adverse events (AEs) Proportion of subjects who develop IgG <3 g/L Changes / abnormalities in vital signs/ routine safety lab parameters Changes over time in vaccine immunization status **Secondary outcome measures:** ACR and DAS28 composite scores at week 26
Starting date	March 2008
Contact information	Carol Marsella, BSc (Hons), carol.marsella@merckserono.net Amanda Clark, RGN, BN, BASc amanda.clark@merckserono.net
Notes	Atacicept in combination with rituximab in subjects with rheumatoid arthritis (August III)

NCT00298272

Trial name or title	A Randomized, Double-Blinded, Placebo Controlled Study to Evaluate the Tolerability and Safety of Rituximab When Given in Combination With Methotrexate and Etanercept (Enbrel) or Methotrexate and Adalimumab (Humira) in Subjects With Active Rheumatoid Arthritis
Methods	This study is being conducted to see how well patients with rheumatoid arthritis are able to tolerate rituximab in combination with methotrexate and etanercept or methotrexate and adalimumab
Participants	18 and 65 years of age: diagnosis of active RA for at least 6 months (diagnosed according to the revised 1987 ACR criteria for the classification of RA); at least 5 tender and 5 swollen joints; treated with etanercept at 50 mg per week (25 mg twice per week or 50 mg once per week) for at least 12 weeks immediately prior enrolment; treated with methotrexate greater than or equal to 15 mg per week and less than or equal to 25 mg per week for at least 12 weeks immediately prior to enrolment; on oral folate; oral glucocorticoids must not exceed 10 mg per day of prednisone (or equivalent dose); any concomitant NSAID must be stable for at least 2 weeks prior enrolment
Interventions	500 mg rituximab on Day 1 and Day 15 Placebo on Day 1 and Day 15
Outcomes	**Primary outcome measures:** The proportion of patients with at least one serious infection through Week 24 **Secondary outcome measures:** The proportion of patients achieving an ACR 20 response at Week 24 The proportion of patients achieving an ACR 50 response at Week 24 The proportion of patients achieving an ACR 70 response at Week 24
Starting date	March 2006
Contact information	Richard Schwartz, MD, Biogen Idec

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NCT00298272 (*Continued*)

Notes	Safety and tolerability of rituxan with methotrexate and etanercept or methotrexate and adalimumab in patients with active rheumatoid arthritis

NCT00422383

Trial name or title	A Randomized, Double-blind Study to Evaluate the Effect of Various Re-treatment Regimens of MabThera in Combination With Methotrexate on Treatment Response in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate
Methods	This study will evaluate the efficacy and safety of various treatment and re-treatment regimens of MabThera. All patients will receive concomitant methotrexate, 10 to 25 mg once weekly either orally or parenterally. The anticipated time on study treatment is 2+ years, and the target sample size is 100 to 500 individuals
Participants	Adult patients $\geq$ 18 years of age; RA for $\geq$ 6 months; receiving outpatient treatment; inadequate response to methotrexate, having received and tolerated it for $\geq$ 12 weeks, with a stable dose for $\geq$ 4 weeks
Interventions	Three treatment arms: i) 500 mg IV on days 1 and 15, and 500 mg IV on days 168 and 182; ii) 500 mg IV on days 1 and 15, and 1000 mg IV on days 168 and 182; iii) 1000 mg IV on days 1 and 15 and 1000 mg IV (or placebo in UK) on days 168 and 182
Outcomes	**Primary outcome measures:** Percentage of patients with ACR 20 response **Secondary outcome measures:** Percentage of patients with ACR 50 and ACR 70 response Change in DAS28, SF-36, FACIT-fatigue assessment from baseline EULAR response rates AEs, laboratory parameters and acute phase reactants
Starting date	February 2006
Contact information	Hoffmann-La Roche
Notes	A study of re-treatment with MabThera (rituximab) in combination with methotrexate in patients with rheumatoid arthritis (RA)

NCT00845832

Trial name or title	A Randomized, Active Controlled, Double-blind, Study to Compare the Safety and Reduction in Disease Activity With the Combination of Rituximab (MabThera®)and Tocilizumab (RoActemra®) Versus Tocilizumab in Patients With Active Rheumatoid Arthritis With an Incomplete Response to Methotrexate
Methods	This 2 part study will investigate the safety, tolerability and efficacy of MabThera in combination with RoActemra in patients with active rheumatoid arthritis despite a stable dose of methotrexate. In Part 1 of the study, patients will be randomised to receive either MabThera 0.5 g IV or placebo on days 1 and 15, followed by RoActemra at one of the ascending doses between 2 mg/kg and 8 mg/kg at weeks 4, 8 and 12 (MabThera arm) or 8 mg/kg (placebo arm). In Part 2, additional patients will be randomised to one of 2 groups to receive MabThera 0.5 g on days 1 and 15 followed by the selected dose (from Part 1) of RoActemra at weeks 4, 8 and 12, or placebo on days 1 and 15 followed by RoActemra 8 mg/kg at weeks 4, 8 and 12. All patients will then be eligible to receive extension treatment withRoActemra every 4 weeks. The anticipated time on study

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NCT00845832 (*Continued*)

	treatment is 12 months, and the target sample size is < 100 individuals
Participants	Adult patients, 18 to 65 years of age; rheumatoid arthritis, functional status I-III; SJC ≥ 4 (28 joint count) and TJC ≥ (28 joint count) at screening and baseline; RF and/or anti-CCP positive; may have failed up to 1 approved anti-TNF agent (infliximab, etanercept or adalimumab); inadequate response to methotrexate, at a dose of 7.5 to 25 mg weekly for at least 12 weeks, at a stable dose for past 4 weeks
Interventions	Rituximab (MabThera) 0.5 g IV on days 1 and 15 (Parts 1 and 2) + tocilizumab (RoActemra) 2 mg/kg to 8 mg/kg IV in Part 1 and selected dose in Part 2, on weeks 4, 8 and 12---Arm 1 8 mg/kg IV on weeks 4, 8 and 12 (Parts 1 and 2)--- Arm 2 Placebo IV on days 1 and 15 (Parts 1 and 2) + tocilizumab 2 mg/kg to 8mg/kg IV in Part 1 and selected dose in Part 2, on weeks 4, 8 and 12---Arm 1 8 mg/kg IV on weeks 4, 8 and 12 (Parts 1 and 2)--- Arm 2
Outcomes	**Primary outcome measures:** Proportion of patients with DAS ≤ 3.2 **Secondary outcome measures:** Proportion of patients in DAS-remission(< 2.6) Proportion of patients with a EULAR good or moderate response Change in DAS-ESR Change in CDAI, SDAI, SJC28, TJC28, HAQ, CRP, ESR
Starting date	March 2009
Contact information	Hoffmann-La Roche
Notes	A Study of Combination Treatment With MabThera (Rituximab) and RoActemra (Tocilizumab) Versus RoActemra in Patients With Rheumatoid Arthritis With an Incomplete Response to Methotrexate

RUMBA

Trial name or title	A Double-Blind, Randomized, Multicenter, Phase II Study of the Safety and Efficacy of Two Rituximab Regimens in Subjects With Moderate to Severe Active Rheumatoid Arthritis Receiving Stable Doses of Methotrexate
Methods	Phase II, randomized, double-blind, multicentre study to evaluate the safety and efficacy of rituximab, administered at two different regimens for 2 years
Participants	Subjects with moderate to severe active RA receiving stable doses of methotrexate, 18 years to 65 years, diagnosis of RA for at least 6 months
Interventions	Drug: rituximab versus placebo Concomitant treatment: methotrexate + folate
Outcomes	**Primary outcome measures:** Proportion of subjects with either an infection or a Grade III or IV adverse event (NCI CTCAE, Version 3.0) **Secondary outcome measures:** DAS28 4(CRP) (primary efficacy endpoint) ACR 20, ACR 50, and ACR 70 ACR major clinical response and/or remission EULAR response and remission using DAS28-4(CRP) Change from baseline in DAS28-4(CRP) Change from baseline in SF-36 summary and subscale scores

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RUMBA (*Continued*)

	Change from baseline in HAQ-DI Change from baseline in FACIT F DAS28-4(ESR) Change from baseline in RF/cyclic citrullinated peptide (CCP) antibodies/cytokines
Starting date	April 2006
Contact information	William Reiss, Pharm.D, Genentech
Notes	A study of the safety and efficacy of rituximab in patients with moderate to severe rheumatoid arthritis receiving methotrexate (RUMBA)

SCORE 2007

Trial name or title	A Randomized, Placebo Controlled, Multicenter Clinical Study Investigating Efficacy of Rituximab (Mabthera/Rituxan) in the Inhibition of Joint Structural Damage Assessed by Magnetic Resonance Imaging in Patients With Rheumatoid Arthritis and Inadequate Response to Methotrexate - the RA SCORE Study
Methods	This 3-arm study will assess the efficacy of MabThera in the prevention of progression of structural joint damage in patients with active rheumatoid arthritis who have an inadequate clinical response to methotrexate. Patients will be randomised to receive MabThera 1000 mg IV, MabThera 500 mg IV or placebo IV on days 1 and 15; all patients will receive concomitant methotrexate at a stable dosage of 12.5 to 25 mg/week throughout the study. Further courses of MabThera will be provided to eligible patients. Structural joint damage will be assessed by magnetic resonance imaging (MRI) at baseline, and at intervals during the study. The anticipated time on study treatment is 1 to 2 years, and the target sample size is 100 to 500 individuals
Participants	**Primary outcome measures:** Changes in MRI bone erosion score from baseline **Secondary outcome measures:** Change from baseline in MRI erosion, synovitis and osteitis DAS 28-CRP, ACR 20, 50, 70, and HAQ AEs, laboratory parameters, C-reactive protein, ESR
Interventions	3 study groups: i) rituximab (MabThera/Rituxan) 1000 mg IV on days 1 and 15 + methotrexate 12.5 to 25 mg/week; ii) rituximab (MabThera/Rituxan) 500 mg IV on days 1 and 15 + methotrexate 12.5 to 25 mg/week; iii) Placebo IV on days 1 and 15 + methotrexate 12.5 to 25 mg/week
Outcomes	**Primary outcome measures:** Changes in MRI bone erosion score from baseline **Secondary outcome measures:** Change from baseline in MRI erosion, synovitis and osteitis DAS 28-CRP, ACR 20, 50, 70, and HAQ AEs, laboratory parameters, C-reactive protein, ESR
Starting date	November 2007
Contact information	Hoffmann-La Roche
Notes	SCORE study: A study of MabThera (rituximab) in patients with rheumatoid arthritis and inadequate response to methotrexate

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DATA AND ANALYSES

Comparison 1. Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 24 weeks	4	1165	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.86, 2.69]
1.2 48-52 weeks	4	852	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.09, 2.13]
1.3 104 weeks	2	579	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.82, 3.01]
2 ACR 50	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 24 weeks	4	1165	Risk Ratio (M-H, Random, 95% CI)	3.25 [2.31, 4.58]
2.2 48-56 weeks	4	852	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.26, 3.95]
2.3 104 weeks	2	579	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.25, 1.77]
3 ACR 70	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 24 weeks	4	1165	Risk Ratio (M-H, Random, 95% CI)	3.91 [1.84, 8.31]
3.2 48-56 weeks	4	852	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.53, 2.49]
3.3 104 weeks	2	579	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.44, 2.37]
4 ACR 90	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.11, 2.96]
4.2 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.22, 2.68]
5 DAS 28	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 24 weeks	5	1661	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.48, -0.92]
5.2 48-56 weeks	1	499	Mean Difference (IV, Random, 95% CI)	-1.15 [-1.37, -0.93]
5.3 104 weeks	1	499	Mean Difference (IV, Random, 95% CI)	-1.59 [-1.81, -1.37]
6 LDA (DAS28 =or<3.2)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 24 weeks	2	834	Risk Ratio (M-H, Random, 95% CI)	4.23 [1.42, 12.56]
6.2 48-52 weeks	3	772	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.60, 2.73]
6.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.50, 2.48]
7 Clinical Remission (DAS28<2.6)	4		Risk Difference (M-H, Random, 95% CI)	Subtotals only
7.1 24 weeks	2	834	Risk Difference (M-H, Random, 95% CI)	0.08 [0.06, 0.11]
7.2 48-52 weeks	3	772	Risk Difference (M-H, Random, 95% CI)	0.11 [0.02, 0.20]
7.3 104 weeks	1	499	Risk Difference (M-H, Random, 95% CI)	0.19 [0.12, 0.26]
8 Moderate or good EULAR response	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 24 weeks	5	1664	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.55, 2.43]
8.2 48 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	2.32 [1.72, 3.14]
8.3 104 weeks	2	579	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.59, 2.64]
9 HAQ-DI	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	4	1318	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.30, -0.18]
9.2 48-52 weeks	2	562	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.38, -0.20]
9.3 72 weeks	1	43	Mean Difference (IV, Fixed, 95% CI)	-0.3 [-0.64, 0.04]
9.4 104 weeks	1	499	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.54, -0.34]
10 HAQ-DI MCID=-0.22	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 24 weeks	4	1161	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.22, 2.12]
10.2 48-56 weeks	2	562	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.71, 3.44]
10.3 72 weeks	1	43	Risk Ratio (M-H, Random, 95% CI)	2.32 [0.78, 6.89]
10.4 104 weeks	2	523	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.25, 1.55]
11 SF-36 PCS	4	1393	Mean Difference (IV, Fixed, 95% CI)	-4.11 [-4.98, -3.25]

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11.1 24 weeks	3	912	Mean Difference (IV, Fixed, 95% CI)	-4.44 [-5.52, -3.36]
11.2 52 weeks	1	481	Mean Difference (IV, Fixed, 95% CI)	-3.53 [-4.97, -2.09]
12 SF-36 PCS (=or>MCID of 5 or 5.42)	4	1526	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.14, 3.36]
12.1 24 weeks	3	1045	Risk Ratio (M-H, Random, 95% CI)	2.32 [1.41, 3.84]
12.2 52 weeks	1	481	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.07, 1.36]
13 SF-36 MCS	4	1393	Mean Difference (IV, Fixed, 95% CI)	-2.22 [-3.52, -0.92]
13.1 24 weeks	3	912	Mean Difference (IV, Fixed, 95% CI)	-2.44 [-4.05, -0.82]
13.2 52 weeks	1	481	Mean Difference (IV, Fixed, 95% CI)	-1.81 [-4.02, 0.39]
14 SF-36 MCS (=or>MCID of 5 or 6.33)	3	1282	Odds Ratio (M-H, Random, 95% CI)	1.75 [1.27, 2.42]
14.1 24 weeks	2	801	Odds Ratio (M-H, Random, 95% CI)	2.07 [1.50, 2.84]
14.2 52 weeks	1	481	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.97, 1.98]
15 FACIT-F	4	1570	Mean Difference (IV, Random, 95% CI)	-5.22 [-7.71, -2.74]
15.1 24 weeks	3	1081	Mean Difference (IV, Random, 95% CI)	-5.84 [-8.81, -2.88]
15.2 52 weeks	1	489	Mean Difference (IV, Random, 95% CI)	-3.45 [-5.33, -1.57]
16 FACIT-F MCID>= 4or 3.56	3	1232	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.00, 2.53]
16.1 24 weeks	2	743	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.65, 2.30]
16.2 52 weeks	1	489	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.99, 1.24]
17 VAS-pain	3	1238	Mean Difference (IV, Random, 95% CI)	-13.89 [-21.31, -6.48]
17.1 24 weeks	2	743	Mean Difference (IV, Random, 95% CI)	-14.57 [-27.37, -1.77]
17.2 52 weeks	1	495	Mean Difference (IV, Random, 95% CI)	-12.2 [-16.87, -7.53]
18 Total radiographic score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 24 weeks	2	975	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.83, -0.13]
18.2 48-56 weeks	2	932	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-1.29, -0.45]
18.3 104 weeks	2	945	Mean Difference (IV, Fixed, 95% CI)	-1.57 [-1.99, -1.16]
19 Joint Space Narrowing	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 24 weeks	2	975	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.35, -0.04]
19.2 48-56 weeks	1	456	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-0.98, -0.18]
19.3 104 weeks	2	944	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.67, -0.29]
20 Radiologic erosions	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 24 weeks	2	975	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.55, -0.11]
20.2 48-56 weeks	2	932	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.83, -0.30]
20.3 104 weeks	2	945	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-1.35, -0.83]
21 No radiographic progression	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 24 weeks	1	476	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [1.03, 1.35]
21.2 52-56 weeks	2	940	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.11, 1.40]
21.3 104 weeks	2	945	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.30, 1.73]
22 No worsening of erosions	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 24 weeks	1	445	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.95, 1.27]
22.2 52-56 weeks	1	464	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.09, 1.52]
22.3 104 weeks	2	945	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.27, 1.67]

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Comparison 2. Benefits - RTX monotherapy versus MTX monotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 48 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 104 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 ACR 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 48-56 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 104 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 ACR 70	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 48-56 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 104 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 DAS 28	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.9 [-1.47, -0.33]
5 Moderate or good EULAR response	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.7 [1.21, 2.38]
6 HAQ-DI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.4 [-0.65, -0.15]
6.2 48 weeks	1	56	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.49, 0.09]
6.3 72 weeks	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.3 [-0.68, 0.08]
7 % of patients achieving HAQ-DI MCID=-0.25	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	75	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.99, 2.25]
7.2 48-56 weeks	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.71, 3.18]
7.3 72 weeks	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.21, 3.73]
7.4 104 weeks	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.13, 17.67]

Comparison 3. Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	3		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	2	584	Risk Difference (M-H, Fixed, 95% CI)	0.30 [0.22, 0.37]
1.2 48-52 weeks	2	598	Risk Difference (M-H, Fixed, 95% CI)	0.14 [0.07, 0.21]
1.3 104 weeks	1	498	Risk Difference (M-H, Fixed, 95% CI)	0.16 [0.08, 0.25]
2 ACR 50	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	2	584	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [1.85, 3.90]
2.2 48-52 weeks	2	598	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.23, 1.74]
2.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.19, 1.69]
3 ACR 70	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 24 weeks	2	584	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.14, 3.77]
3.2 48-52 weeks	2	598	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.71, 2.86]

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3.3 104 weeks	1	498	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.31, 2.20]
4 ACR 90	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 52 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 104 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 DAS 28	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	3	1079	Mean Difference (IV, Fixed, 95% CI)	-0.96 [-1.11, -0.81]
5.2 52 weeks	1	498	Mean Difference (IV, Fixed, 95% CI)	-0.99 [-1.21, -0.77]
5.3 104 weeks	1	498	Mean Difference (IV, Fixed, 95% CI)	-1.59 [-1.81, -1.37]
6 LDA (DAS28 =or<3.2)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	339	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [1.76, 7.93]
6.2 48-52 weeks	2	598	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.48, 2.56]
6.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.40, 2.33]
7 Clinical Remission (DAS28<2.6)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [1.36, 11.80]
7.2 48 weeks	2	598	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.40, 2.96]
7.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [1.84, 3.83]
8 Moderate or good EULAR response	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 24 weeks	3	1082	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.58, 2.17]
8.2 52 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.56, 2.86]
8.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.48, 2.52]
9 HAQ-DI	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	2	742	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.30, -0.14]
9.2 52 weeks	1	498	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.37, -0.18]
9.3 104 weeks	1	498	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.44, -0.24]
10 HAQ-DI MCID=-0.22	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 24 weeks	2	582	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.18, 2.11]
10.2 52 weeks	1	498	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.04, 1.22]
10.3 104 weeks	1	498	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.21, 1.52]
11 SF-36 PCS	3	1018	Mean Difference (IV, Fixed, 95% CI)	-3.52 [-4.49, -2.56]
11.1 24 weeks	2	543	Mean Difference (IV, Fixed, 95% CI)	-4.07 [-5.36, -2.78]
11.2 52 weeks	1	475	Mean Difference (IV, Fixed, 95% CI)	-2.84 [-4.29, -1.39]
12 SF-36 PCS (=or>MCID of 5 or 5.42)	3	1018	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.98, 2.39]
12.1 24 weeks	2	543	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.21, 2.80]
12.2 52 weeks	1	475	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.97, 1.26]
13 SF-36 MCS	3	1021	Mean Difference (IV, Fixed, 95% CI)	-1.81 [-3.25, -0.36]
13.1 24 weeks	2	546	Mean Difference (IV, Fixed, 95% CI)	-2.16 [-4.07, -0.25]
13.2 52 weeks	1	475	Mean Difference (IV, Fixed, 95% CI)	-1.33 [-3.55, 0.88]
14 SF-36 MCS (=or>MCID of 6.33)	2	774	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.87, 1.55]
14.1 24 weeks	1	299	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.03]
14.2 52 weeks	1	475	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.24]
15 FACIT-F	3	1063	Mean Difference (IV, Fixed, 95% CI)	-3.09 [-4.35, -1.83]
15.1 24 weeks	2	580	Mean Difference (IV, Fixed, 95% CI)	-3.54 [-5.23, -1.85]
15.2 52 weeks	1	483	Mean Difference (IV, Fixed, 95% CI)	-2.53 [-4.42, -0.64]
16 FACIT-F (= or > MCID of 3.5 or 4)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 24 weeks	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.18, 2.09]
17 VAS pain	2	739	Mean Difference (IV, Fixed, 95% CI)	-8.30 [-12.25, -4.35]
17.1 24 weeks	1	245	Mean Difference (IV, Fixed, 95% CI)	-8.1 [-14.96, -1.24]
17.2 52 weeks	1	494	Mean Difference (IV, Fixed, 95% CI)	-8.40 [-13.23, -3.57]

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18 Total radiographic score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 24 weeks	1	471	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.61, 0.37]
18.2 52 weeks	1	471	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.92, 0.06]
18.3 104 weeks	1	472	Mean Difference (IV, Fixed, 95% CI)	-1.19 [-1.68, -0.70]
19 Joint Space Narrowing	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 104 weeks	1	472	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.59, -0.15]
20 Radiologic erosions	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 52 weeks	1	471	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.59, 0.02]
20.2 104 weeks	1	472	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-1.13, -0.51]
21 No radiographic progression	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 24 weeks	1	472	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.07, 1.64]
22 No increase in erosion score	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 24 weeks	1	472	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.14, 1.70]

Comparison 4. Benefits - RTX (2 x 1000 mg) + CTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.30, 3.12]
1.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [1.22, 4.89]
1.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.31, 3.11]
2 ACR 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	3.32 [1.35, 8.13]
2.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	4.88 [1.14, 20.89]
2.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.26, 3.64]
3 ACR 70	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.63, 13.65]
3.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	8.79 [0.49, 158.07]
3.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.21, 4.55]
4 DAS 28	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	81	Mean Difference (IV, Fixed, 95% CI)	-1.3 [-1.89, -0.71]
5 Moderate or good EULAR response	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.22, 2.39]
6 HAQ-DI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	74	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.48, 0.08]
6.2 48 weeks	1	59	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.31, 0.31]
6.3 72 weeks	1	37	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.19, 0.59]
7 HAQ-DI MCID=-0.22	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.83, 2.01]
7.2 48-56 weeks	1	59	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.64, 2.92]
7.3 72 weeks	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.32, 4.05]
7.4 104 weeks	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.05, 8.73]

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Comparison 5. Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.57, 5.77]
2 ACR 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.18, 11.75]
3 LDA (DAS28 =or<3.2)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.52, 9.20]
4 Clinical Remission (DAS28<2.6)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	3.27 [0.43, 25.11]
5 HAQ-DI MCID=-0.25	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	3.82 [1.59, 9.17]

Comparison 6. Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total discontinuations	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 24 weeks	4	1282	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.32, 0.50]
1.2 48-52 weeks	4	1444	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.40, 0.91]
1.3 72 weeks	1	80	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.28, 0.82]
1.4 104 weeks	2	579	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.45, 0.75]
2 Lack of efficacy	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	4	1282	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.23, 0.39]
2.2 48-52 weeks	3	927	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.06, 0.36]
2.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.15, 1.33]
2.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.09, 0.64]
3 Adverse Events	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	4	1282	Risk Ratio (M-H, Fixed, 95% CI)	2.72 [1.04, 7.13]
3.2 48-52 weeks	3	927	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.44, 2.29]
3.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.07]
3.4 104 weeks	2	579	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.25, 1.25]
4 Other reasons	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	4	1282	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.32, 1.81]
4.2 48-52 weeks	3	927	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.47, 1.49]
4.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.24, 1.21]
4.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.74, 2.32]

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Comparison 7. Withdrawals - RTX monotherapy versus MTX monotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total discontinuations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.78]
1.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.30, 1.21]
1.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.32]
1.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.25]
2 Lack of efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.04]
2.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.29]
2.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.10, 1.14]
2.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.72]
3 Adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.18]
3.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.32, 5.58]
3.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.43, 6.51]
3.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.36, 4.32]
4 Other reasons	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.15, 2.34]
4.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.63, 2.10]
4.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [1.21, 3.30]

Comparison 8. Withdrawals - RTX (2 x 500 mg) + MTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total discontinuations	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	2	613	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.18, 0.50]
1.2 48-52 weeks	2	844	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.43, 0.94]
1.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.36, 0.73]
2 Lack of efficacy	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	2	613	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.10, 0.39]
2.2 48-52 weeks	2	844	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.19, 0.73]
3 Adverse Events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	2	613	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [0.56, 10.36]
3.2 48-52 weeks	2	844	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.27, 2.16]
3.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.37, 1.89]
4 Other reasons	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 24 weeks	2	613	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.05, 2.99]
4.2 48-52 weeks	2	844	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.54, 1.87]

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Comparison 9. Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total discontinuations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.31, 5.45]
1.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.21, 1.00]
1.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.49, 1.11]
1.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.13]
2 Lack of efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 3.94]
2.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.06, 1.26]
2.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.30]
2.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.08, 0.62]
3 Adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 20.68]
3.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.11, 3.69]
3.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.31, 5.45]
3.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.26, 3.64]
4 Other reasons	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	4.88 [0.24, 98.60]
4.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.15, 2.29]
4.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.42, 1.62]
4.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.13, 3.12]

Comparison 10. Withdrawals - RTX + MTX + TNFi versus MTX + TNFi

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total discontinuations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.13, 50.83]
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.13, 50.83]

Comparison 11. Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any Adverse Event	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 24 weeks	4	1280	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.95, 1.18]
1.2 48-56 weeks	2	579	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.07]
1.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.08]
2 Serious Adverse Events	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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2.1 24 weeks	4	1280	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.69, 1.49]
2.2 48-56 weeks	2	579	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.57, 1.53]
2.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.51, 1.19]
3 Infections	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 24 weeks	2	683	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.68, 1.48]
3.2 52 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.88, 1.24]
3.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.95, 1.26]
4 Serious infections	4	1841	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.42, 1.10]
4.1 24 weeks	3	763	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.27, 2.25]
4.2 48-56 weeks	2	579	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.31, 1.59]
4.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.31, 1.27]
5 Death	5		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	4	1280	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.01]
5.2 52 weeks	1	499	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.00]
5.3 104 weeks	1	499	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.02, 0.01]
6 Arthralgia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	3	938	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.76, 2.34]
7 Cardiac event (any)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [0.72, 9.98]
8 Cardiac event (serious)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	7.03 [0.36, 135.36]
9 Cough	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 24 weeks	2	597	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.17, 6.49]
10 Diarrhea	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 24 weeks	2	858	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.22]
11 Exacerbation of RA	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 24 weeks	3	938	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.37, 0.58]
11.2 48-56 weeks	2	579	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.18, 22.00]
12 Fatigue	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 24 weeks	2	858	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.59, 1.79]
13 HACA	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 24 weeks	3	1200	Risk Ratio (M-H, Random, 95% CI)	3.17 [0.76, 13.25]
14 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 24 weeks	2	858	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.60, 1.34]
15 Hypertension	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 24 weeks	3	938	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.96, 2.61]
16 Infusion-related reactions (1st course -1st infusion)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 24 weeks	4	1280	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.29, 1.96]
16.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.98, 2.27]
16.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.97, 2.25]
17 Infusion-related reaction (1st course -2nd infusion)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 24 weeks	2	761	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.52, 1.22]
18 Infusion-related reaction (2nd course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.62, 1.97]
18.2 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.56, 1.78]
19 Infusion-related reaction (3rd course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.49, 3.41]
19.2 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.53, 2.72]

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20 Infusion-related reaction (4th course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.32, 1.99]
21 Infusion-related reaction (5th course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.25, 8.86]
22 Lower gastrointestinal events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 24 weeks	2	683	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.43, 1.26]
23 Malignancy	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 24 weeks	3	1175	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.16, 4.63]
23.2 48-56 weeks	2	579	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.71]
23.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.11, 1.63]
24 Nasopharyngitis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 24 weeks	3	938	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.66, 1.74]
25 Nausea	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 24 weeks	3	938	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.52, 1.43]
26 Pyrexia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 24 weeks	1	517	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.60, 3.50]
27 Upper respiratory tract infection	2	1016	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.60, 1.97]
27.1 24 weeks	1	517	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.62, 2.20]
27.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 3.97]
28 Urinary tract infection	3	1357	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.29, 1.28]
28.1 24 weeks	2	858	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.27, 1.56]
28.2 52 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.16]
29 Vascular disorders	4	1262	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.00, 2.38]
29.1 24 weeks	3	763	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.03, 3.51]
29.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.67, 2.29]

Comparison 12. Harms - RTX monotherapy versus MTX monotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any Adverse Event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.80, 1.24]
1.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.25]
2 Serious Adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.78]
2.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.27, 3.72]
3 Serious Infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.18]
3.2 48-56 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.51]
4 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.51]
5 Any Event Associated with 1st Infusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.84, 2.69]
6 Arthralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.66]

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7 Back pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.39, 10.31]
8 Cough	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 24 weeks	1	80	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.22 [1.36, 49.69]
9 Dyspnea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.50, 161.86]
10 Exacerbation of RA	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.16, 0.86]
10.2 48-56 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.51]
11 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.35, 2.84]
12 Hypotension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.75, 3.90]
13 Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.20, 2.18]
14 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.18]
15 Rash	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.47, 34.24]

Comparison 13. Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any Adverse Event	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.99, 1.18]
1.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.85, 1.02]
1.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.89, 1.03]
2 Serious Adverse Events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 24 weeks	2	612	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.16, 6.45]
2.2 52 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.52, 1.51]
2.3 104 weeks	1	498	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.32]
3 Infections	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.29]
3.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.86, 1.22]
3.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.97, 1.27]
4 Serious Infections	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.04, 1.47]
4.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.18, 1.20]
4.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.35, 1.35]
5 Death	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	3.33 [0.35, 31.82]
5.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.76]
5.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 3.96]
6 Arthralgia	1	273	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.36, 4.06]
6.1 24 weeks	1	273	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.36, 4.06]
7 Cardiac event (any)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.20, 4.93]
8 Cardiac event (serious)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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8.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	5.02 [0.24, 104.04]
9 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	1	273	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.39, 2.82]
10 Exacerbation of RA	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.36, 0.89]
10.1 MTX vs RTX 500 mg + MTX	1	273	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.36, 0.91]
10.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.18]
11 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 24 weeks	1	273	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.25, 2.24]
12 HACA	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.17, 6.40]
13 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 24 weeks	1	273	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.46, 1.69]
14 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 24 weeks	1	273	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.41, 5.47]
15 Infusion-related reactions (1st course - 1st infusion)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 24 weeks	2	584	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.46, 1.36]
15.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.72, 1.78]
15.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.72, 1.77]
16 Infusion related reaction (1st course -2nd infusion)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.10, 2.09]
17 Infusion related reaction (2nd course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.52, 1.74]
17.2 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.53, 1.71]
18 Infusion related reaction (3rd course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.37]
18.2 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.48, 2.54]
19 Infusion related reaction (4th course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.42, 2.36]
20 Infusion related reaction (5th course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.48]
21 Lower gastrointestinal events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.52, 1.50]
22 Malignancy	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.06, 16.33]
22.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.05]
22.3 104 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.29, 2.51]
23 Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 24 weeks	1	273	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.39, 2.82]
24 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 24 weeks	1	273	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.32, 1.73]
25 Upper respiratory tract infection	2	772	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.49, 2.35]
25.1 24 weeks	1	273	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.56, 3.18]
25.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.20]
26 Vascular disorders	3	1111	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.74, 2.09]

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26.1 24 weeks	2	612	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.62, 3.74]
26.2 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.60, 2.11]

Comparison 14. Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any Adverse Event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.16]
1.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.20]
2 Serious Adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.52, 7.27]
2.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.54, 5.38]
3 Serious Infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 20.68]
3.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Death	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	81	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
5 Any Event Associated with 1st Infusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.55, 2.03]
6 Arthralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.00]
7 Back pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.26, 8.30]
8 Cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 69.83]
9 Dyspnea	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	1	81	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
10 Exacerbation of RA	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.16, 0.84]
10.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.13, 1.82]
12 Hypotension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.73, 3.81]
13 Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.52]
14 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [0.46, 33.42]
15 Pruritus	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	8.79 [0.49, 158.07]
16 Rash	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [0.46, 33.42]
16.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Comparison 15. Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any Adverse Event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.90, 1.41]
2 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [0.14, 55.23]
3 Grade 3 adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	6.15 [0.36, 105.22]
4 All infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.55, 1.45]
5 Grade 3 infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	3.91 [0.21, 71.77]
6 Serious infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.07, 39.16]
7 Any Event Associated with 1st infusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	5.45 [0.76, 39.26]
8 Any Event Associated with 2nd infusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.15, 4.45]
9 Arthralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.15, 4.45]
10 Coronary artery occlusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.07, 39.16]
11 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.18, 14.61]
12 Exacerbation of RA	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.18, 2.90]
13 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [0.29, 88.46]
14 HACA	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.07, 39.16]
15 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.15, 4.45]
16 Influenza	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.07, 39.16]
17 Muscle spasms	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.03, 2.81]
18 Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.11, 11.22]
19 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.29, 6.34]
20 Peripheral edema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.15, 4.45]
21 Pneumonia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.07, 39.16]
22 Postoperative infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.07, 39.16]
23 Pruritus	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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23.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [0.29, 88.46]
24 Sinusitits	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.12, 2.43]
25 Upper respiratory tract infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.23, 1.85]
26 Urinary tract infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.11, 11.22]
27 Vaginal Mycosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 24 weeks	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.11, 11.22]

Comparison 16. Disease duration (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 = or < 4 years	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.30, 1.84]
1.2 > 4 years	4	1165	Risk Ratio (M-H, Fixed, 95% CI)	3.41 [2.52, 4.63]

Comparison 17. Previous treatment (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Methotrexate-naive	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.30, 1.84]
1.2 DMARDs failure	2	422	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [1.86, 4.63]
1.3 DMARD and TNFi failure	2	743	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [2.51, 5.66]

Comparison 18. Study quality (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low risk of bias	2	579	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.96, 4.26]
1.2 High risk of bias	3	1085	Risk Ratio (M-H, Random, 95% CI)	3.27 [2.10, 5.09]

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Comparison 19. Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 24 weeks	3	809	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.87, 1.26]
1.2 48-52 weeks	4	1218	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.96, 1.11]
1.3 104 weeks	1	436	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.02]
2 ACR 50	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	2	582	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.77, 1.28]
2.2 48-56 weeks	4	1218	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.97, 1.21]
2.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.91, 1.20]
3 ACR 70	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	2	582	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.85, 2.04]
3.2 48-56 weeks	4	1218	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.91, 1.28]
3.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.90, 1.34]
4 ACR 90	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 52 weeks	1	500	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.65, 1.41]
4.2 104 weeks	1	500	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.82, 1.59]
5 DAS 28-ESR	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	3	1081	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.22, 0.09]
5.2 48-56 weeks	3	1063	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.29, 0.02]
5.3 104 weeks	1	499	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.23, 0.23]
6 LDA (DAS28 =or<3.2)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	335	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.20]
6.2 48 weeks	4	1215	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.31]
6.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.29]
7 Clinical Remission (DAS28<2.6)	4	2049	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.87, 1.39]
7.1 24 weeks	1	335	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.51, 1.90]
7.2 48-52 weeks	4	1215	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.85, 1.78]
7.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.20]
8 Moderate or good EULAR response	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 24 weeks	3	1082	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.05]
8.2 48-52 weeks	3	1063	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.28]
8.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.90, 1.31]
9 HAQ-DI	3	1969	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.17, 0.11]
9.1 24 weeks	2	744	Mean Difference (IV, Random, 95% CI)	0.09 [-0.13, 0.30]
9.2 48-52 weeks	2	726	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.13, 0.05]
9.3 104 weeks	1	499	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.31, -0.09]
10 HAQ-DI MCID=-0.22	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 24 weeks	2	580	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.18]
10.2 48-56 weeks	3	1061	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.05]
10.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.95, 1.10]
11 SF-36 PCS	4	1167	Mean Difference (IV, Fixed, 95% CI)	0.53 [-0.49, 1.54]
11.1 24 weeks	2	545	Mean Difference (IV, Fixed, 95% CI)	0.02 [-1.39, 1.44]
11.2 48-52 weeks	2	622	Mean Difference (IV, Fixed, 95% CI)	1.05 [-0.39, 2.49]
12 SF-36 PCS (=or>MCID of 5 or 5.42)	4	1287	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.97, 1.16]
12.1 24 weeks	2	582	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.85, 1.19]
12.2 48-52 weeks	2	705	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.99, 1.21]

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13 SF-36 MCS	4	1167	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-1.42, 1.38]
13.1 24 weeks	2	545	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-2.21, 2.06]
13.2 48-52 weeks	2	622	Mean Difference (IV, Fixed, 95% CI)	0.02 [-1.83, 1.88]
14 SF-36 MCS (=or>MCID of 6.33)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 48-52 weeks	2	705	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.92, 1.23]
15 FACIT-F	4	1218	Mean Difference (IV, Fixed, 95% CI)	1.04 [-0.11, 2.18]
15.1 24 weeks	2	578	Mean Difference (IV, Fixed, 95% CI)	0.83 [-0.87, 2.53]
15.2 48-54 weeks	2	640	Mean Difference (IV, Fixed, 95% CI)	1.21 [-0.34, 2.77]
16 FACIT-F (=or>MCID of 3.5)	2	461	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.03, 1.38]
16.1 24 weeks	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.97, 1.46]
16.2 48 weeks	1	216	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.98, 1.47]
17 VAS Pain	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 52 weeks	2	671	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-6.62, 2.02]
18 Total radiographic score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 24 weeks	1	483	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.09, 0.59]
18.2 52 weeks	1	483	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.05, 0.63]
18.3 104 weeks	1	483	Mean Difference (IV, Fixed, 95% CI)	0.35 [0.01, 0.69]
19 Joint space narrowing	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 24 weeks	1	480	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.07, 0.21]
19.2 104 weeks	1	483	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.06, 0.22]
20 Radiographic erosions	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 24 weeks	1	480	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.05, 0.41]
20.2 52 weeks	1	483	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.01, 0.45]
20.3 104 weeks	1	483	Mean Difference (IV, Fixed, 95% CI)	0.27 [0.04, 0.50]
21 No radiographic progression	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 24 weeks	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.97, 1.25]
21.2 52 weeks	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.95, 1.27]
21.3 104 weeks	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.98, 1.38]
22 No worsening of erosions	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 104 weeks	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.95, 1.30]
23 Total discontinuations	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 24 weeks	2	656	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.79, 2.47]
23.2 48-52 weeks	3	1093	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.34, 1.58]
23.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.65, 1.52]
24 Discontinuation due to lack of efficacy	4	1749	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.41, 1.29]
24.1 24 weeks	2	656	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.53, 2.53]
24.2 48-52 weeks	3	1093	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.03]
25 Discontinuations due to adverse Events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 24 weeks	2	656	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.46, 4.00]
25.2 48-52 weeks	3	1093	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.25, 3.45]
25.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.32, 1.99]
26 Discontinuations due to other reasons	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 24 weeks	2	656	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.55, 7.30]
26.2 48-52 weeks	3	1693	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.68, 1.99]
27 Any Adverse Event	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 24 weeks	2	653	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.11]
27.2 48-52 weeks	3	1062	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.06]
27.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.13]

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28 Serious Adverse Events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
28.1 24 weeks	2	653	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.57, 3.82]
28.2 48-52 weeks	3	1062	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.87, 1.77]
28.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.57, 1.37]
29 Infections	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
29.1 24 weeks	2	653	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.13]
29.2 48-52 weeks	3	1062	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.17]
29.3 104 weeks	1	499	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]
30 Serious Infections	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 24 weeks	2	653	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.38, 5.86]
30.2 48-56 weeks	3	1062	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.50, 2.34]
30.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.43, 1.98]
31 Death	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 24 weeks	2	653	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 5.26]
31.2 48-52 weeks	3	1062	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.06]
31.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.46]
32 Arthralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 24 weeks	1	316	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.51, 3.99]
33 Cardiac event (any)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 24 weeks	1	337	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.45, 4.25]
33.2 48-52 weeks	2	835	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.68, 3.06]
34 Cardiac event (Serious)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.1 24 weeks	1	337	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.04, 5.37]
34.2 48-52 weeks	2	835	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.25, 3.94]
35 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 24 weeks	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.19, 1.61]
36 Exacerbation of RA	2	814	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.55, 1.51]
36.1 24 weeks	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.49, 1.40]
36.2 52 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 103.62]
37 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 24 weeks	1	316	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.35, 3.09]
38 HACA	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 24 weeks	2	543	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.20, 1.38]
39 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
39.1 24 weeks	1	316	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.56, 4.29]
40 Infusion-related reactions (1st course -1st infusion)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
40.1 24 weeks	2	653	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.02, 1.78]
40.2 48-56 weeks	3	1062	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.33]
40.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.87, 1.96]
41 Infusion-related reaction (1st course -2nd infusion)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
41.1 24 weeks	2	582	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.59, 1.85]
42 Infusion-related reaction (2nd course)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
42.1 48-52 weeks	3	1062	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.79, 1.70]
42.2 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.58, 1.88]
43 Infusion-related reaction (3rd course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
43.1 52 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [0.98, 20.62]
43.2 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.49, 2.42]

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44 Infusion-related reaction (4th course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
44.1 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.32, 1.99]
45 Infusion-related reaction (5th course)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
45.1 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [0.31, 28.53]
46 Lower gastrointestinal events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
46.1 24 weeks	1	337	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.51, 1.90]
46.2 48 weeks	1	337	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.65, 1.94]
47 Malignancy	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
47.1 24 weeks	1	337	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [0.18, 21.46]
47.2 48-52 weeks	3	1062	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.27, 4.31]
47.3 104 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.13, 1.97]
48 Pneumonia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
48.1 52 weeks	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.14]
49 Urinary tract infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
49.1 52 weeks	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.16]
50 Vascular disorders	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
50.1 24 weeks	1	337	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.39, 3.34]
50.2 48-52 weeks	2	835	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.59, 1.57]

Comparison 20. Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.35]
1.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.49, 1.06]
1.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.15, 0.96]
2 ACR 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.58, 1.63]
2.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.40, 1.48]
2.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.16, 1.49]
3 ACR 70	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.25, 1.66]
3.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.20, 2.13]
3.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.17, 3.06]
4 DAS 28	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	81	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.61, 0.61]
5 Moderate or good EULAR response	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.85, 1.25]
6 HAQ-DI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	76	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.29, 0.29]
6.2 48 weeks	1	72	Mean Difference (IV, Fixed, 95% CI)	0.3 [0.01, 0.59]
6.3 72 weeks	1	50	Mean Difference (IV, Fixed, 95% CI)	0.5 [0.15, 0.85]
7 HAQ-DI MCID=-0.22	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.65, 1.32]
7.2 48 weeks	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.90]

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7.3 72 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.21, 1.17]
7.4 104 weeks	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.05, 2.93]
8 Total discontinuations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [0.46, 33.42]
8.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	3.41 [0.75, 15.46]
8.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.87, 2.75]
8.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.03, 1.96]
9 Withdrawals due to lack of efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 20.68]
9.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.26, 3.64]
9.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.26, 3.64]
10 Withdrawals due to adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 20.68]
10.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 20.68]
10.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [0.46, 33.42]
10.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [0.46, 33.42]
11 Withdrawals due to other reasons	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	4.88 [0.24, 98.60]
11.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	6.83 [0.36, 128.20]
11.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.66, 3.56]
11.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.93, 2.22]
12 Any Adverse Event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.08]
12.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.16]
13 Serious Adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.52, 7.27]
13.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.54, 5.38]
14 Serious Infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	4.88 [0.24, 98.60]
14.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.76]
15 Exacerbation of RA	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.63, 13.65]
15.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Death	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
16.1 24 weeks	1	81	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
17 Any Event Associated with 1st Infusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.52, 1.84]
18 Arthralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 2.09]
19 Back pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	6.83 [0.36, 128.20]
20 Cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.05, 5.17]
21 Dyspnea	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
21.1 24 weeks	1	81	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
22 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.09, 0.99]

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23 Hypotension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 24 weeks	1	82	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.75, 3.91]
24 Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.52]
25 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	8.79 [0.49, 158.07]
26 Pruritus	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	8.79 [0.49, 158.07]
27 Rash	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [0.46, 33.42]
27.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 21. Concomitant treatment MTX versus none (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.83, 1.50]
1.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [1.21, 3.30]
1.3 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [1.34, 14.05]
2 ACR 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.74, 2.32]
2.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [1.00, 5.46]
2.3 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.76, 9.33]
3 ACR 70	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.59, 3.82]
3.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.54, 7.45]
3.3 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.47, 34.24]
4 DAS 28	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 16-24 weeks	2	120	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.76, -0.36]
5 Moderate or good EULAR response	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 16-24 weeks	2	120	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.88, 1.23]
5.2 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.25 [1.16, 9.12]
6 HAQ-DI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	80	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.06, 0.46]
6.2 48 weeks	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.36, 0.16]
6.3 72 weeks	1	80	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.26, 0.26]
7 HAQ-DI MCID=-0.22	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.68, 1.29]
7.2 48 weeks	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.02, 2.60]
7.3 72 weeks	1	45	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [0.87, 7.91]
7.4 104 weeks	1	22	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.17, 7.09]
8 Total discontinuations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.30]
8.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 0.96]
8.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.90]
8.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.45, 0.82]

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9 Withdrawals due to lack of efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.30]
9.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.32, 5.58]
9.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.23, 2.76]
10 Withdrawals due to adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.30]
10.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.14]
10.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.02, 1.64]
10.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.02, 1.64]
11 Withdrawals due to other reasons	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
11.3 72 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.21, 1.02]
11.4 104 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.43, 1.00]
12 Any Adverse Event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.30]
12.2 48-56 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.14]
13 Serious Adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.26, 8.50]
13.2 48-56 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.27, 3.72]
14 Serious Infections	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 16-24 weeks	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.03]
14.2 48-56 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.44]
15 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.95]
16 Any Event Associated with 1st Infusion	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 16-24 weeks	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.47, 1.36]
17 Arthralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.32, 5.58]
18 Back pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.00]
19 Cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.08, 1.94]
20 Dyspnea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.00]
21 Exacerbation of RA	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.55]
21.2 48-56 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.95]
22 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.67, 4.15]
23 Hypotension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.26, 1.33]
24 Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.27, 3.72]
25 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.04]
26 Pruritus	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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26.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.00]
27 Rash	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.14]
27.2 48 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.95]

Comparison 22. Concomitant treatment CTX versus none (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.87, 1.55]
1.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.87, 2.59]
1.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.42, 6.36]
2 ACR 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.72, 2.27]
2.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.73, 4.37]
2.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.31, 5.45]
3 ACR 70	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.34, 2.77]
3.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.31, 5.45]
3.3 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.32, 26.97]
4 DAS 28	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	81	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.03, 0.23]
5 Moderate or good EULAR response	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.20]
6 HAQ-DI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	75	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.08, 0.48]
6.2 48 weeks	1	65	Mean Difference (IV, Fixed, 95% CI)	0.2 [-0.10, 0.50]
6.3 72 weeks	1	39	Mean Difference (IV, Fixed, 95% CI)	0.5 [0.12, 0.88]
7 HAQ-DI MCID=-0.22	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.62, 1.22]
7.2 48 weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.50, 1.65]
7.3 72 weeks	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.36, 4.65]
7.4 104 weeks	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.04, 5.46]
8 Total discontinuations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.38, 10.06]
8.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.31, 1.84]
8.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.53, 1.23]
8.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.05]
9 Withdrawals due to lack of efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.59]
9.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.31, 5.45]
9.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.23, 2.70]
10 Withdrawals due to adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.59]

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10.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.52]
10.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.23, 2.70]
10.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.23, 2.70]
11 Withdrawals due to other reasons	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	4.88 [0.24, 98.60]
11.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.21, 4.55]
11.3 72 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.36]
11.4 104 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.67, 1.31]
12 Any Adverse Event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.16]
12.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.12]
13 Serious Adverse Events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.63, 13.65]
13.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.54, 5.38]
14 Serious Infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.59]
14.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.76]
15 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.76]
16 Any Event Associated with 1st Infusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.40, 1.24]
17 Arthralgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.00]
18 Back pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.17, 3.06]
19 Cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.60]
20 Dyspnea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.95]
21 Exacerbation of RA	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.34, 2.77]
21.2 48-56 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.76]
22 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.13, 1.82]
23 Hypotension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.50, 1.91]
24 Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.52]
25 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 24 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.39, 10.31]
26 Rash	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 24 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.26, 3.64]
26.2 48 weeks	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.76]

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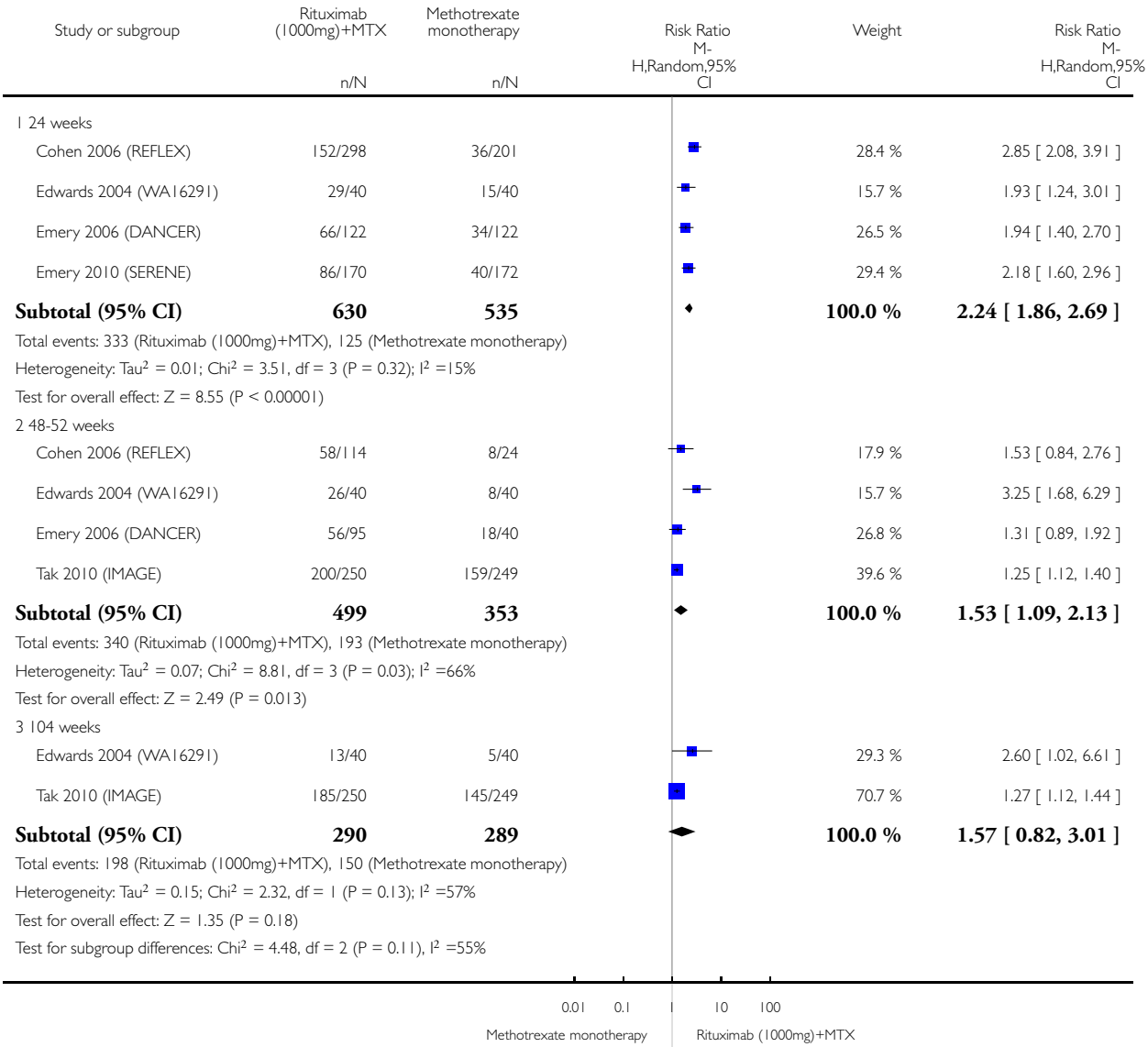
Analysis 1.1. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 1 ACR20.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 1 ACR20



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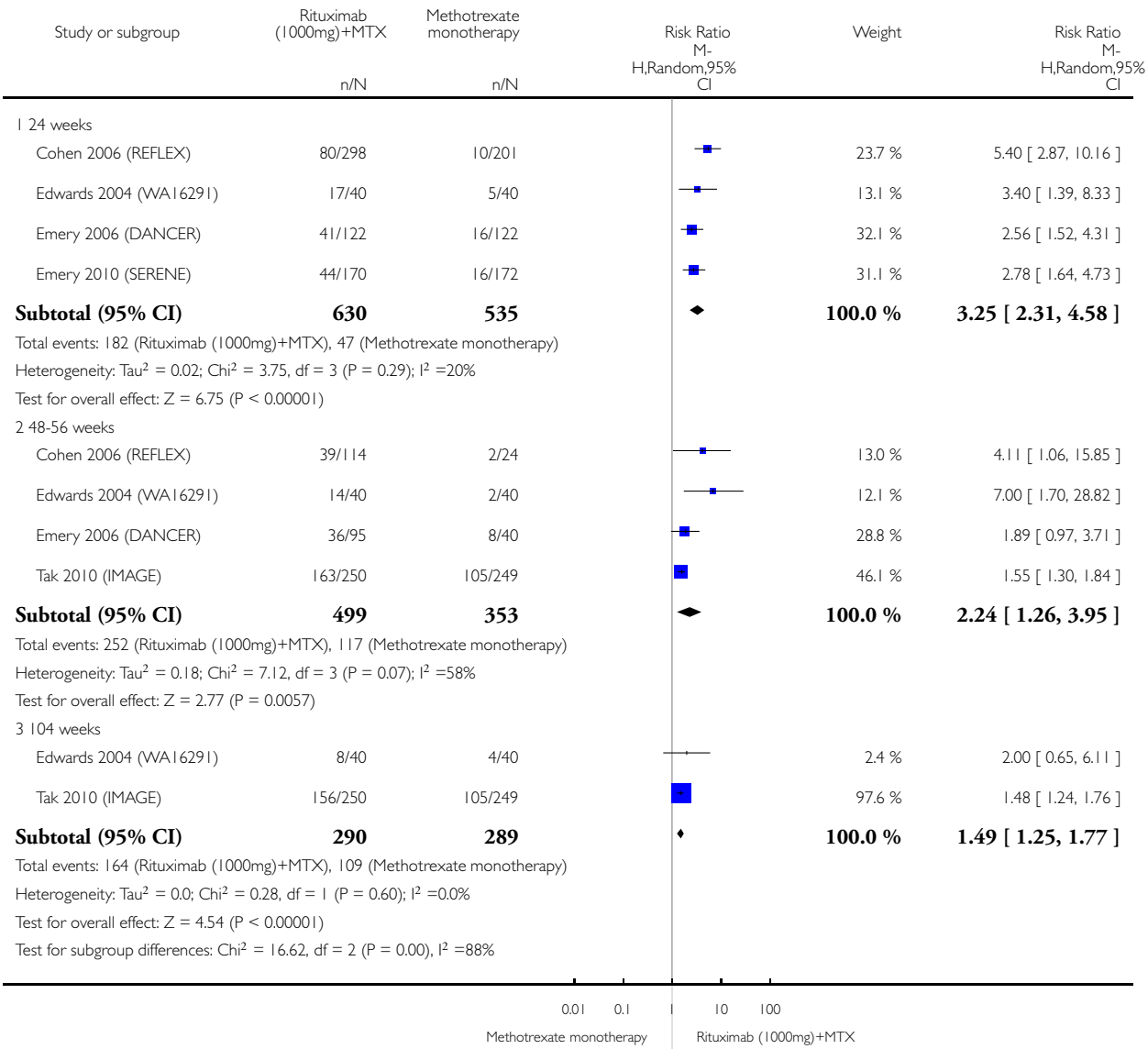
Analysis 1.2. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 2 ACR 50



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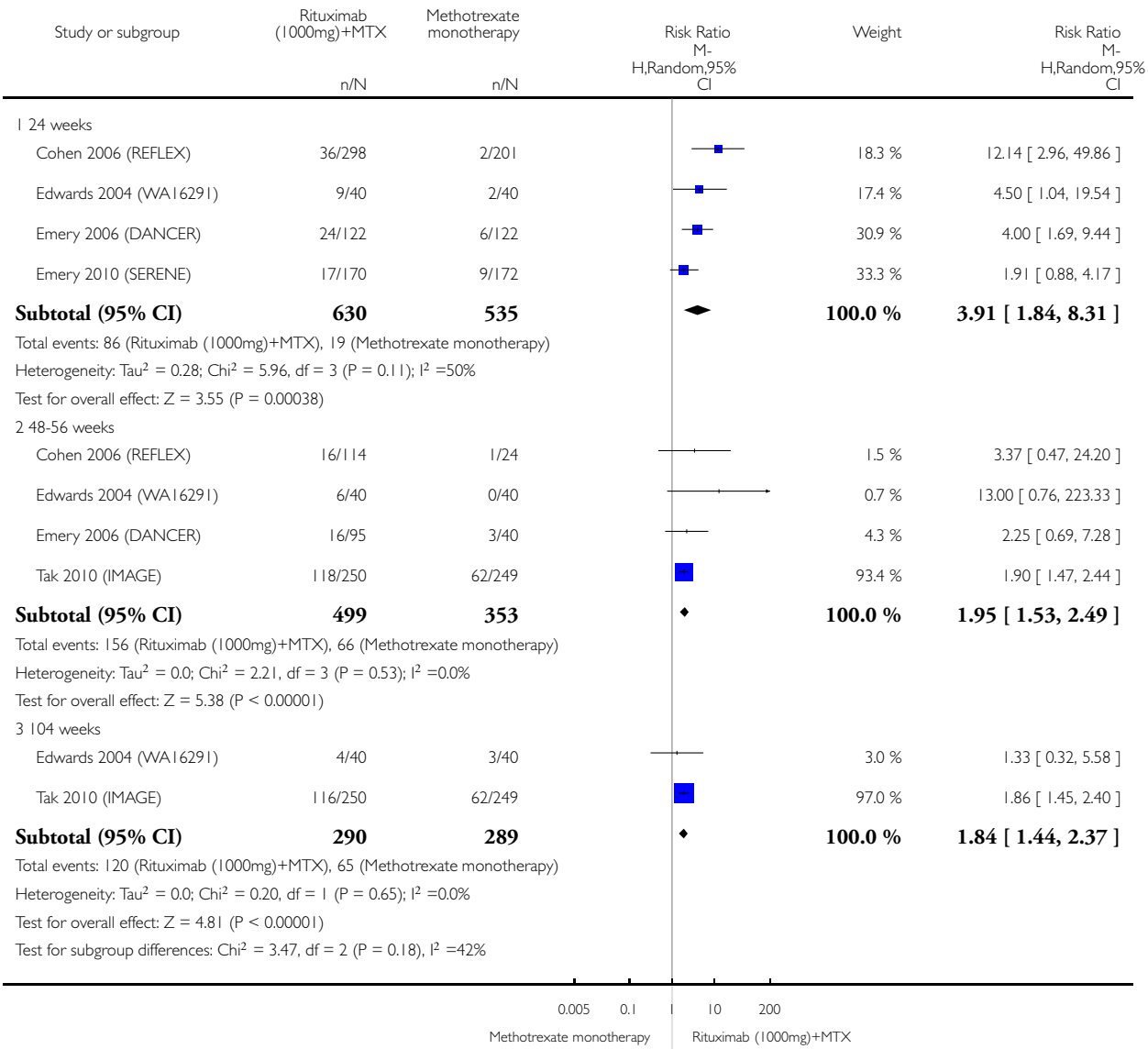
Analysis 1.3. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 3 ACR 70.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 3 ACR 70



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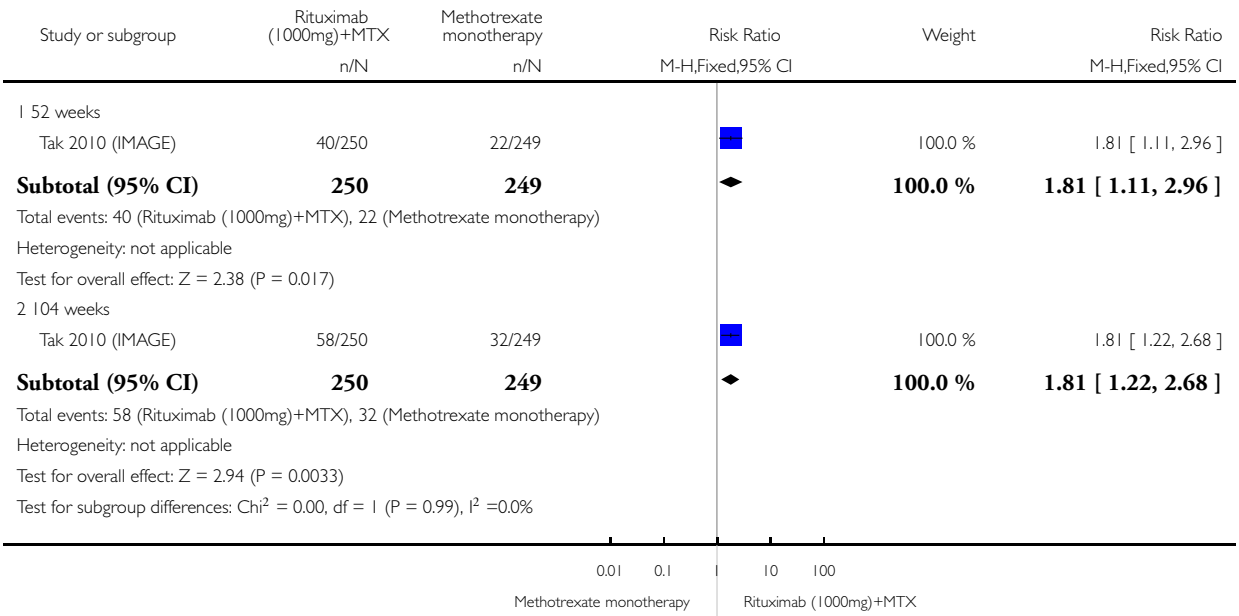
Analysis 1.4. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 4 ACR 90.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 4 ACR 90



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Analysis 1.5. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 5 DAS 28.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 5 DAS 28

Study or subgroup	Rituximab (1000mg)+MTX N	Mean(SD)	Methotrexate monotherapy N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 24 weeks							
Cohen 2006 (REFLEX)	298	-1.9 (0.967)	201	-0.4 (1.015)		22.7 %	-1.50 [-1.68, -1.32]
Edwards 2004 (WA16291)	40	-2.6 (1.3)	40	-1.3 (1.2)		12.7 %	-1.30 [-1.85, -0.75]
Emery 2006 (DANCER)	122	-2.05 (0.967)	122	-0.67 (1.015)		20.9 %	-1.38 [-1.63, -1.13]
Emery 2010 (SERENE)	168	-1.69 (0.967)	171	-0.75 (1.015)		21.9 %	-0.94 [-1.15, -0.73]
Tak 2010 (IMAGE)	250	-2.9 (1.3)	249	-2 (1.2)		21.7 %	-0.90 [-1.12, -0.68]
Subtotal (95% CI)	**878**		**783**			**100.0 %**	**-1.20 [-1.48, -0.92]**
Heterogeneity: Tau^2 = 0.08; Chi^2 = 26.02, df = 4 (P = 0.00003); I^2 =85%							
Test for overall effect: Z = 8.40 (P < 0.00001)							
2 48-56 weeks							
Tak 2010 (IMAGE)	250	-3.21 (1.3)	249	-2.06 (1.2)		100.0 %	-1.15 [-1.37, -0.93]
Subtotal (95% CI)	**250**		**249**			**100.0 %**	**-1.15 [-1.37, -0.93]**
Heterogeneity: not applicable							
Test for overall effect: Z = 10.27 (P < 0.00001)							
3 104 weeks							
Tak 2010 (IMAGE)	250	-3.79 (1.3)	249	-2.2 (1.2)		100.0 %	-1.59 [-1.81, -1.37]
Subtotal (95% CI)	**250**		**249**			**100.0 %**	**-1.59 [-1.81, -1.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 14.20 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 8.85, df = 2 (P = 0.01), I^2 =77%							

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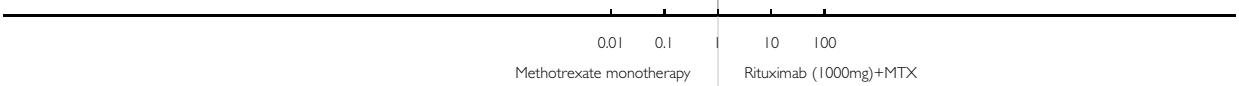
Analysis 1.6. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 6 LDA (DAS28 =or<3.2).

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 6 LDA (DAS28 =or<3.2)

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	45/298	4/201		45.8 %	7.59 [2.77, 20.77]
Emery 2010 (SERENE)	21/169	8/166		54.2 %	2.58 [1.18, 5.66]
Subtotal (95% CI)	**467**	**367**		**100.0 %**	**4.23 [1.42, 12.56]**
Total events: 66 (Rituximab (1000mg)+MTX), 12 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.41; Chi^2 = 2.93, df = 1 (P = 0.09); I^2 =66%					
Test for overall effect: Z = 2.60 (P = 0.0094)					
2 48-52 weeks					
Cohen 2006 (REFLEX)	27/114	2/24		3.8 %	2.84 [0.72, 11.15]
Emery 2006 (DANCER)	21/95	6/40		10.2 %	1.47 [0.64, 3.38]
Tak 2010 (IMAGE)	108/250	50/249		86.0 %	2.15 [1.62, 2.86]
Subtotal (95% CI)	**459**	**313**		**100.0 %**	**2.09 [1.60, 2.73]**
Total events: 156 (Rituximab (1000mg)+MTX), 58 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.92, df = 2 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 5.46 (P < 0.00001)					
3 104 weeks					
Tak 2010 (IMAGE)	120/250	62/249		100.0 %	1.93 [1.50, 2.48]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**1.93 [1.50, 2.48]**
Total events: 120 (Rituximab (1000mg)+MTX), 62 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.12 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.95, df = 2 (P = 0.38), I^2 =0.0%					



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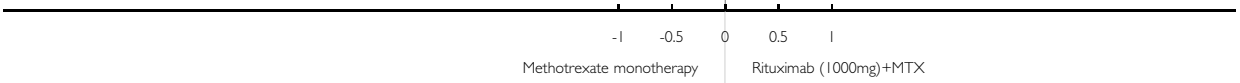
Analysis 1.7. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 7 Clinical Remission (DAS28<2.6).

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 7 Clinical Remission (DAS28<2.6)

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	27/298	0/201		69.0 %	0.09 [0.06, 0.12]
Emery 2010 (SERENE)	16/169	4/166		31.0 %	0.07 [0.02, 0.12]
Subtotal (95% CI)	**467**	**367**		**100.0 %**	**0.08 [0.06, 0.11]**
Total events: 43 (Rituximab (1000mg)+MTX), 4 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 5.95 (P < 0.00001)					
2 48-52 weeks					
Cohen 2006 (REFLEX)	14/114	1/24		30.5 %	0.08 [-0.02, 0.18]
Emery 2006 (DANCER)	10/95	2/40		32.4 %	0.06 [-0.04, 0.15]
Tak 2010 (IMAGE)	78/250	32/249		37.1 %	0.18 [0.11, 0.25]
Subtotal (95% CI)	**459**	**313**		**100.0 %**	**0.11 [0.02, 0.20]**
Total events: 102 (Rituximab (1000mg)+MTX), 35 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 6.87, df = 2 (P = 0.03); I^2 =71%					
Test for overall effect: Z = 2.33 (P = 0.020)					
3 104 weeks					
Tak 2010 (IMAGE)	80/250	32/249		100.0 %	0.19 [0.12, 0.26]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**0.19 [0.12, 0.26]**
Total events: 80 (Rituximab (1000mg)+MTX), 32 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.27 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 7.60, df = 2 (P = 0.02), I^2 =74%					



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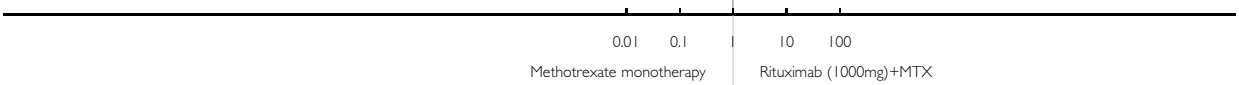
Analysis 1.8. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 8 Moderate or good EULAR response.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 8 Moderate or good EULAR response

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	194/298	44/201		20.8 %	2.97 [2.26, 3.91]
Edwards 2004 (WA16291)	33/40	20/40		17.8 %	1.65 [1.17, 2.32]
Emery 2006 (DANCER)	82/122	45/122		21.3 %	1.82 [1.40, 2.37]
Emery 2010 (SERENE)	107/170	58/172		22.4 %	1.87 [1.47, 2.37]
Tak 2010 (IMAGE)	66/250	42/249		17.7 %	1.57 [1.11, 2.21]
Subtotal (95% CI)	**880**	**784**		**100.0 %**	**1.94 [1.55, 2.43]**
Total events: 482 (Rituximab (1000mg)+MTX), 209 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 12.32, df = 4 (P = 0.02); I^2 =68%					
Test for overall effect: Z = 5.75 (P < 0.00001)					
2 48 weeks					
Tak 2010 (IMAGE)	105/250	45/249		100.0 %	2.32 [1.72, 3.14]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**2.32 [1.72, 3.14]**
Total events: 105 (Rituximab (1000mg)+MTX), 45 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.47 (P < 0.00001)					
3 104 weeks					
Edwards 2004 (WA16291)	13/40	5/40		7.4 %	2.60 [1.02, 6.61]
Tak 2010 (IMAGE)	115/250	57/249		92.6 %	2.01 [1.54, 2.62]
Subtotal (95% CI)	**290**	**289**		**100.0 %**	**2.05 [1.59, 2.64]**
Total events: 128 (Rituximab (1000mg)+MTX), 62 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.27, df = 1 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 5.52 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.88, df = 2 (P = 0.64), I^2 =0.0%					



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Analysis 1.9. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 9 HAQ-DI.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 9 HAQ-DI

Study or subgroup	Rituximab (1000mg)+MTX N	Mean(SD)	Methotrexate monotherapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Cohen 2006 (REFLEX)	298	-0.4 (0.6)	201	-0.1 (0.5)		37.1 %	-0.30 [-0.40, -0.20]
Edwards 2004 (WA16291)	39	-0.6 (0.6)	37	-0.4 (0.5)		5.7 %	-0.20 [-0.45, 0.05]
Emery 2006 (DANCER)	122	-0.49 (0.55)	122	-0.28 (0.5)		20.1 %	-0.21 [-0.34, -0.08]
Tak 2010 (IMAGE)	250	-0.8 (0.6)	249	-0.6 (0.5)		37.2 %	-0.20 [-0.30, -0.10]
Subtotal (95% CI)	**709**		**609**			**100.0 %**	**-0.24 [-0.30, -0.18]**
Heterogeneity: Chi^2 = 2.42, df = 3 (P = 0.49); I^2 =0.0%							
Test for overall effect: Z = 7.93 (P < 0.00001)							
2 48-52 weeks							
Edwards 2004 (WA16291)	38	-0.6 (0.6)	25	-0.3 (0.5)		11.2 %	-0.30 [-0.57, -0.03]
Tak 2010 (IMAGE)	250	-0.916 (0.6)	249	-0.63 (0.5)		88.8 %	-0.29 [-0.38, -0.19]
Subtotal (95% CI)	**288**		**274**			**100.0 %**	**-0.29 [-0.38, -0.20]**
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.94); I^2 =0.0%							
Test for overall effect: Z = 6.21 (P < 0.00001)							
3 72 weeks							
Edwards 2004 (WA16291)	28	-0.6 (0.6)	15	-0.3 (0.5)		100.0 %	-0.30 [-0.64, 0.04]
Subtotal (95% CI)	**28**		**15**			**100.0 %**	**-0.30 [-0.64, 0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.75 (P = 0.081)							
4 104 weeks							
Tak 2010 (IMAGE)	250	-1.2 (0.6)	249	-0.76 (0.5)		100.0 %	-0.44 [-0.54, -0.34]
Subtotal (95% CI)	**250**		**249**			**100.0 %**	**-0.44 [-0.54, -0.34]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.90 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 12.05, df = 3 (P = 0.01), I^2 =75%							

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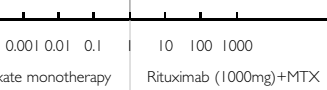
Analysis 1.10. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 10 HAQ-DI MCID=-0.22.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 10 HAQ-DI MCID=-0.22

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	190/298	65/201		27.7 %	1.97 [1.59, 2.45]
Edwards 2004 (WA16291)	25/39	17/37		18.7 %	1.40 [0.92, 2.13]
Emery 2006 (DANCER)	82/122	42/122		25.1 %	1.95 [1.48, 2.57]
Emery 2010 (SERENE)	99/170	82/172		28.4 %	1.22 [1.00, 1.49]
Subtotal (95% CI)	**629**	**532**		**100.0 %**	**1.61 [1.22, 2.12]**
Total events: 396 (Rituximab (1000mg)+MTX), 206 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 13.08, df = 3 (P = 0.004); I^2 =77%					
Test for overall effect: Z = 3.40 (P = 0.00067)					
2 48-56 weeks					
Edwards 2004 (WA16291)	26/38	7/25		41.5 %	2.44 [1.26, 4.75]
Tak 2010 (IMAGE)	220/250	192/249		58.5 %	1.14 [1.05, 1.24]
Subtotal (95% CI)	**288**	**274**		**100.0 %**	**1.57 [0.71, 3.44]**
Total events: 246 (Rituximab (1000mg)+MTX), 199 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.27; Chi^2 = 5.70, df = 1 (P = 0.02); I^2 =82%					
Test for overall effect: Z = 1.11 (P = 0.27)					
3 72 weeks					
Edwards 2004 (WA16291)	13/28	3/15		100.0 %	2.32 [0.78, 6.89]
Subtotal (95% CI)	**28**	**15**		**100.0 %**	**2.32 [0.78, 6.89]**
Total events: 13 (Rituximab (1000mg)+MTX), 3 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					
4 104 weeks					
Edwards 2004 (WA16291)	5/18	1/6		0.3 %	1.67 [0.24, 11.58]
Tak 2010 (IMAGE)	215/250	154/249		99.7 %	1.39 [1.25, 1.55]
Subtotal (95% CI)	**268**	**255**		**100.0 %**	**1.39 [1.25, 1.55]**
Total events: 220 (Rituximab (1000mg)+MTX), 155 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.03, df = 1 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 5.91 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.76, df = 3 (P = 0.62), I^2 =0.0%					



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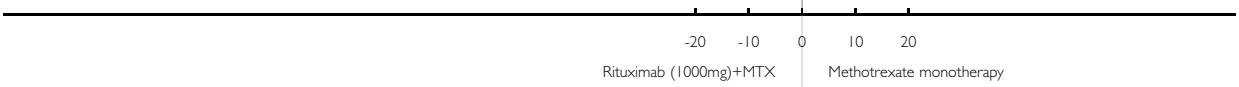
Analysis 1.11. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 11 SF-36 PCS.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 11 SF-36 PCS

Study or subgroup	Rituximab (1000mg)+MTX N	Mean(SD)	Methotrexate monotherapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Cohen 2006 (REFLEX)	258	-6.64 (8.74)	116	-1.48 (7.32)		25.6 %	-5.16 [-6.87, -3.45]
Emery 2006 (DANCER)	115	-7.4 (8.36)	121	-2.36 (8.58)		15.9 %	-5.04 [-7.20, -2.88]
Emery 2010 (SERENE)	155	-5.7 (8.74)	147	-2.49 (7.32)		22.6 %	-3.21 [-5.02, -1.40]
Subtotal (95% CI)	**528**		**384**			**64.1 %**	**-4.44 [-5.52, -3.36]**
Heterogeneity: Chi^2 = 2.74, df = 2 (P = 0.25); I^2 =27%							
Test for overall effect: Z = 8.08 (P < 0.00001)							
2 52 weeks							
Tak 2010 (IMAGE)	242	-10.763 (8.74)	239	-7.24 (7.32)		35.9 %	-3.53 [-4.97, -2.09]
Subtotal (95% CI)	**242**		**239**			**35.9 %**	**-3.53 [-4.97, -2.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.80 (P < 0.00001)							
Total (95% CI)	**770**		**623**			**100.0 %**	**-4.11 [-4.98, -3.25]**
Heterogeneity: Chi^2 = 3.74, df = 3 (P = 0.29); I^2 =20%							
Test for overall effect: Z = 9.34 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.00, df = 1 (P = 0.32), I^2 =0.0%							



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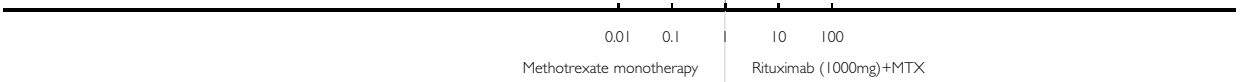
Analysis 1.12. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 12 SF-36 PCS (=or>MCID of 5 or 5.42).

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 12 SF-36 PCS (=or>MCID of 5 or 5.42)

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	148/298	27/201		24.0 %	3.70 [2.56, 5.35]
Emery 2006 (DANCER)	64/122	29/122		24.2 %	2.21 [1.54, 3.16]
Emery 2010 (SERENE)	75/155	45/147		25.1 %	1.58 [1.18, 2.12]
Subtotal (95% CI)	**575**	**470**		**73.3 %**	**2.32 [1.41, 3.84]**
Total events: 287 (Rituximab (1000mg)+MTX), 101 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 13.19, df = 2 (P = 0.001); I^2 =85%					
Test for overall effect: Z = 3.28 (P = 0.0010)					
2 52 weeks					
Tak 2010 (IMAGE)	185/242	151/239		26.7 %	1.21 [1.07, 1.36]
Subtotal (95% CI)	**242**	**239**		**26.7 %**	**1.21 [1.07, 1.36]**
Total events: 185 (Rituximab (1000mg)+MTX), 151 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.13 (P = 0.0018)					
Total (95% CI)	**817**	**709**		**100.0 %**	**1.96 [1.14, 3.36]**
Total events: 472 (Rituximab (1000mg)+MTX), 252 (Methotrexate monotherapy)					
Heterogeneity: Tau^2 = 0.28; Chi^2 = 50.18, df = 3 (P<0.00001); I^2 =94%					
Test for overall effect: Z = 2.43 (P = 0.015)					
Test for subgroup differences: Chi^2 = 6.12, df = 1 (P = 0.01), I^2 =84%					



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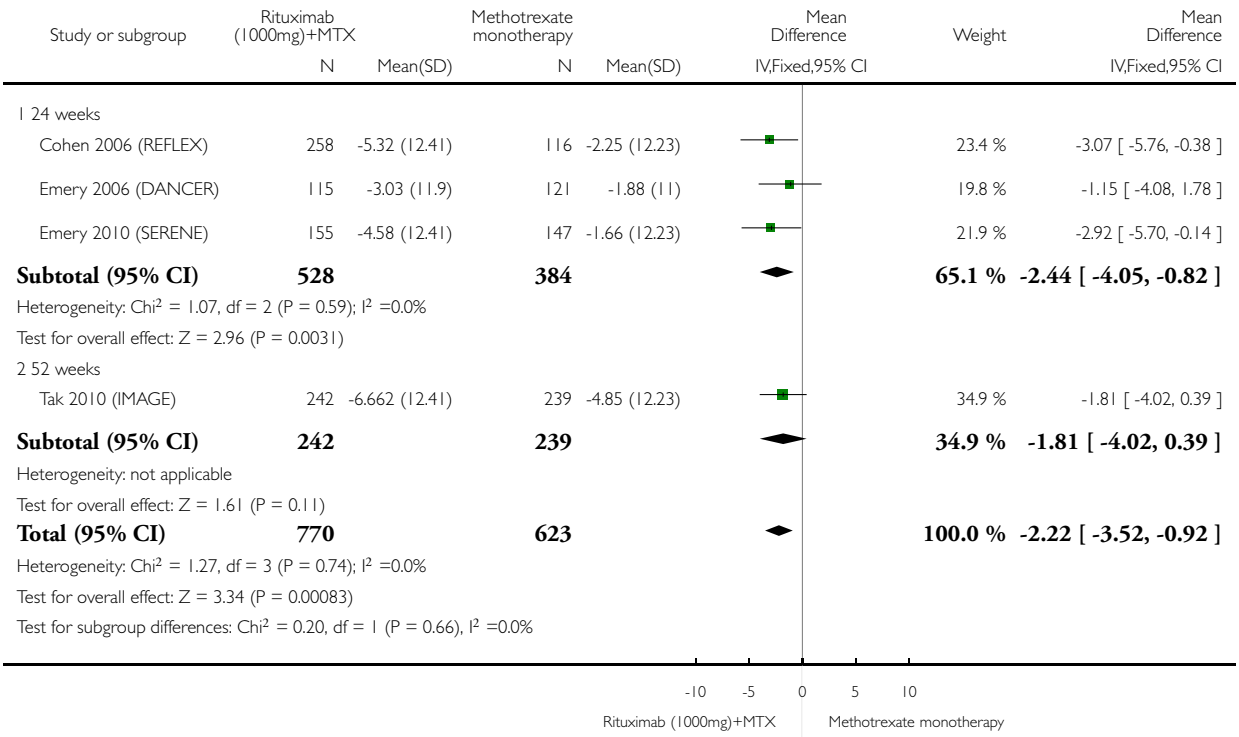
Analysis 1.13. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 13 SF-36 MCS.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 13 SF-36 MCS



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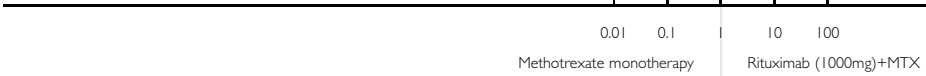
Analysis 1.14. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 14 SF-36 MCS (=or>MCID of 5 or 6.33).

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 14 SF-36 MCS (=or>MCID of 5 or 6.33)

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	116/298	43/201		34.2 %	2.34 [1.55, 3.53]
Emery 2010 (SERENE)	54/155	35/147		26.7 %	1.71 [1.03, 2.83]
Subtotal (95% CI)	**453**	**348**		**60.9 %**	**2.07 [1.50, 2.84]**
Total events: 170 (Rituximab (1000mg)+MTX), 78 (Methotrexate monotherapy)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.90$, df = 1 (P = 0.34); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.48 (P < 0.00001)					
2 52 weeks					
Tak 2010 (IMAGE)	138/242	117/239		39.1 %	1.38 [0.97, 1.98]
Subtotal (95% CI)	**242**	**239**		**39.1 %**	**1.38 [0.97, 1.98]**
Total events: 138 (Rituximab (1000mg)+MTX), 117 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.077)					
Total (95% CI)	**695**	**587**		**100.0 %**	**1.75 [1.27, 2.42]**
Total events: 308 (Rituximab (1000mg)+MTX), 195 (Methotrexate monotherapy)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 3.59$, df = 2 (P = 0.17); $I^2 = 44\%$					
Test for overall effect: Z = 3.39 (P = 0.00069)					
Test for subgroup differences: $Chi^2 = 2.69$, df = 1 (P = 0.10), $I^2 = 63\%$					



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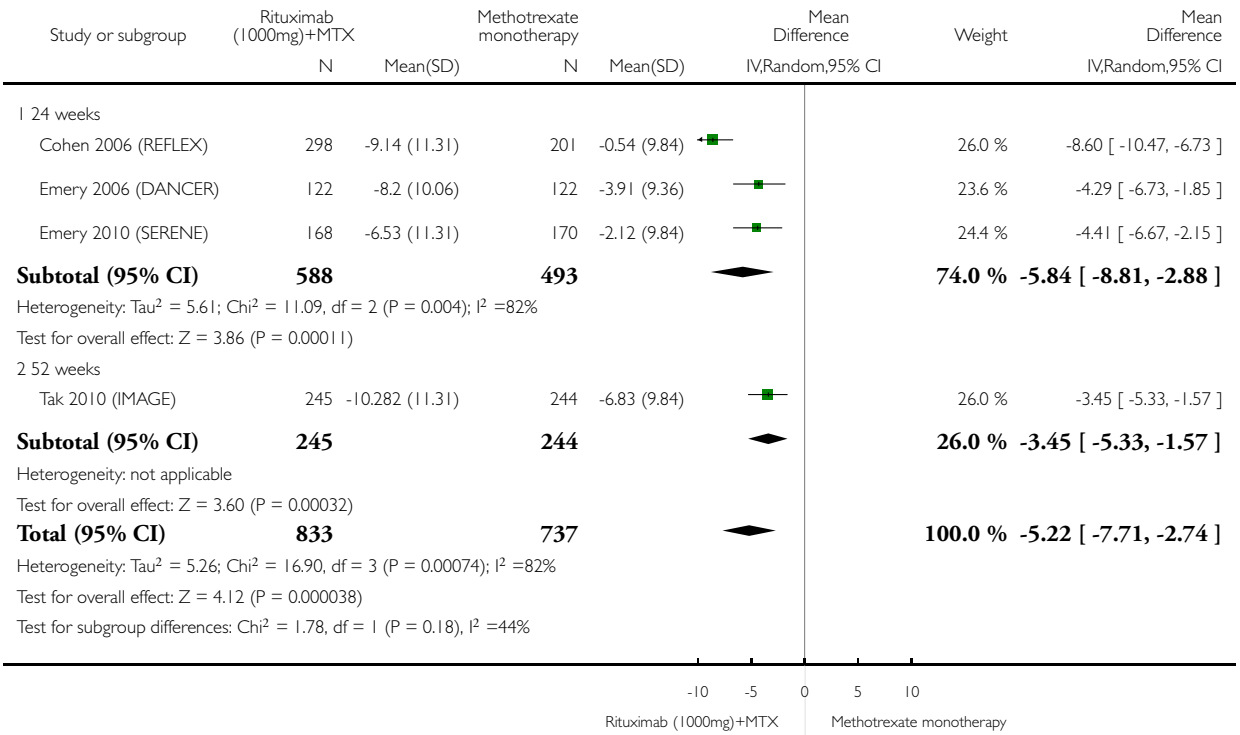
Analysis 1.15. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 15 FACIT-F.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 15 FACIT-F

Study or subgroup	Rituximab (1000mg)+MTX N	Mean(SD)	Methotrexate monotherapy N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 24 weeks							
Cohen 2006 (REFLEX)	298	-9.14 (11.31)	201	-0.54 (9.84)		26.0 %	-8.60 [-10.47, -6.73]
Emery 2006 (DANCER)	122	-8.2 (10.06)	122	-3.91 (9.36)		23.6 %	-4.29 [-6.73, -1.85]
Emery 2010 (SERENE)	168	-6.53 (11.31)	170	-2.12 (9.84)		24.4 %	-4.41 [-6.67, -2.15]
Subtotal (95% CI)	**588**		**493**			**74.0 %**	**-5.84 [-8.81, -2.88]**
Heterogeneity: Tau² = 5.61; Chi² = 11.09, df = 2 (P = 0.004); I² =82%							
Test for overall effect: Z = 3.86 (P = 0.00011)							
2 52 weeks							
Tak 2010 (IMAGE)	245	-10.282 (11.31)	244	-6.83 (9.84)		26.0 %	-3.45 [-5.33, -1.57]
Subtotal (95% CI)	**245**		**244**			**26.0 %**	**-3.45 [-5.33, -1.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.60 (P = 0.00032)							
Total (95% CI)	**833**		**737**			**100.0 %**	**-5.22 [-7.71, -2.74]**
Heterogeneity: Tau² = 5.26; Chi² = 16.90, df = 3 (P = 0.00074); I² =82%							
Test for overall effect: Z = 4.12 (P = 0.000038)							
Test for subgroup differences: Chi² = 1.78, df = 1 (P = 0.18), I² =44%							



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Analysis 1.16. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 16 FACIT-F MCID>= 4or 3.56.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 16 FACIT-F MCID>= 4or 3.56

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	199/298	67/201		33.2 %	2.00 [1.62, 2.47]
Emery 2006 (DANCER)	80/122	43/122		31.8 %	1.86 [1.42, 2.44]
Subtotal (95% CI)	**420**	**323**		**65.0 %**	**1.95 [1.65, 2.30]**
Total events: 279 (Rituximab (1000mg)+MTX), 110 (Methotrexate monotherapy)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0.0\%$					
Test for overall effect: Z = 7.83 (P < 0.00001)					
2 52 weeks					
Tak 2010 (IMAGE)	184/245	165/244		35.0 %	1.11 [0.99, 1.24]
Subtotal (95% CI)	**245**	**244**		**35.0 %**	**1.11 [0.99, 1.24]**
Total events: 184 (Rituximab (1000mg)+MTX), 165 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.82 (P = 0.068)					
Total (95% CI)	**665**	**567**		**100.0 %**	**1.59 [1.00, 2.53]**
Total events: 463 (Rituximab (1000mg)+MTX), 275 (Methotrexate monotherapy)					
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 34.83$, df = 2 (P<0.00001); $I^2 = 94\%$					
Test for overall effect: Z = 1.96 (P = 0.049)					
Test for subgroup differences: $Chi^2 = 29.88$, df = 1 (P = 0.00), $I^2 = 97\%$					

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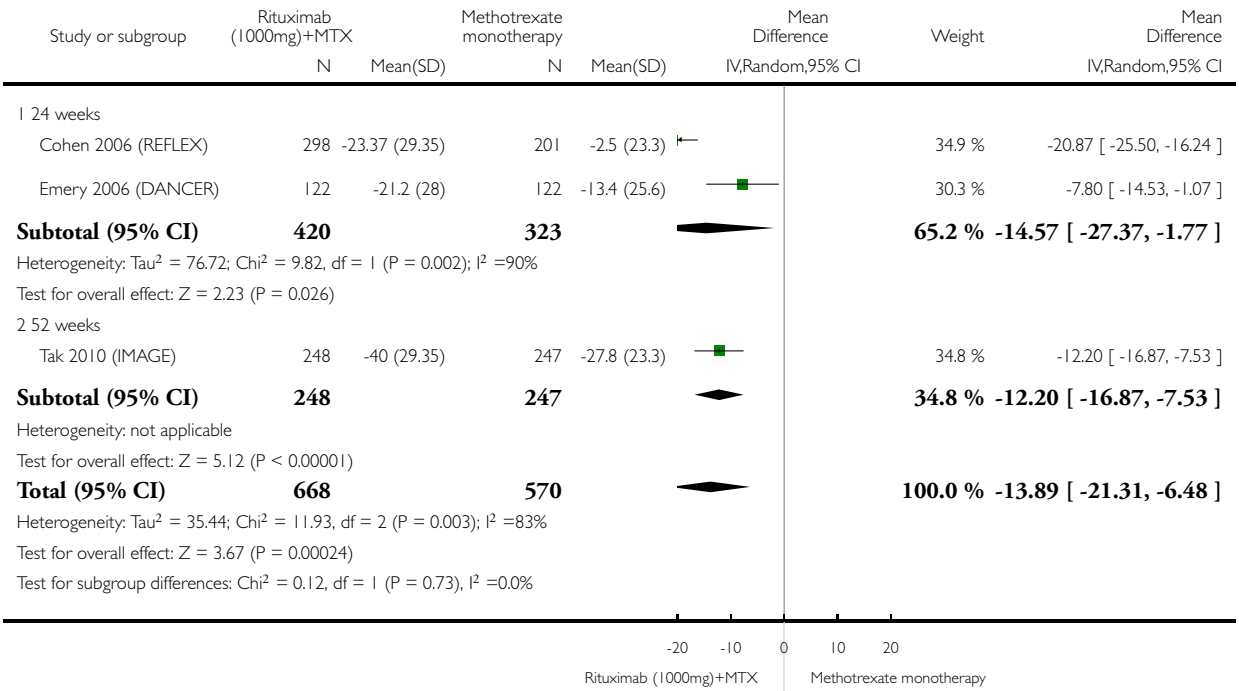
Analysis 1.17. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 17 VAS-pain.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 17 VAS-pain



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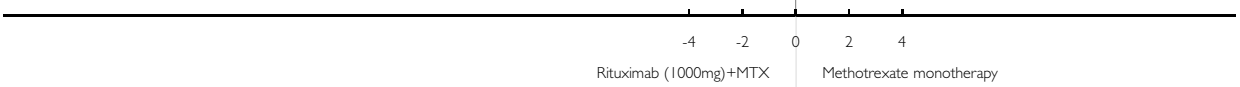
Analysis 1.18. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 18 Total radiographic score.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 18 Total radiographic score

Study or subgroup	Rituximab (1000mg)+MTX N	Mean(SD)	Methotrexate monotherapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Cohen 2006 (REFLEX)	298	0.6 (1.9)	201	1.2 (3.3)		48.2 %	-0.60 [-1.10, -0.10]
Tak 2010 (IMAGE)	244	0.328 (1.9)	232	0.7 (3.3)		51.8 %	-0.37 [-0.86, 0.11]
Subtotal (95% CI)	**542**		**433**			**100.0 %**	**-0.48 [-0.83, -0.13]**
Heterogeneity: Chi^2 = 0.40, df = 1 (P = 0.53); I^2 =0.0%							
Test for overall effect: Z = 2.70 (P = 0.0070)							
2 48-56 weeks							
Cohen 2006 (REFLEX)	272	1 (2.76)	184	2.31 (5.28)		25.6 %	-1.31 [-2.14, -0.48]
Tak 2010 (IMAGE)	244	0.359 (1.9)	232	1.08 (3.3)		74.4 %	-0.72 [-1.21, -0.23]
Subtotal (95% CI)	**516**		**416**			**100.0 %**	**-0.87 [-1.29, -0.45]**
Heterogeneity: Chi^2 = 1.44, df = 1 (P = 0.23); I^2 =31%							
Test for overall effect: Z = 4.06 (P = 0.000048)							
3 104 weeks							
Cohen 2006 (REFLEX)	281	1.14 (2.76)	187	2.81 (5.28)		25.9 %	-1.67 [-2.49, -0.85]
Tak 2010 (IMAGE)	244	0.41 (1.9)	233	1.95 (3.3)		74.1 %	-1.54 [-2.03, -1.05]
Subtotal (95% CI)	**525**		**420**			**100.0 %**	**-1.57 [-1.99, -1.16]**
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%							
Test for overall effect: Z = 7.37 (P < 0.00001)							



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Analysis 1.19. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 19 Joint Space Narrowing.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 19 Joint Space Narrowing

Study or subgroup	Rituximab (1000mg)+MTX N	Mean(SD)	Methotrexate monotherapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Cohen 2006 (REFLEX)	298	0.2 (0.8)	201	0.5 (1.5)		48.0 %	-0.30 [-0.53, -0.07]
Tak 2010 (IMAGE)	244	0.11 (0.8)	232	0.21 (1.5)		52.0 %	-0.10 [-0.32, 0.12]
Subtotal (95% CI)	**542**		**433**			**100.0 %**	**-0.20 [-0.35, -0.04]**
Heterogeneity: Chi^2 = 1.56, df = 1 (P = 0.21); I^2 =36%							
Test for overall effect: Z = 2.45 (P = 0.014)							
2 48-56 weeks							
Cohen 2006 (REFLEX)	272	0.41 (1.33)	184	0.99 (2.57)		100.0 %	-0.58 [-0.98, -0.18]
Subtotal (95% CI)	**272**		**184**			**100.0 %**	**-0.58 [-0.98, -0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.82 (P = 0.0049)							
3 104 weeks							
Cohen 2006 (REFLEX)	281	0.42 (1.33)	187	1 (2.57)		22.8 %	-0.58 [-0.98, -0.18]
Tak 2010 (IMAGE)	244	0.18 (0.8)	232	0.63 (1.5)		77.2 %	-0.45 [-0.67, -0.23]
Subtotal (95% CI)	**525**		**419**			**100.0 %**	**-0.48 [-0.67, -0.29]**
Heterogeneity: Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%							
Test for overall effect: Z = 4.92 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 6.63, df = 2 (P = 0.04), I^2 =70%							

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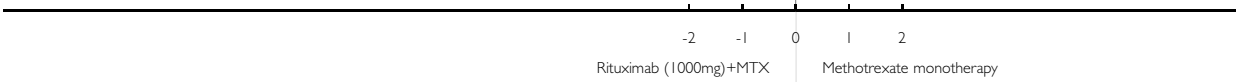
Analysis 1.20. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 20 Radiologic erosions.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 20 Radiologic erosions

Study or subgroup	Rituximab (1000mg)+MTX N	Mean(SD)	Methotrexate monotherapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Cohen 2006 (REFLEX)	298	0.4 (1.3)	201	0.8 (2)		48.6 %	-0.40 [-0.71, -0.09]
Tak 2010 (IMAGE)	244	0.22 (1.3)	232	0.49 (2)		51.4 %	-0.27 [-0.57, 0.03]
Subtotal (95% CI)	**542**		**433**			**100.0 %**	**-0.33 [-0.55, -0.11]**
Heterogeneity: Chi^2 = 0.34, df = 1 (P = 0.56); I^2 =0.0%							
Test for overall effect: Z = 2.99 (P = 0.0028)							
2 48-56 weeks							
Cohen 2006 (REFLEX)	272	0.59 (1.85)	184	1.32 (3.16)		26.6 %	-0.73 [-1.24, -0.22]
Tak 2010 (IMAGE)	244	0.233 (1.3)	232	0.74 (2)		73.4 %	-0.51 [-0.81, -0.20]
Subtotal (95% CI)	**516**		**416**			**100.0 %**	**-0.56 [-0.83, -0.30]**
Heterogeneity: Chi^2 = 0.56, df = 1 (P = 0.46); I^2 =0.0%							
Test for overall effect: Z = 4.24 (P = 0.000022)							
3 104 weeks							
Cohen 2006 (REFLEX)	281	0.72 (1.85)	187	1.8 (3.16)		26.9 %	-1.08 [-1.58, -0.58]
Tak 2010 (IMAGE)	244	0.23 (1.3)	233	1.32 (2)		73.1 %	-1.09 [-1.39, -0.79]
Subtotal (95% CI)	**525**		**420**			**100.0 %**	**-1.09 [-1.35, -0.83]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%							
Test for overall effect: Z = 8.19 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 19.19, df = 2 (P = 0.00), I^2 =90%							



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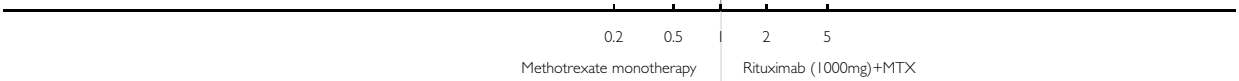
Analysis 1.21. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 21 No radiographic progression.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 21 No radiographic progression

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Tak 2010 (IMAGE)	170/244	137/232		100.0 %	1.18 [1.03, 1.35]
Subtotal (95% CI)	**244**	**232**		**100.0 %**	**1.18 [1.03, 1.35]**
Total events: 170 (Rituximab (1000mg)+MTX), 137 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.39 (P = 0.017)					
2 52-56 weeks					
Cohen 2006 (REFLEX)	167/278	86/186		45.0 %	1.30 [1.08, 1.56]
Tak 2010 (IMAGE)	156/244	123/232		55.0 %	1.21 [1.03, 1.41]
Subtotal (95% CI)	**522**	**418**		**100.0 %**	**1.25 [1.11, 1.40]**
Total events: 323 (Rituximab (1000mg)+MTX), 209 (Methotrexate monotherapy)					
Heterogeneity: Chi^2 = 0.38, df = 1 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 3.68 (P = 0.00023)					
3 104 weeks					
Cohen 2006 (REFLEX)	160/281	73/187		49.9 %	1.46 [1.19, 1.79]
Tak 2010 (IMAGE)	139/244	86/233		50.1 %	1.54 [1.26, 1.89]
Subtotal (95% CI)	**525**	**420**		**100.0 %**	**1.50 [1.30, 1.73]**
Total events: 299 (Rituximab (1000mg)+MTX), 159 (Methotrexate monotherapy)					
Heterogeneity: Chi^2 = 0.15, df = 1 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 5.55 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 6.26, df = 2 (P = 0.04), I^2 =68%					



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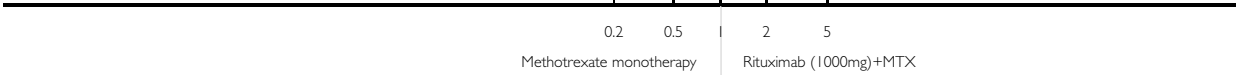
Analysis 1.22. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 22 No worsening of erosions.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 22 No worsening of erosions

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	176/268	106/177		100.0 %	1.10 [0.95, 1.27]
Subtotal (95% CI)	**268**	**177**		**100.0 %**	**1.10 [0.95, 1.27]**
Total events: 176 (Rituximab (1000mg)+MTX), 106 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					
2 52-56 weeks					
Cohen 2006 (REFLEX)	183/278	95/186		100.0 %	1.29 [1.09, 1.52]
Subtotal (95% CI)	**278**	**186**		**100.0 %**	**1.29 [1.09, 1.52]**
Total events: 183 (Rituximab (1000mg)+MTX), 95 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.03 (P = 0.0025)					
3 104 weeks					
Cohen 2006 (REFLEX)	169/281	82/187		52.0 %	1.37 [1.14, 1.66]
Tak 2010 (IMAGE)	144/244	89/233		48.0 %	1.55 [1.27, 1.88]
Subtotal (95% CI)	**525**	**420**		**100.0 %**	**1.45 [1.27, 1.67]**
Total events: 313 (Rituximab (1000mg)+MTX), 171 (Methotrexate monotherapy)					
Heterogeneity: Chi^2 = 0.75, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 5.44 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 7.63, df = 2 (P = 0.02), I^2 =74%					



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Analysis 2.1. Comparison 2 Benefits - RTX monotherapy versus MTX monotherapy, Outcome 1 ACR 20.

Review: Rituximab for rheumatoid arthritis

Comparison: 2 Benefits - RTX monotherapy versus MTX monotherapy

Outcome: 1 ACR 20

Study or subgroup	Rituximab n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 24 weeks				
Edwards 2004 (WA16291)	26/40	15/40		1.73 [1.09, 2.75]
2 48 weeks				
Edwards 2004 (WA16291)	13/40	8/40		1.63 [0.76, 3.49]
3 104 weeks				
Edwards 2004 (WA16291)	3/40	5/40		0.60 [0.15, 2.34]

Analysis 2.2. Comparison 2 Benefits - RTX monotherapy versus MTX monotherapy, Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 2 Benefits - RTX monotherapy versus MTX monotherapy

Outcome: 2 ACR 50

Study or subgroup	Rituximab n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 24 weeks				
Edwards 2004 (WA16291)	13/40	5/40		2.60 [1.02, 6.61]
2 48-56 weeks				
Edwards 2004 (WA16291)	5/40	2/40		2.50 [0.51, 12.14]
3 104 weeks				
Edwards 2004 (WA16291)	3/40	4/40		0.75 [0.18, 3.14]

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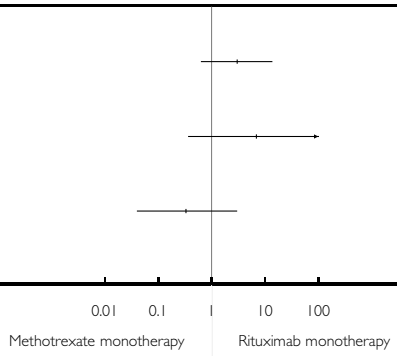
Analysis 2.3. Comparison 2 Benefits - RTX monotherapy versus MTX monotherapy, Outcome 3 ACR 70.

Review: Rituximab for rheumatoid arthritis

Comparison: 2 Benefits - RTX monotherapy versus MTX monotherapy

Outcome: 3 ACR 70

Study or subgroup	Rituximab n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 24 weeks				
Edwards 2004 (WA16291)	6/40	2/40		3.00 [0.64, 13.98]
2 48-56 weeks				
Edwards 2004 (WA16291)	3/40	0/40		7.00 [0.37, 131.28]
3 104 weeks				
Edwards 2004 (WA16291)	1/40	3/40		0.33 [0.04, 3.07]



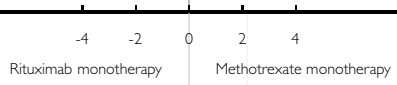
Analysis 2.4. Comparison 2 Benefits - RTX monotherapy versus MTX monotherapy, Outcome 4 DAS 28.

Review: Rituximab for rheumatoid arthritis

Comparison: 2 Benefits - RTX monotherapy versus MTX monotherapy

Outcome: 4 DAS 28

Study or subgroup	Rituximab N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Edwards 2004 (WA16291)	40	-2.2 (1.4)	40	-1.3 (1.2)		100.0 %	-0.90 [-1.47, -0.33]
Subtotal (95% CI)	**40**		**40**			**100.0 %**	**-0.90 [-1.47, -0.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.09 (P = 0.0020)							
Test for subgroup differences: Not applicable							



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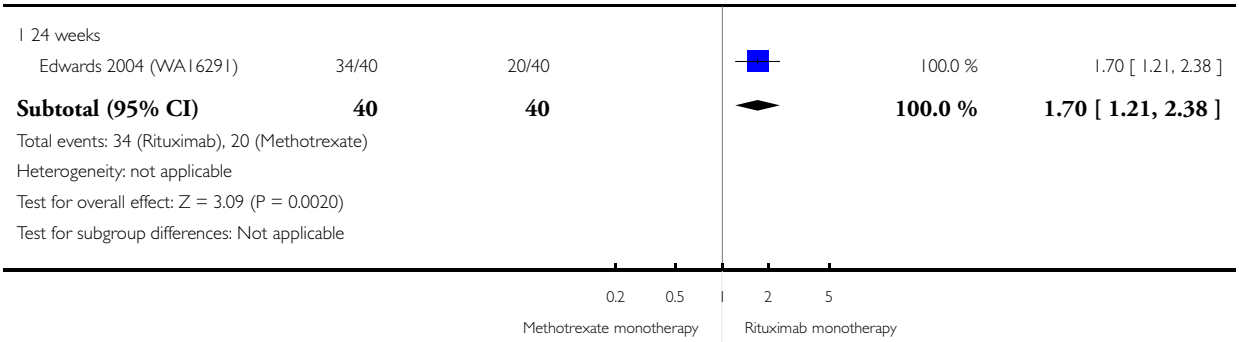
Analysis 2.5. Comparison 2 Benefits - RTX monotherapy versus MTX monotherapy, Outcome 5 Moderate or good EULAR response.

Review: Rituximab for rheumatoid arthritis

Comparison: 2 Benefits - RTX monotherapy versus MTX monotherapy

Outcome: 5 Moderate or good EULAR response

Study or subgroup	Rituximab n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	34/40	20/40		100.0 %	1.70 [1.21, 2.38]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**1.70 [1.21, 2.38]**
Total events: 34 (Rituximab), 20 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.09 (P = 0.0020)					
Test for subgroup differences: Not applicable					



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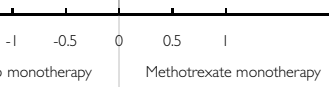
Analysis 2.6. Comparison 2 Benefits - RTX monotherapy versus MTX monotherapy, Outcome 6 HAQ-DI.

Review: Rituximab for rheumatoid arthritis

Comparison: 2 Benefits - RTX monotherapy versus MTX monotherapy

Outcome: 6 HAQ-DI

Study or subgroup	Rituximab N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Edwards 2004 (WA16291)	38	-0.8 (0.6)	37	-0.4 (0.5)		100.0 %	-0.40 [-0.65, -0.15]
Subtotal (95% CI)	**38**		**37**			**100.0 %**	**-0.40 [-0.65, -0.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.14 (P = 0.0017)							
2 48 weeks							
Edwards 2004 (WA16291)	31	-0.5 (0.6)	25	-0.3 (0.5)		100.0 %	-0.20 [-0.49, 0.09]
Subtotal (95% CI)	**31**		**25**			**100.0 %**	**-0.20 [-0.49, 0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.36 (P = 0.17)							
3 72 weeks							
Edwards 2004 (WA16291)	17	-0.6 (0.6)	15	-0.3 (0.5)		100.0 %	-0.30 [-0.68, 0.08]
Subtotal (95% CI)	**17**		**15**			**100.0 %**	**-0.30 [-0.68, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.54 (P = 0.12)							
Test for subgroup differences: Chi^2 = 1.06, df = 2 (P = 0.59), I^2 =0.0%							



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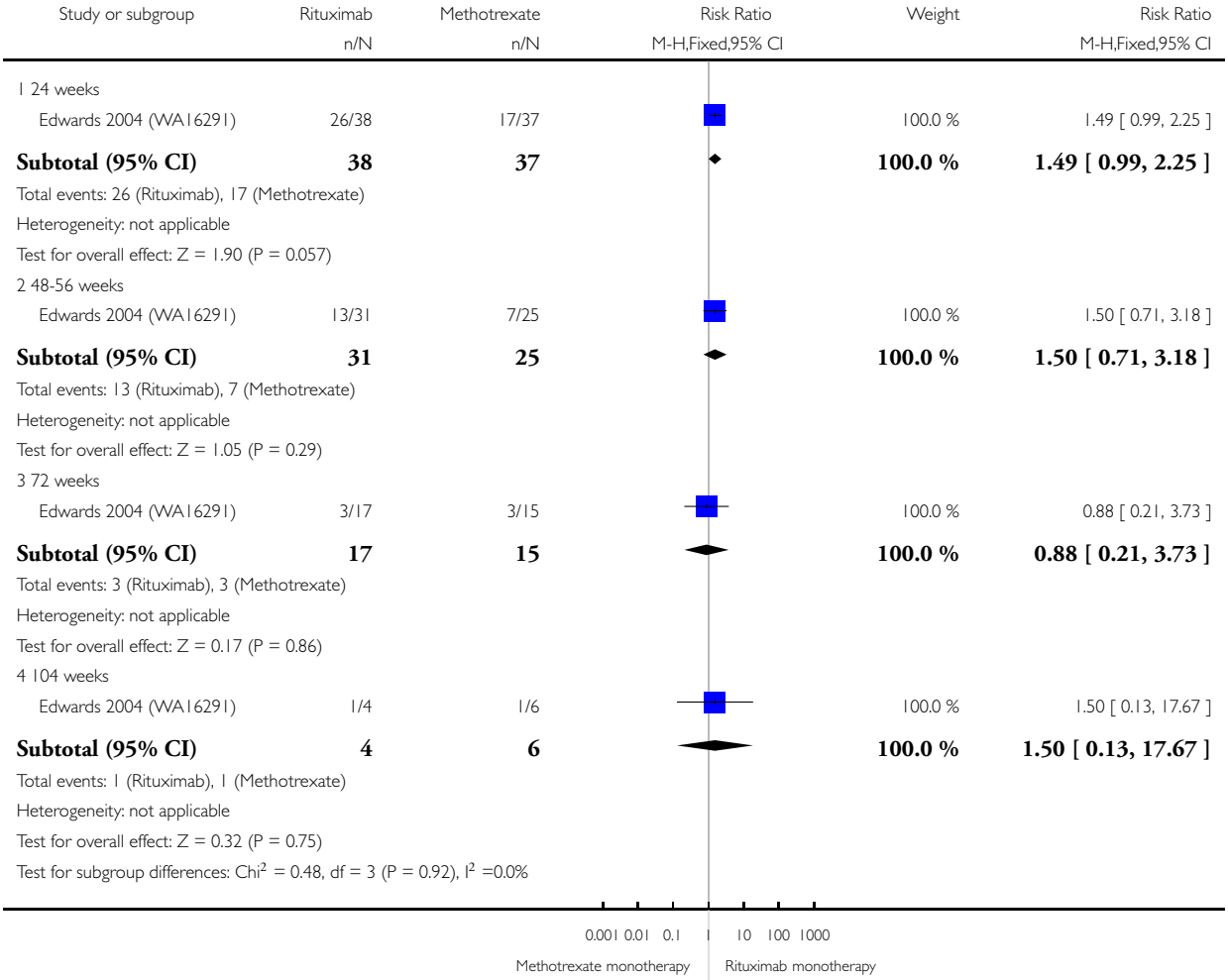
Analysis 2.7. Comparison 2 Benefits - RTX monotherapy versus MTX monotherapy, Outcome 7 % of patients achieving HAQ-DI MCID=-0.25.

Review: Rituximab for rheumatoid arthritis

Comparison: 2 Benefits - RTX monotherapy versus MTX monotherapy

Outcome: 7 % of patients achieving HAQ-DI MCID=-0.25



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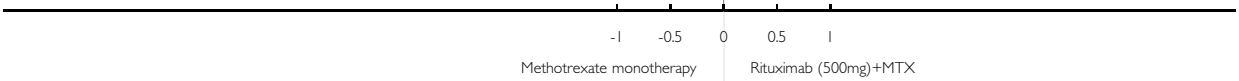
Analysis 3.1. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 1 ACR 20.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 1 ACR 20

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	68/123	34/122		42.0 %	0.27 [0.16, 0.39]
Emery 2010 (SERENE)	91/167	40/172		58.0 %	0.31 [0.21, 0.41]
Subtotal (95% CI)	**290**	**294**		**100.0 %**	**0.30 [0.22, 0.37]**
Total events: 159 (Rituximab (500mg)+MTX), 74 (Methotrexate)					
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 7.67 (P < 0.00001)					
2 48-52 weeks					
Emery 2006 (DANCER)	40/60	18/40		16.2 %	0.22 [0.02, 0.41]
Tak 2010 (IMAGE)	191/249	160/249		83.8 %	0.12 [0.05, 0.20]
Subtotal (95% CI)	**309**	**289**		**100.0 %**	**0.14 [0.07, 0.21]**
Total events: 231 (Rituximab (500mg)+MTX), 178 (Methotrexate)					
Heterogeneity: Chi^2 = 0.74, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 3.71 (P = 0.00021)					
3 104 weeks					
Tak 2010 (IMAGE)	186/249	145/249		100.0 %	0.16 [0.08, 0.25]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**0.16 [0.08, 0.25]**
Total events: 186 (Rituximab (500mg)+MTX), 145 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.95 (P = 0.000077)					
Test for subgroup differences: Chi^2 = 9.53, df = 2 (P = 0.01), I^2 =79%					



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Analysis 3.2. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 2 ACR 50

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	41/123	16/122		50.5 %	2.54 [1.51, 4.28]
Emery 2010 (SERENE)	44/167	16/172		49.5 %	2.83 [1.67, 4.82]
Subtotal (95% CI)	**290**	**294**		**100.0 %**	**2.69 [1.85, 3.90]**
Total events: 85 (Rituximab (500mg)+MTX), 32 (Methotrexate)					
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² =0.0%					
Test for overall effect: Z = 5.21 (P < 0.00001)					
2 48-52 weeks					
Emery 2006 (DANCER)	25/60	8/40		8.4 %	2.08 [1.05, 4.15]
Tak 2010 (IMAGE)	148/249	105/249		91.6 %	1.41 [1.18, 1.68]
Subtotal (95% CI)	**309**	**289**		**100.0 %**	**1.47 [1.23, 1.74]**
Total events: 173 (Rituximab (500mg)+MTX), 113 (Methotrexate)					
Heterogeneity: Chi² = 1.19, df = 1 (P = 0.28); I² =16%					
Test for overall effect: Z = 4.31 (P = 0.000017)					
3 104 weeks					
Tak 2010 (IMAGE)	149/249	105/249		100.0 %	1.42 [1.19, 1.69]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**1.42 [1.19, 1.69]**
Total events: 149 (Rituximab (500mg)+MTX), 105 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.86 (P = 0.00011)					
Test for subgroup differences: Chi² = 9.71, df = 2 (P = 0.01), I² =79%					

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Analysis 3.3. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 3 ACR 70.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 3 ACR 70

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Emery 2006 (DANCER)	16/123	6/122		43.8 %	2.64 [1.07, 6.53]
Emery 2010 (SERENE)	15/167	9/172		56.2 %	1.72 [0.77, 3.81]
Subtotal (95% CI)	**290**	**294**		**100.0 %**	**2.07 [1.14, 3.77]**
Total events: 31 (Rituximab (500mg)+MTX), 15 (Methotrexate)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.49, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 2.39 (P = 0.017)					
2 48-52 weeks					
Emery 2006 (DANCER)	12/60	3/40		24.0 %	2.67 [0.80, 8.86]
Tak 2010 (IMAGE)	105/249	90/249		76.0 %	1.17 [0.94, 1.45]
Subtotal (95% CI)	**309**	**289**		**100.0 %**	**1.42 [0.71, 2.86]**
Total events: 117 (Rituximab (500mg)+MTX), 93 (Methotrexate)					
Heterogeneity: Tau^2 = 0.16; Chi^2 = 1.80, df = 1 (P = 0.18); I^2 =44%					
Test for overall effect: Z = 0.99 (P = 0.32)					
3 104 weeks					
Tak 2010 (IMAGE)	105/249	62/249		100.0 %	1.69 [1.31, 2.20]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**1.69 [1.31, 2.20]**
Total events: 105 (Rituximab (500mg)+MTX), 62 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.97 (P = 0.000072)					
Test for subgroup differences: Chi^2 = 0.67, df = 2 (P = 0.72), I^2 =0.0%					

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Analysis 3.4. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 4 ACR 90.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 4 ACR 90

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 52 weeks				
Tak 2010 (IMAGE)	43/249	20/249		2.15 [1.30, 3.55]
2 104 weeks				
Tak 2010 (IMAGE)	51/249	32/249		1.59 [1.06, 2.39]

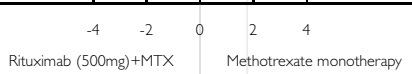
Analysis 3.5. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 5 DAS 28.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 5 DAS 28

Study or subgroup	Rituximab (500mg)+MTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Emery 2006 (DANCER)	122	-1.79 (1.3)	122	-0.67 (1.2)		22.6 %	-1.12 [-1.43, -0.81]
Emery 2010 (SERENE)	166	-1.76 (1.3)	171	-0.75 (1.2)		31.2 %	-1.01 [-1.28, -0.74]
Tak 2010 (IMAGE)	249	-2.85 (1.3)	249	-2 (1.2)		46.2 %	-0.85 [-1.07, -0.63]
Subtotal (95% CI)	**537**		**542**			**100.0 %**	**-0.96 [-1.11, -0.81]**
Heterogeneity: Chi^2 = 2.09, df = 2 (P = 0.35); I^2 =5%							
Test for overall effect: Z = 12.61 (P < 0.00001)							
2 52 weeks							
Tak 2010 (IMAGE)	249	-3.05 (1.3)	249	-2.06 (1.2)		100.0 %	-0.99 [-1.21, -0.77]



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Study or subgroup	Rituximab (500mg)+MTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**249**		**249**			**100.0 %**	**-0.99 [-1.21, -0.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.83 (P < 0.00001)							
3 104 weeks							
Tak 2010 (IMAGE)	249	-3.79 (1.3)	249	-2.2 (1.2)		100.0 %	-1.59 [-1.81, -1.37]
Subtotal (95% CI)	**249**		**249**			**100.0 %**	**-1.59 [-1.81, -1.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 14.18 (P < 0.00001)							

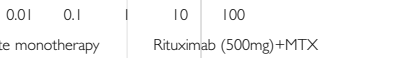
Analysis 3.6. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 6 LDA (DAS28 =or<3.2).

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 6 LDA (DAS28 =or<3.2)

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2010 (SERENE)	29/167	8/172		100.0 %	3.73 [1.76, 7.93]
Subtotal (95% CI)	**167**	**172**		**100.0 %**	**3.73 [1.76, 7.93]**
Total events: 29 (Rituximab (500mg)+MTX), 8 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.43 (P = 0.00061)					
2 48-52 weeks					
Emery 2006 (DANCER)	14/60	6/40		12.6 %	1.56 [0.65, 3.71]
Tak 2010 (IMAGE)	100/249	50/249		87.4 %	2.00 [1.50, 2.67]
Subtotal (95% CI)	**309**	**289**		**100.0 %**	**1.94 [1.48, 2.56]**
Total events: 114 (Rituximab (500mg)+MTX), 56 (Methotrexate)					



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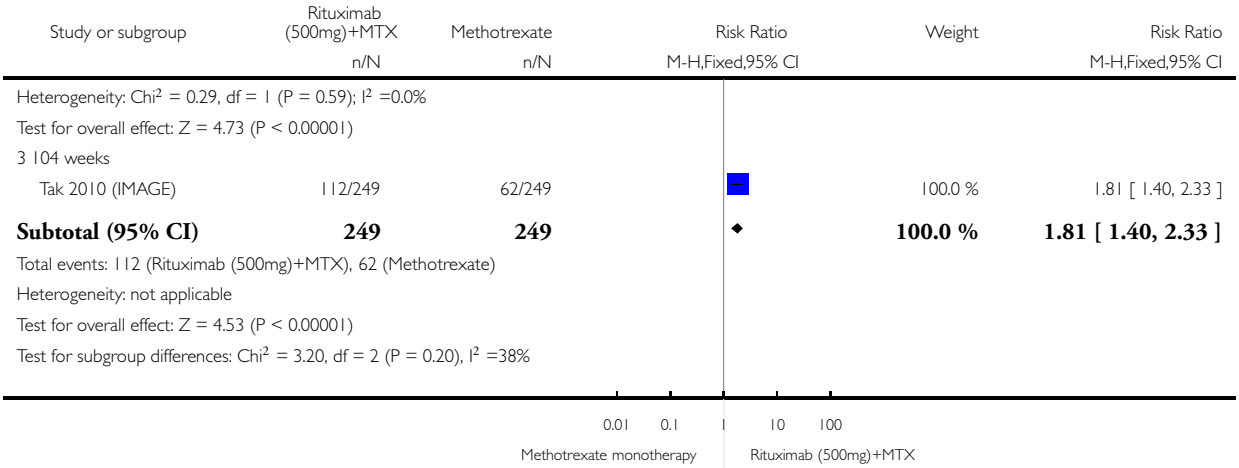
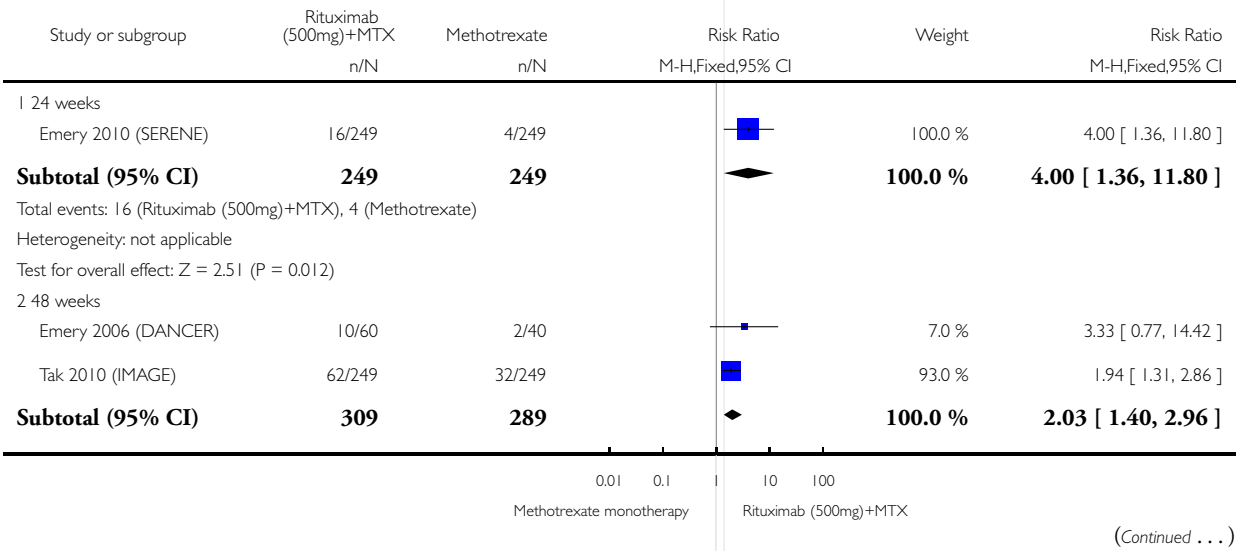


Analysis 3.7. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 7 Clinical Remission (DAS28<2.6).

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 7 Clinical Remission (DAS28<2.6)



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Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 72 (Rituximab (500mg)+MTX), 34 (Methotrexate)					
Heterogeneity: $Chi^2 = 0.50$, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.70 (P = 0.00022)					
3 104 weeks					
Tak 2010 (IMAGE)	85/249	32/249		100.0 %	2.66 [1.84, 3.83]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**2.66 [1.84, 3.83]**
Total events: 85 (Rituximab (500mg)+MTX), 32 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.22 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 1.89$, df = 2 (P = 0.39), I^2 =0.0%					

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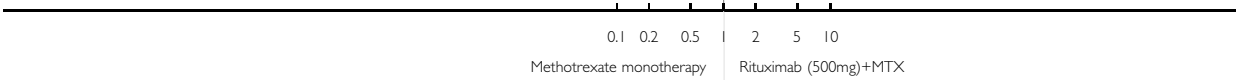
Analysis 3.8. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 8 Moderate or good EULAR response.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 8 Moderate or good EULAR response

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	90/123	45/122		31.3 %	1.98 [1.54, 2.56]
Emery 2010 (SERENE)	111/167	58/172		39.6 %	1.97 [1.56, 2.49]
Tak 2010 (IMAGE)	65/249	42/249		29.1 %	1.55 [1.09, 2.19]
Subtotal (95% CI)	**539**	**543**		**100.0 %**	**1.85 [1.58, 2.17]**
Total events: 266 (Rituximab (500mg)+MTX), 145 (Methotrexate)					
Heterogeneity: Chi^2 = 1.58, df = 2 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 7.70 (P < 0.00001)					
2 52 weeks					
Tak 2010 (IMAGE)	97/249	46/249		100.0 %	2.11 [1.56, 2.86]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**2.11 [1.56, 2.86]**
Total events: 97 (Rituximab (500mg)+MTX), 46 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.81 (P < 0.00001)					
3 104 weeks					
Tak 2010 (IMAGE)	110/249	57/249		100.0 %	1.93 [1.48, 2.52]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**1.93 [1.48, 2.52]**
Total events: 110 (Rituximab (500mg)+MTX), 57 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.82 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.56, df = 2 (P = 0.75), I^2 =0.0%					



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Analysis 3.9. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 9 HAQ-DI.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 9 HAQ-DI

Study or subgroup	Rituximab (500mg)+MTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Emery 2006 (DANCER)	122	-0.43 (0.6)	122	-0.16 (0.5)		32.9 %	-0.27 [-0.41, -0.13]
Tak 2010 (IMAGE)	249	-0.8 (0.6)	249	-0.6 (0.5)		67.1 %	-0.20 [-0.30, -0.10]
Subtotal (95% CI)	**371**		**371**			**100.0 %**	**-0.22 [-0.30, -0.14]**
Heterogeneity: Chi^2 = 0.66, df = 1 (P = 0.42); I^2 =0.0%							
Test for overall effect: Z = 5.50 (P < 0.00001)							
2 52 weeks							
Tak 2010 (IMAGE)	249	-0.905 (0.6)	249	-0.63 (0.5)		100.0 %	-0.28 [-0.37, -0.18]
Subtotal (95% CI)	**249**		**249**			**100.0 %**	**-0.28 [-0.37, -0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.60 (P < 0.00001)							
3 104 weeks							
Tak 2010 (IMAGE)	249	-1.1 (0.6)	249	-0.76 (0.5)		100.0 %	-0.34 [-0.44, -0.24]
Subtotal (95% CI)	**249**		**249**			**100.0 %**	**-0.34 [-0.44, -0.24]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.87 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.36, df = 2 (P = 0.19), I^2 =40%							

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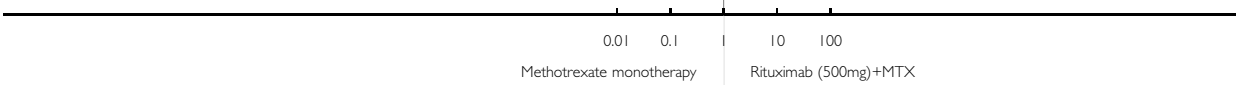
Analysis 3.10. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 10 HAQ-DI MCID=-0.22.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 10 HAQ-DI MCID=-0.22

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Emery 2006 (DANCER)	77/123	41/122		43.5 %	1.86 [1.40, 2.48]
Emery 2010 (SERENE)	109/165	82/172		56.5 %	1.39 [1.14, 1.68]
Subtotal (95% CI)	**288**	**294**		**100.0 %**	**1.58 [1.18, 2.11]**
Total events: 186 (Rituximab (500mg)+MTX), 123 (Methotrexate)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 2.92, df = 1 (P = 0.09); I^2 =66%					
Test for overall effect: Z = 3.07 (P = 0.0021)					
2 52 weeks					
Tak 2010 (IMAGE)	216/249	192/249		100.0 %	1.13 [1.04, 1.22]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**1.13 [1.04, 1.22]**
Total events: 216 (Rituximab (500mg)+MTX), 192 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.77 (P = 0.0056)					
3 104 weeks					
Tak 2010 (IMAGE)	209/249	154/249		100.0 %	1.36 [1.21, 1.52]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**1.36 [1.21, 1.52]**
Total events: 209 (Rituximab (500mg)+MTX), 154 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.36 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 10.13, df = 2 (P = 0.01), I^2 =80%					



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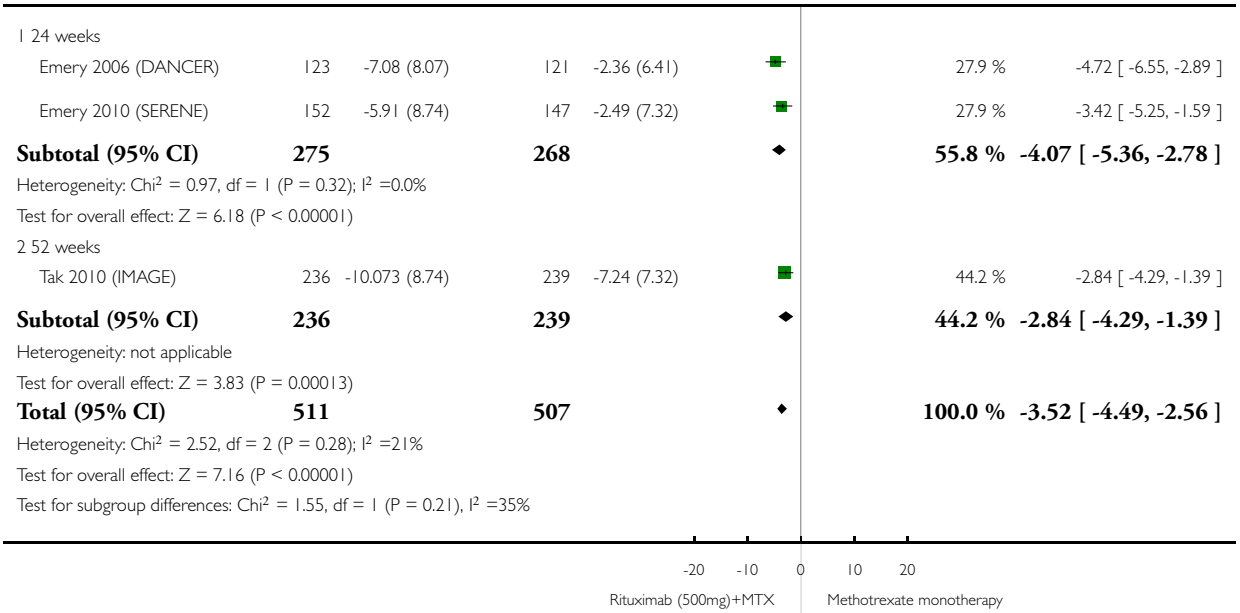
Analysis 3.11. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 11 SF-36 PCS.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 11 SF-36 PCS

Study or subgroup	Rituximab (500mg)+MTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Emery 2006 (DANCER)	123	-7.08 (8.07)	121	-2.36 (6.41)		27.9 %	-4.72 [-6.55, -2.89]
Emery 2010 (SERENE)	152	-5.91 (8.74)	147	-2.49 (7.32)		27.9 %	-3.42 [-5.25, -1.59]
Subtotal (95% CI)	**275**		**268**			**55.8 %**	**-4.07 [-5.36, -2.78]**
Heterogeneity: Chi^2 = 0.97, df = 1 (P = 0.32); I^2 =0.0%							
Test for overall effect: Z = 6.18 (P < 0.00001)							
2 52 weeks							
Tak 2010 (IMAGE)	236	-10.073 (8.74)	239	-7.24 (7.32)		44.2 %	-2.84 [-4.29, -1.39]
Subtotal (95% CI)	**236**		**239**			**44.2 %**	**-2.84 [-4.29, -1.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.83 (P = 0.00013)							
Total (95% CI)	**511**		**507**			**100.0 %**	**-3.52 [-4.49, -2.56]**
Heterogeneity: Chi^2 = 2.52, df = 2 (P = 0.28); I^2 =21%							
Test for overall effect: Z = 7.16 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.55, df = 1 (P = 0.21), I^2 =35%							



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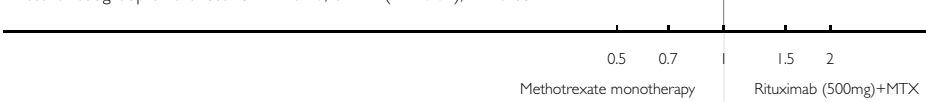
Analysis 3.12. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 12 SF-36 PCS (=or>MCID of 5 or 5.42).

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 12 SF-36 PCS (=or>MCID of 5 or 5.42)

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Emery 2006 (DANCER)	68/123	29/121		30.6 %	2.31 [1.62, 3.29]
Emery 2010 (SERENE)	70/152	45/147		32.5 %	1.50 [1.12, 2.03]
Subtotal (95% CI)	**275**	**268**		**63.1 %**	**1.84 [1.21, 2.80]**
Total events: 138 (Rituximab (500mg)+MTX), 74 (Methotrexate)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 3.28, df = 1 (P = 0.07); I^2 =69%					
Test for overall effect: Z = 2.86 (P = 0.0043)					
2 52 weeks					
Tak 2010 (IMAGE)	165/236	151/239		36.9 %	1.11 [0.97, 1.26]
Subtotal (95% CI)	**236**	**239**		**36.9 %**	**1.11 [0.97, 1.26]**
Total events: 165 (Rituximab (500mg)+MTX), 151 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
Total (95% CI)	**511**	**507**		**100.0 %**	**1.53 [0.98, 2.39]**
Total events: 303 (Rituximab (500mg)+MTX), 225 (Methotrexate)					
Heterogeneity: Tau^2 = 0.13; Chi^2 = 18.29, df = 2 (P = 0.00011); I^2 =89%					
Test for overall effect: Z = 1.88 (P = 0.060)					
Test for subgroup differences: Chi^2 = 5.20, df = 1 (P = 0.02), I^2 =81%					



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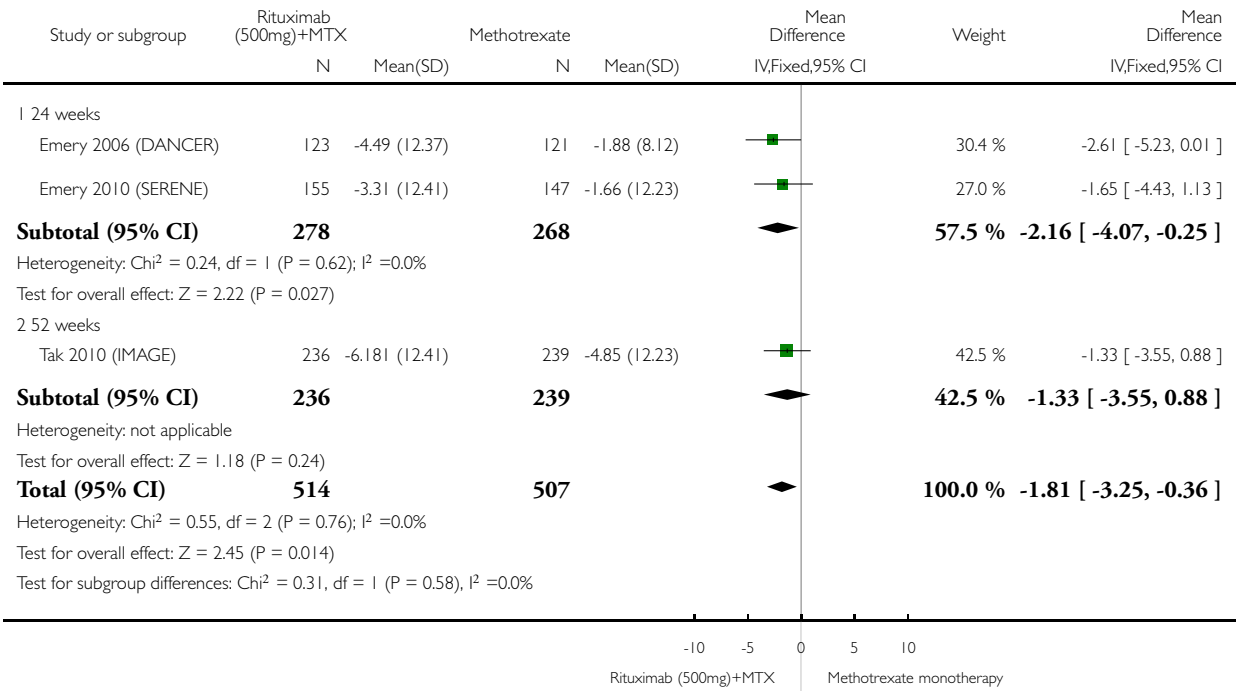
Analysis 3.13. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 13 SF-36 MCS.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 13 SF-36 MCS



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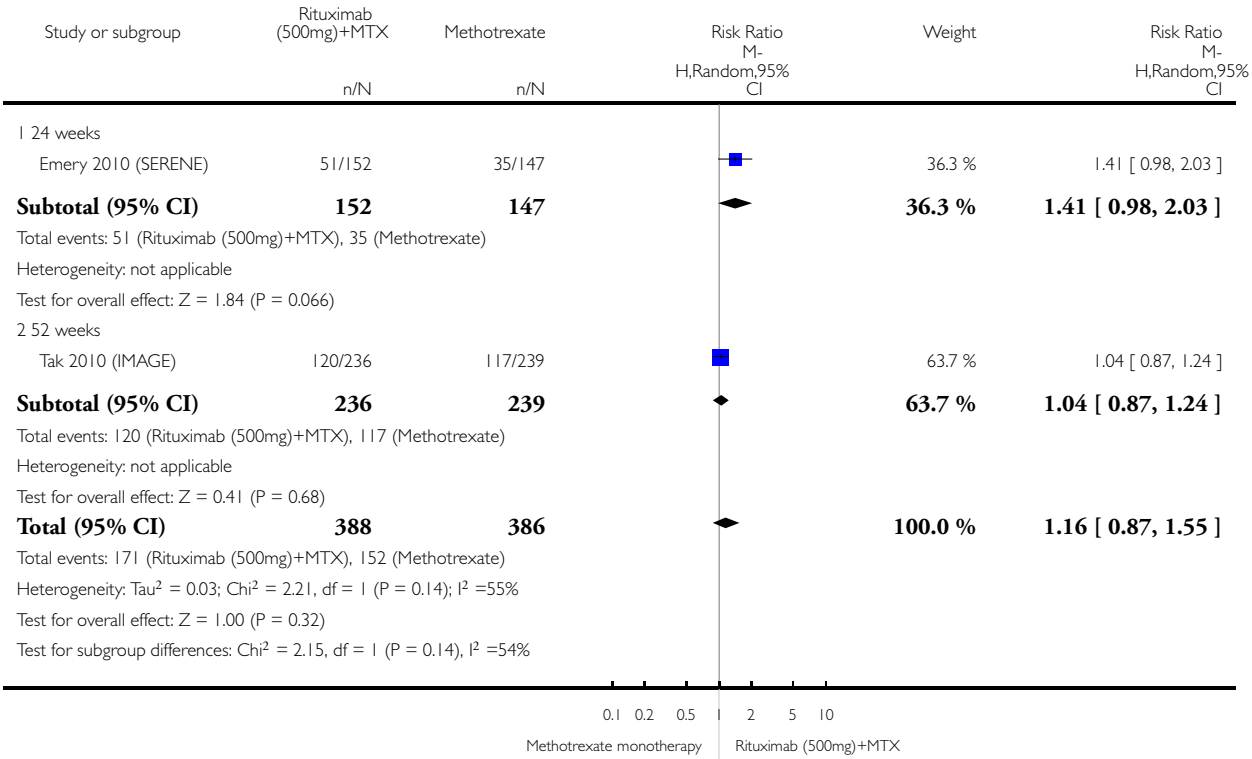
Analysis 3.14. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 14 SF-36 MCS (=or>MCID of 6.33).

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 14 SF-36 MCS (=or>MCID of 6.33)



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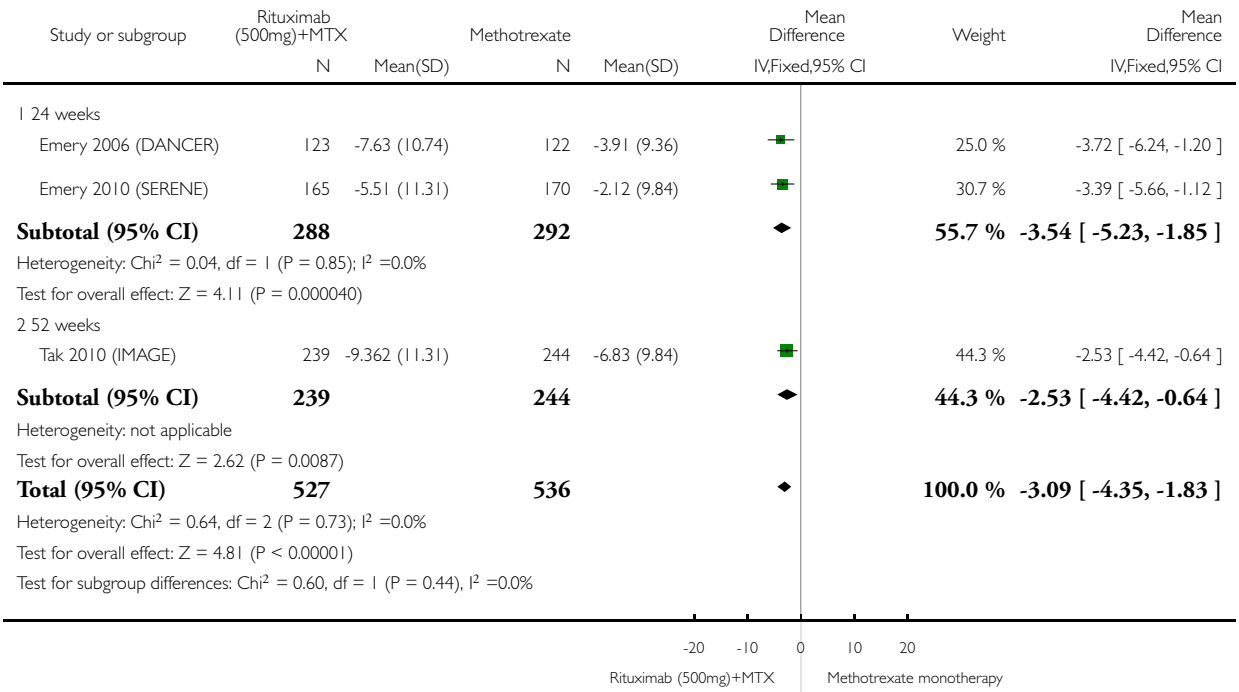
Analysis 3.15. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 15 FACIT-F.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 15 FACIT-F



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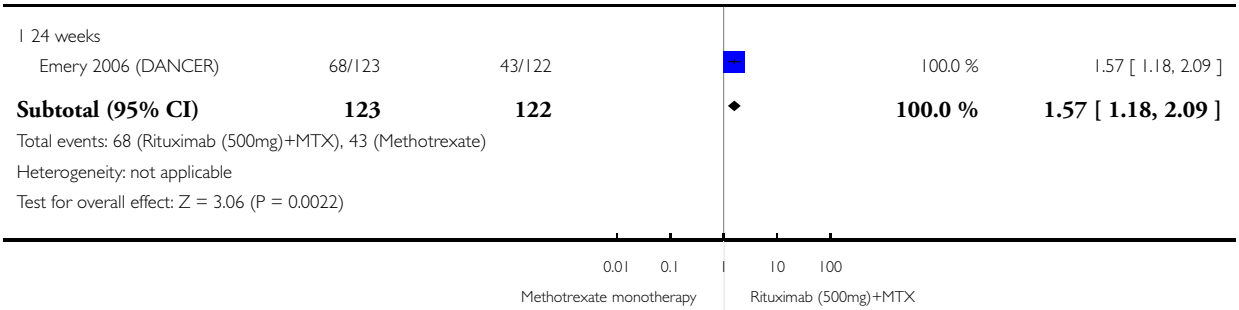
Analysis 3.16. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 16 FACIT-F (= or > MCID of 3.5 or 4).

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 16 FACIT-F (= or > MCID of 3.5 or 4)

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	68/123	43/122		100.0 %	1.57 [1.18, 2.09]
Subtotal (95% CI)	**123**	**122**		**100.0 %**	**1.57 [1.18, 2.09]**
Total events: 68 (Rituximab (500mg)+MTX), 43 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.06 (P = 0.0022)					



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Analysis 3.17. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 17 VAS pain.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 17 VAS pain

Study or subgroup	Rituximab (500mg)+MTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Emery 2006 (DANCER)	123	-21.5 (29.1)	122	-13.4 (25.6)		33.2 %	-8.10 [-14.96, -1.24]
Subtotal (95% CI)	**123**		**122**			**33.2 %**	**-8.10 [-14.96, -1.24]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.31 (P = 0.021)							
2 52 weeks							
Tak 2010 (IMAGE)	247	-36.2 (29.1)	247	-27.8 (25.6)		66.8 %	-8.40 [-13.23, -3.57]
Subtotal (95% CI)	**247**		**247**			**66.8 %**	**-8.40 [-13.23, -3.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.41 (P = 0.00066)							
Total (95% CI)	**370**		**369**			**100.0 %**	**-8.30 [-12.25, -4.35]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.94); I^2 =0.0%							
Test for overall effect: Z = 4.12 (P = 0.000038)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.94), I^2 =0.0%							

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Analysis 3.18. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 18 Total radiographic score.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 18 Total radiographic score

Study or subgroup	Rituximab (500mg)+MTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Tak 2010 (IMAGE)	239	0.58 (1.9)	232	0.7 (3.3)		100.0 %	-0.12 [-0.61, 0.37]
Subtotal (95% CI)	**239**		**232**			**100.0 %**	**-0.12 [-0.61, 0.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.49 (P = 0.63)							
2 52 weeks							
Tak 2010 (IMAGE)	239	0.646 (1.9)	232	1.08 (3.3)		100.0 %	-0.43 [-0.92, 0.06]
Subtotal (95% CI)	**239**		**232**			**100.0 %**	**-0.43 [-0.92, 0.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.74 (P = 0.082)							
3 104 weeks							
Tak 2010 (IMAGE)	239	0.76 (1.9)	233	1.95 (3.3)		100.0 %	-1.19 [-1.68, -0.70]
Subtotal (95% CI)	**239**		**233**			**100.0 %**	**-1.19 [-1.68, -0.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.79 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 9.76, df = 2 (P = 0.01), I^2 =80%							

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Analysis 3.19. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 19 Joint Space Narrowing.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 19 Joint Space Narrowing

Study or subgroup	Rituximab (500mg)+MTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 104 weeks							
Tak 2010 (IMAGE)	239	0.26 (0.8)	233	0.63 (1.5)		100.0 %	-0.37 [-0.59, -0.15]
Subtotal (95% CI)	**239**		**233**			**100.0 %**	**-0.37 [-0.59, -0.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.33 (P = 0.00086)							
Test for subgroup differences: Not applicable							

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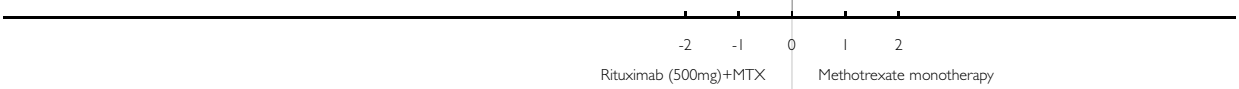
Analysis 3.20. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 20 Radiologic erosions.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 20 Radiologic erosions

Study or subgroup	Rituximab (500mg)+MTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 52 weeks							
Tak 2010 (IMAGE)	239	0.453 (1.3)	232	0.74 (2)		100.0 %	-0.29 [-0.59, 0.02]
Subtotal (95% CI)	**239**		**232**			**100.0 %**	**-0.29 [-0.59, 0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.83 (P = 0.068)							
2 104 weeks							
Tak 2010 (IMAGE)	239	0.5 (1.3)	233	1.32 (2)		100.0 %	-0.82 [-1.13, -0.51]
Subtotal (95% CI)	**239**		**233**			**100.0 %**	**-0.82 [-1.13, -0.51]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.27 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 5.90, df = 1 (P = 0.02), I^2 =83%							



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Analysis 3.21. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 21 No radiographic progression.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 21 No radiographic progression

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Tak 2010 (IMAGE)	117/239	86/233		100.0 %	1.33 [1.07, 1.64]
Subtotal (95% CI)	**239**	**233**		**100.0 %**	**1.33 [1.07, 1.64]**
Total events: 117 (Rituximab (500mg)+MTX), 86 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.61 (P = 0.0090)					
Test for subgroup differences: Not applicable					

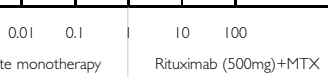
Analysis 3.22. Comparison 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX, Outcome 22 No increase in erosion score.

Review: Rituximab for rheumatoid arthritis

Comparison: 3 Benefits - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 22 No increase in erosion score

Study or subgroup	Rituximab (500mg)+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Tak 2010 (IMAGE)	127/239	89/233		100.0 %	1.39 [1.14, 1.70]
Subtotal (95% CI)	**239**	**233**		**100.0 %**	**1.39 [1.14, 1.70]**
Total events: 127 (Rituximab (500mg)+MTX), 89 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.20 (P = 0.0014)					
Test for subgroup differences: Not applicable					



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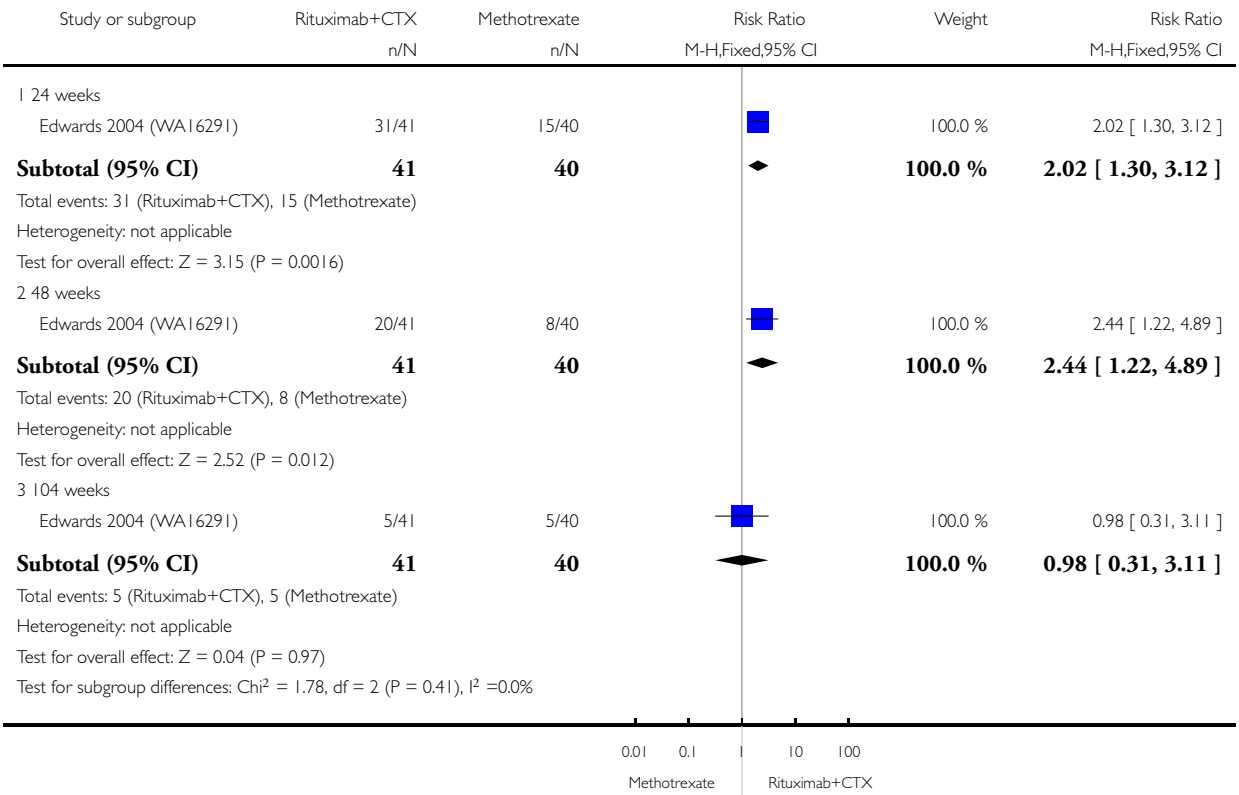
Analysis 4.1. Comparison 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 1 ACR 20.

Review: Rituximab for rheumatoid arthritis

Comparison: 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 1 ACR 20



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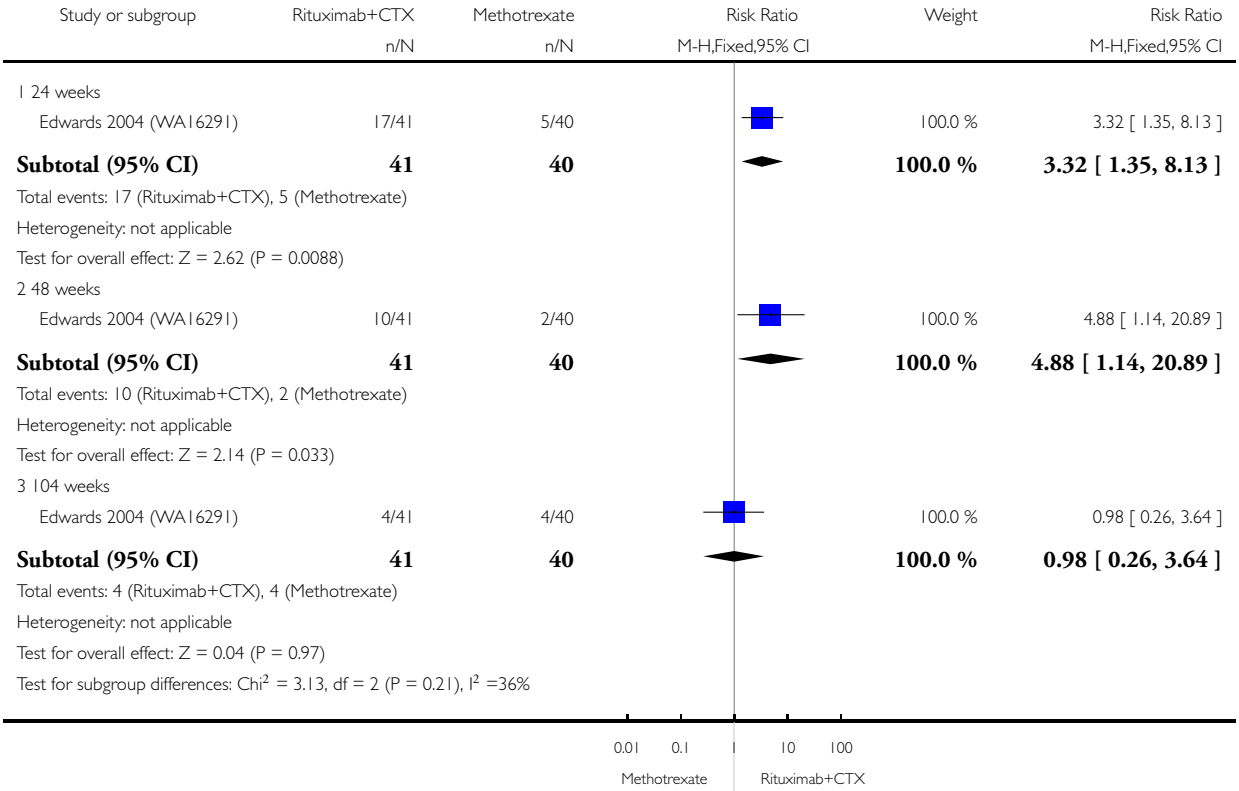
Analysis 4.2. Comparison 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 2 ACR 50



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Analysis 4.3. Comparison 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 3 ACR 70.

Review: Rituximab for rheumatoid arthritis

Comparison: 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 3 ACR 70

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	6/41	2/40		100.0 %	2.93 [0.63, 13.65]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**2.93 [0.63, 13.65]**
Total events: 6 (Rituximab+CTX), 2 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 48 weeks					
Edwards 2004 (WA16291)	4/41	0/40		100.0 %	8.79 [0.49, 158.07]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**8.79 [0.49, 158.07]**
Total events: 4 (Rituximab+CTX), 0 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					
3 104 weeks					
Edwards 2004 (WA16291)	3/41	3/40		100.0 %	0.98 [0.21, 4.55]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.98 [0.21, 4.55]**
Total events: 3 (Rituximab+CTX), 3 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.97)					
Test for subgroup differences: Chi^2 = 2.07, df = 2 (P = 0.35), I^2 =3%					

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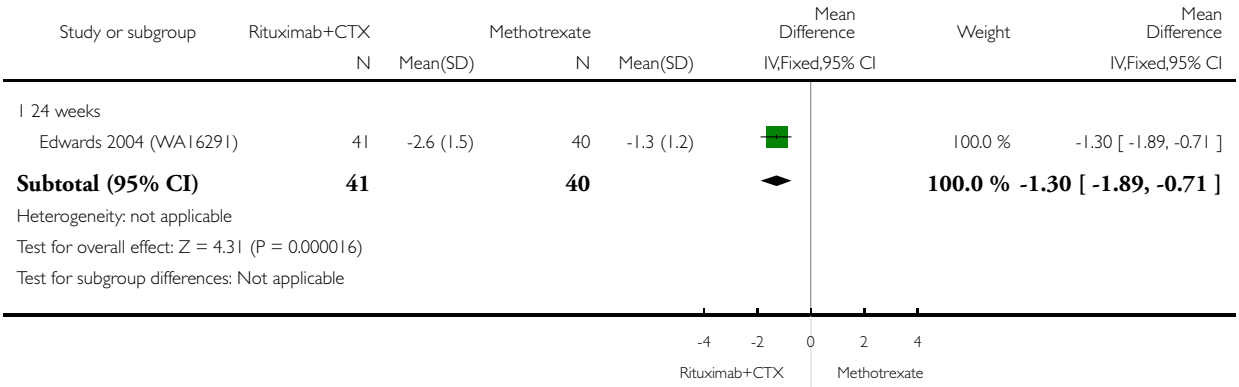
Analysis 4.4. Comparison 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 4 DAS 28.

Review: Rituximab for rheumatoid arthritis

Comparison: 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 4 DAS 28

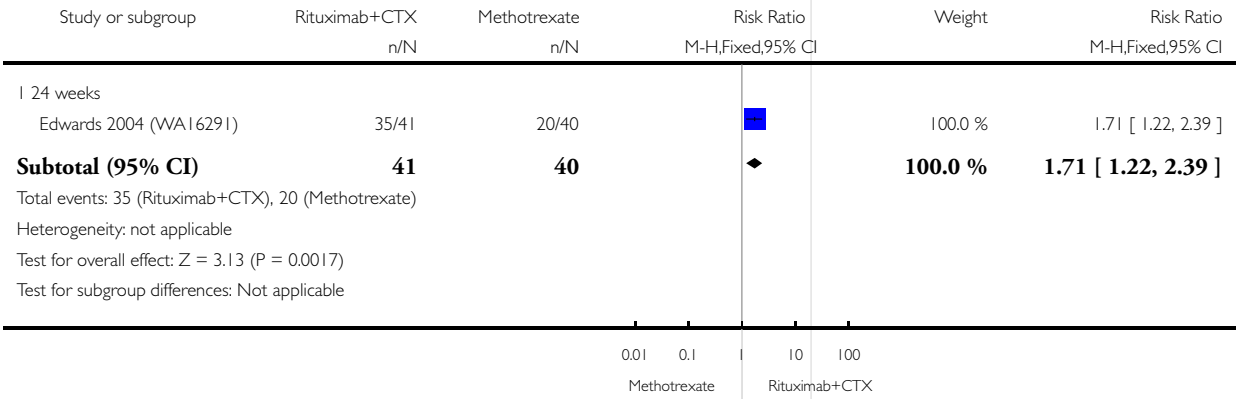


Analysis 4.5. Comparison 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 5 Moderate or good EULAR response.

Review: Rituximab for rheumatoid arthritis

Comparison: 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 5 Moderate or good EULAR response



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Analysis 4.6. Comparison 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 6 HAQ-DI.

Review: Rituximab for rheumatoid arthritis

Comparison: 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 6 HAQ-DI

Study or subgroup	Rituximab+CTX N	Mean(SD)	Methotrexate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Edwards 2004 (WA16291)	37	-0.6 (0.7)	37	-0.4 (0.5)		100.0 %	-0.20 [-0.48, 0.08]
Subtotal (95% CI)	**37**		**37**			**100.0 %**	**-0.20 [-0.48, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.41 (P = 0.16)							
2 48 weeks							
Edwards 2004 (WA16291)	34	-0.3 (0.68)	25	-0.3 (0.54)		100.0 %	0.0 [-0.31, 0.31]
Subtotal (95% CI)	**34**		**25**			**100.0 %**	**0.0 [-0.31, 0.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
3 72 weeks							
Edwards 2004 (WA16291)	22	-0.1 (0.68)	15	-0.3 (0.54)		100.0 %	0.20 [-0.19, 0.59]
Subtotal (95% CI)	**22**		**15**			**100.0 %**	**0.20 [-0.19, 0.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
Test for subgroup differences: Chi^2 = 2.76, df = 2 (P = 0.25), I^2 =28%							

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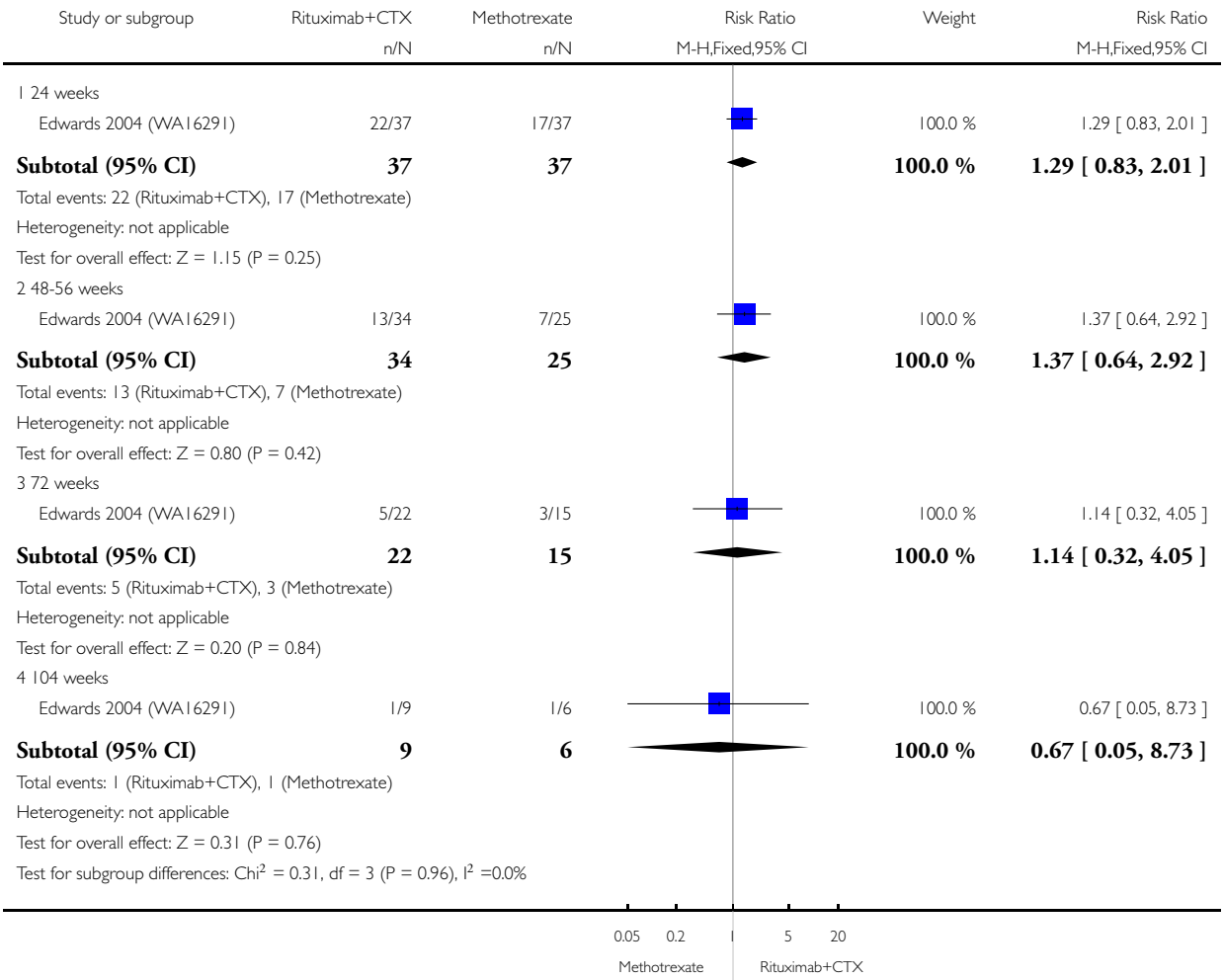
Analysis 4.7. Comparison 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 7 HAQ-DI MCID=-0.22.

Review: Rituximab for rheumatoid arthritis

Comparison: 4 Benefits - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 7 HAQ-DI MCID=-0.22



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Analysis 5.1. Comparison 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi, Outcome 1 ACR 20.

Review: Rituximab for rheumatoid arthritis

Comparison: 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi

Outcome: 1 ACR 20

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	10/33	3/18		100.0 %	1.82 [0.57, 5.77]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**1.82 [0.57, 5.77]**
Total events: 10 (RTX+MTX+TNFi), 3 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
Test for subgroup differences: Not applicable					

Analysis 5.2. Comparison 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi, Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi

Outcome: 2 ACR 50

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	4/33	1/12		100.0 %	1.45 [0.18, 11.75]
Subtotal (95% CI)	**33**	**12**		**100.0 %**	**1.45 [0.18, 11.75]**
Total events: 4 (RTX+MTX+TNFi), 1 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.73)					
Test for subgroup differences: Not applicable					

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Analysis 5.3. Comparison 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi, Outcome 3 LDA (DAS28 =or<3.2).

Review: Rituximab for rheumatoid arthritis

Comparison: 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi

Outcome: 3 LDA (DAS28 =or<3.2)

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	8/33	2/18		100.0 %	2.18 [0.52, 9.20]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**2.18 [0.52, 9.20]**
Total events: 8 (RTX+MTX+TNFi), 2 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
Test for subgroup differences: Not applicable					

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Analysis 5.4. Comparison 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi, Outcome 4 Clinical Remission (DAS28<2.6).

Review: Rituximab for rheumatoid arthritis

Comparison: 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi

Outcome: 4 Clinical Remission (DAS28<2.6)

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	6/33	1/18		100.0 %	3.27 [0.43, 25.11]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**3.27 [0.43, 25.11]**
Total events: 6 (RTX+MTX+TNFi), 1 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.14 (P = 0.25)					
Test for subgroup differences: Not applicable					

Analysis 5.5. Comparison 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi, Outcome 5 HAQ-DI MCID=-0.25.

Review: Rituximab for rheumatoid arthritis

Comparison: 5 Benefits - RTX (2 x 500 mg) + MTX + TNFi versus MTX + TNFi

Outcome: 5 HAQ-DI MCID=-0.25

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	28/33	4/18		100.0 %	3.82 [1.59, 9.17]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**3.82 [1.59, 9.17]**
Total events: 28 (RTX+MTX+TNFi), 4 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.00 (P = 0.0027)					
Test for subgroup differences: Not applicable					

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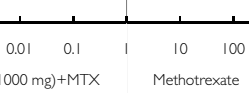
Analysis 6.1. Comparison 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 1 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 1 Total discontinuations

Study or subgroup	Rituximab+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	55/308	96/209		63.8 %	0.39 [0.29, 0.51]
Edwards 2004 (WA16291)	1/40	3/40		1.0 %	0.33 [0.04, 3.07]
Emery 2006 (DANCER)	27/192	52/149		29.6 %	0.40 [0.27, 0.61]
Emery 2010 (SERENE)	6/172	13/172		5.7 %	0.46 [0.18, 1.19]
Subtotal (95% CI)	**712**	**570**		**100.0 %**	**0.40 [0.32, 0.50]**
Total events: 89 (Rituximab+MTX), 164 (Methotrexate)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.15, df = 3 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 8.09 (P < 0.00001)					
2 48-52 weeks					
Cohen 2006 (REFLEX)	194/308	185/209		44.5 %	0.71 [0.64, 0.79]
Edwards 2004 (WA16291)	2/40	15/40		7.2 %	0.13 [0.03, 0.55]
Emery 2010 (SERENE)	15/172	18/172		21.2 %	0.83 [0.43, 1.60]
Tak 2010 (IMAGE)	21/251	39/252		27.2 %	0.54 [0.33, 0.89]
Subtotal (95% CI)	**771**	**673**		**100.0 %**	**0.61 [0.40, 0.91]**
Total events: 232 (Rituximab+MTX), 257 (Methotrexate)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 7.82, df = 3 (P = 0.05); I^2 =62%					
Test for overall effect: Z = 2.39 (P = 0.017)					
3 72 weeks					
Edwards 2004 (WA16291)	12/40	25/40		100.0 %	0.48 [0.28, 0.82]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.48 [0.28, 0.82]**
Total events: 12 (Rituximab+MTX), 25 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.71 (P = 0.0067)					
4 104 weeks					



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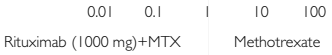
Study or subgroup	Rituximab+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Edwards 2004 (WA16291)	22/40	34/40		56.1 %	0.65 [0.48, 0.88]
Tak 2010 (IMAGE)	37/250	72/249		43.9 %	0.51 [0.36, 0.73]
Subtotal (95% CI)	**290**	**289**		**100.0 %**	**0.58 [0.45, 0.75]**
Total events: 59 (Rituximab+MTX), 106 (Methotrexate)					
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 1 (P = 0.28); I² =13%					
Test for overall effect: Z = 4.22 (P = 0.000025)					
Test for subgroup differences: Chi² = 6.36, df = 3 (P = 0.10), I² =53%					



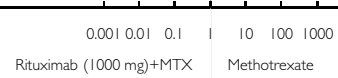
Analysis 6.2. Comparison 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 2 Lack of efficacy.

Review: Rituximab for rheumatoid arthritis

Comparison: 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 2 Lack of efficacy

Study or subgroup	Rituximab+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	46/308	94/209		64.4 %	0.33 [0.24, 0.45]
Edwards 2004 (WA16291)	0/40	2/40		1.4 %	0.20 [0.01, 4.04]
Emery 2006 (DANCER)	16/192	46/149		29.8 %	0.27 [0.16, 0.46]
Emery 2010 (SERENE)	0/172	7/172		4.3 %	0.07 [0.00, 1.16]
Subtotal (95% CI)	**712**	**570**		**100.0 %**	**0.30 [0.23, 0.39]**
Total events: 62 (Rituximab+MTX), 149 (Methotrexate)					
Heterogeneity: Chi² = 1.71, df = 3 (P = 0.63); I² =0.0%					
Test for overall effect: Z = 8.93 (P < 0.00001)					
2 48-52 weeks					
Edwards 2004 (WA16291)	1/40	7/40		18.7 %	0.14 [0.02, 1.11]



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(. . . *Continued*)

Study or subgroup	Rituximab+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Emery 2010 (SERENE)	0/172	11/172		30.7 %	0.04 [0.00, 0.73]
Tak 2010 (IMAGE)	4/251	19/252		50.6 %	0.21 [0.07, 0.61]
Subtotal (95% CI)	**463**	**464**		**100.0 %**	**0.15 [0.06, 0.36]**
Total events: 5 (Rituximab+MTX), 37 (Methotrexate)					
Heterogeneity: Chi^2 = 1.16, df = 2 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 4.25 (P = 0.000021)					
3 72 weeks					
Edwards 2004 (WA16291)	4/40	9/40		100.0 %	0.44 [0.15, 1.33]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.44 [0.15, 1.33]**
Total events: 4 (Rituximab+MTX), 9 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
4 104 weeks					
Edwards 2004 (WA16291)	4/40	17/40		100.0 %	0.24 [0.09, 0.64]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.24 [0.09, 0.64]**
Total events: 4 (Rituximab+MTX), 17 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.84 (P = 0.0045)					
Test for subgroup differences: Chi^2 = 3.08, df = 3 (P = 0.38), I^2 =3%					

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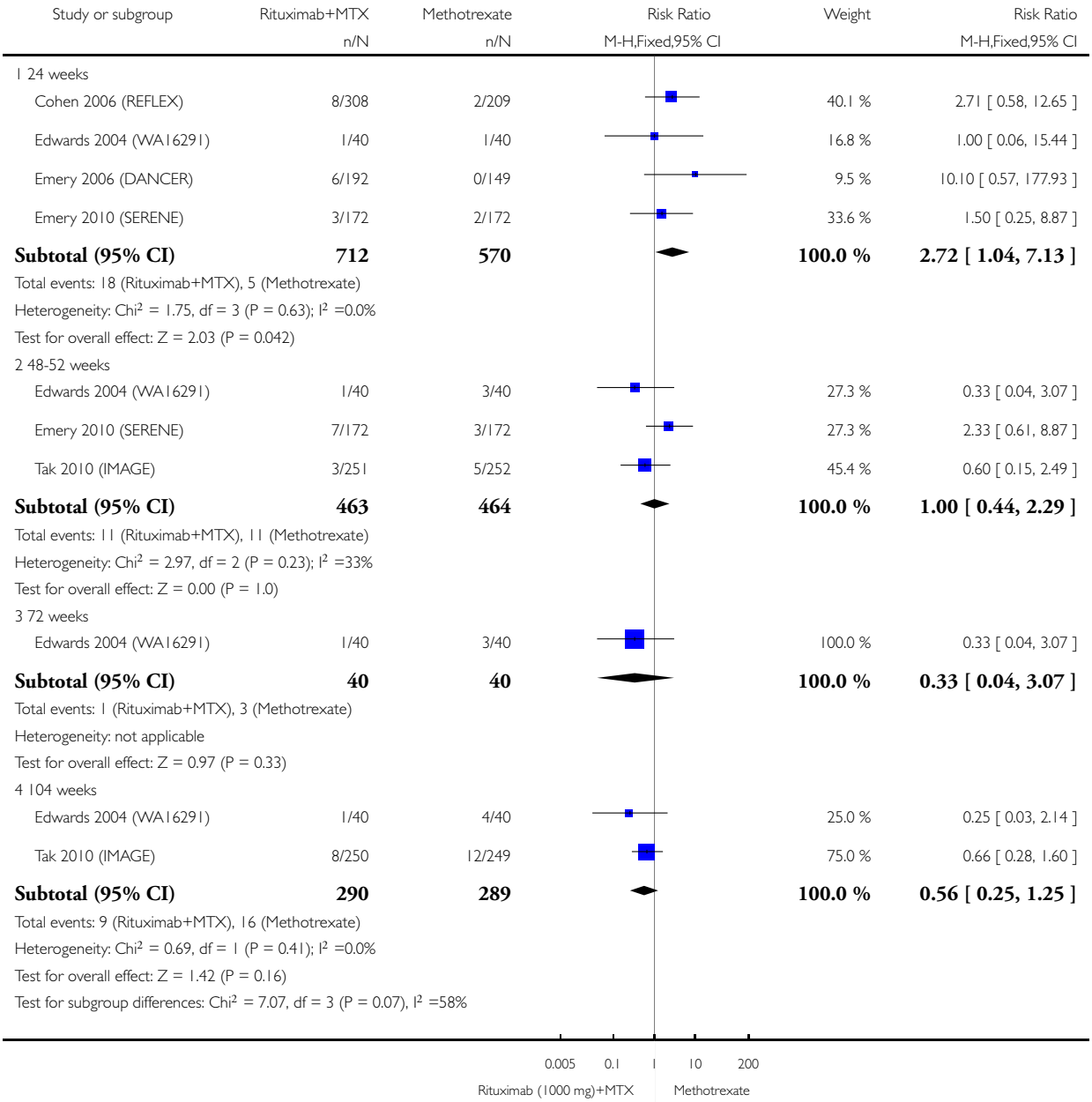
Analysis 6.3. Comparison 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 3 Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 3 Adverse Events



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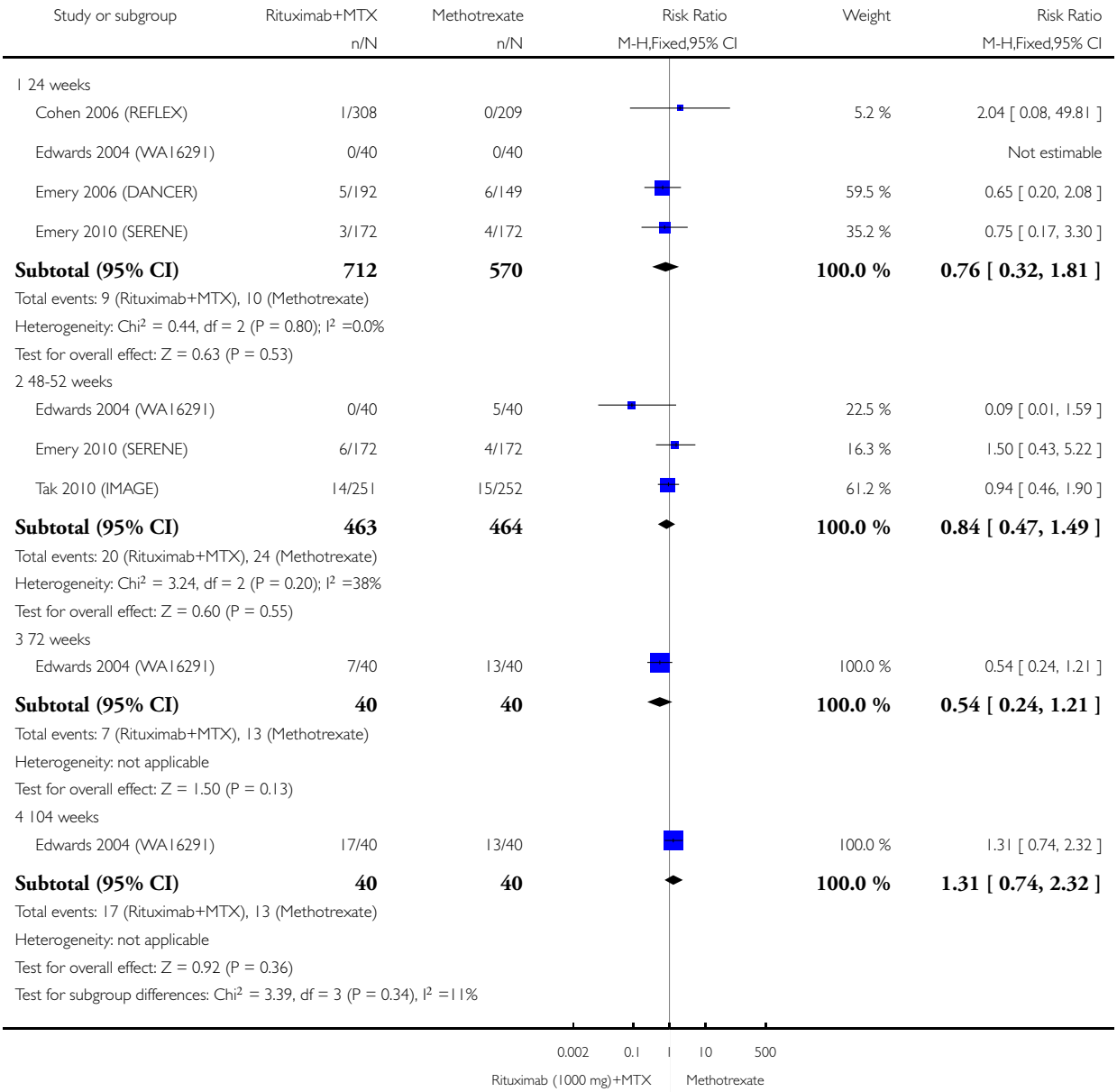
Analysis 6.4. Comparison 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 4 Other reasons.

Review: Rituximab for rheumatoid arthritis

Comparison: 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 4 Other reasons



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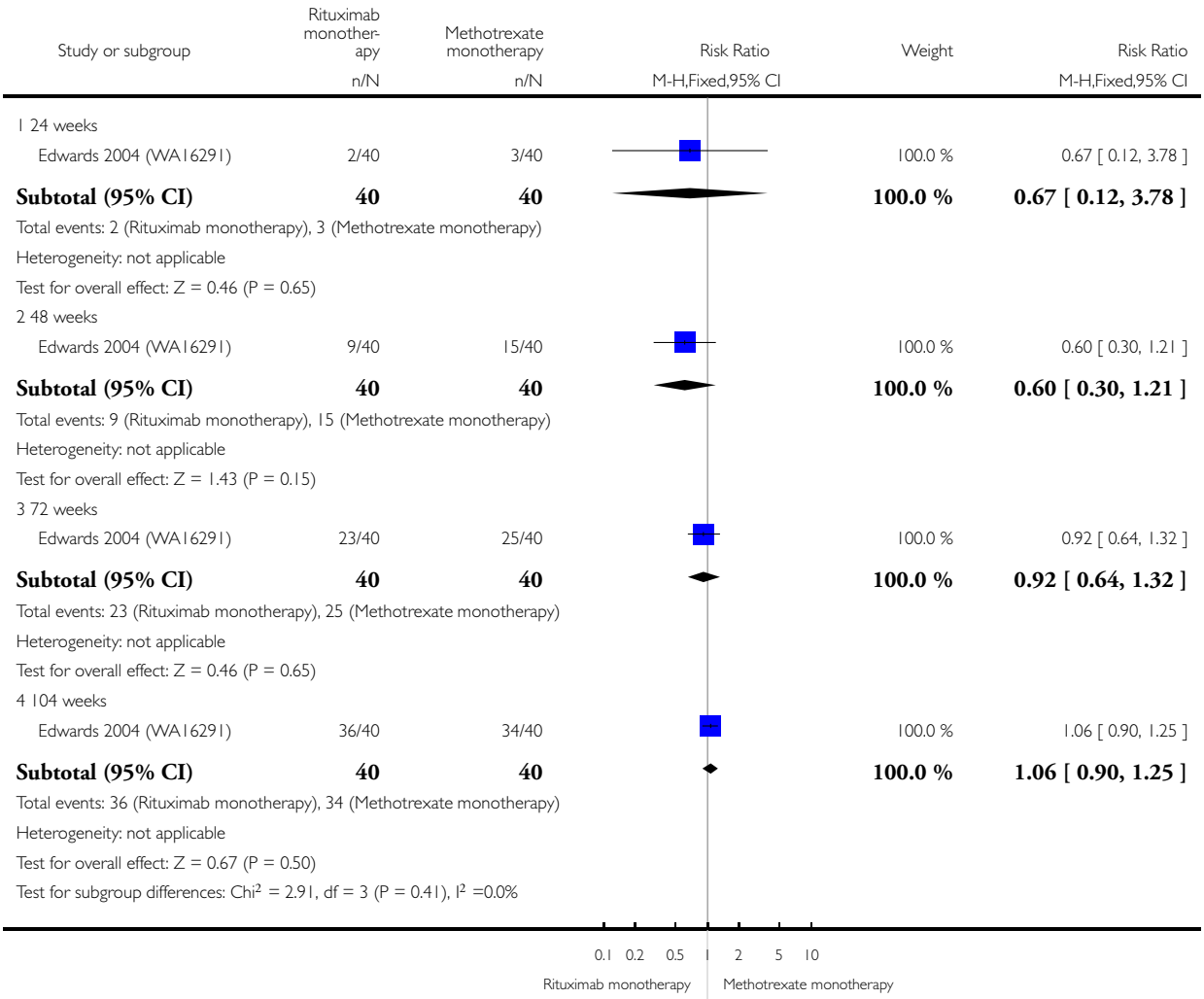
Analysis 7.1. Comparison 7 Withdrawals - RTX monotherapy versus MTX monotherapy, Outcome 1 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 7 Withdrawals - RTX monotherapy versus MTX monotherapy

Outcome: 1 Total discontinuations



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Analysis 7.2. Comparison 7 Withdrawals - RTX monotherapy versus MTX monotherapy, Outcome 2 Lack of efficacy.

Review: Rituximab for rheumatoid arthritis

Comparison: 7 Withdrawals - RTX monotherapy versus MTX monotherapy

Outcome: 2 Lack of efficacy

Study or subgroup	Rituximab monotherapy n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/40	2/40		100.0 %	0.20 [0.01, 4.04]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.20 [0.01, 4.04]**
Total events: 0 (Rituximab monotherapy), 2 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
2 48 weeks					
Edwards 2004 (WA16291)	2/40	7/40		100.0 %	0.29 [0.06, 1.29]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.29 [0.06, 1.29]**
Total events: 2 (Rituximab monotherapy), 7 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.63 (P = 0.10)					
3 72 weeks					
Edwards 2004 (WA16291)	3/40	9/40		100.0 %	0.33 [0.10, 1.14]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.33 [0.10, 1.14]**
Total events: 3 (Rituximab monotherapy), 9 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.080)					
4 104 weeks					
Edwards 2004 (WA16291)	5/40	17/40		100.0 %	0.29 [0.12, 0.72]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.29 [0.12, 0.72]**
Total events: 5 (Rituximab monotherapy), 17 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.68 (P = 0.0074)					
Test for subgroup differences: Chi^2 = 0.10, df = 3 (P = 0.99), I^2 =0.0%					

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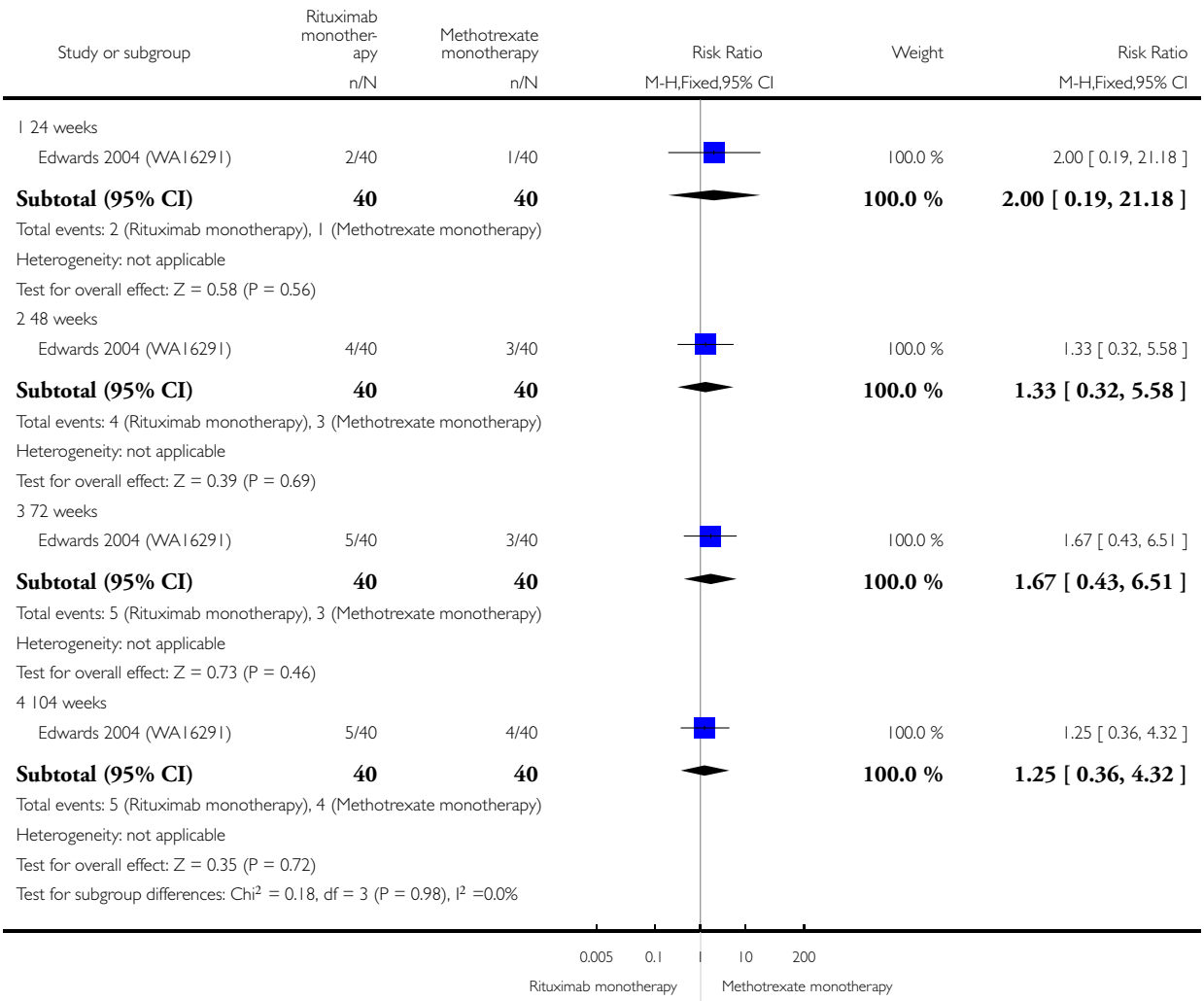
Analysis 7.3. Comparison 7 Withdrawals - RTX monotherapy versus MTX monotherapy, Outcome 3 Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 7 Withdrawals - RTX monotherapy versus MTX monotherapy

Outcome: 3 Adverse Events



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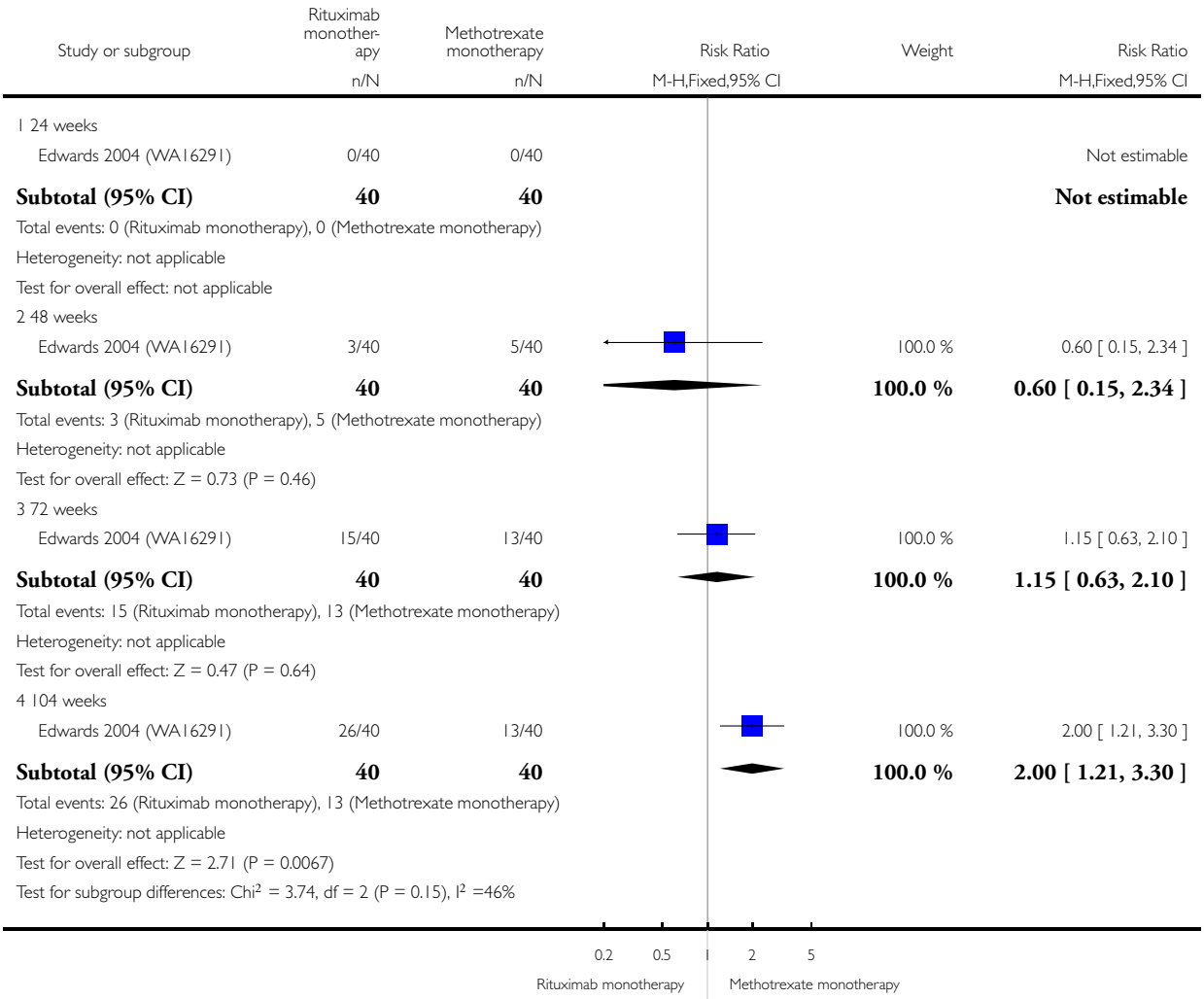
Analysis 7.4. Comparison 7 Withdrawals - RTX monotherapy versus MTX monotherapy, Outcome 4 Other reasons.

Review: Rituximab for rheumatoid arthritis

Comparison: 7 Withdrawals - RTX monotherapy versus MTX monotherapy

Outcome: 4 Other reasons



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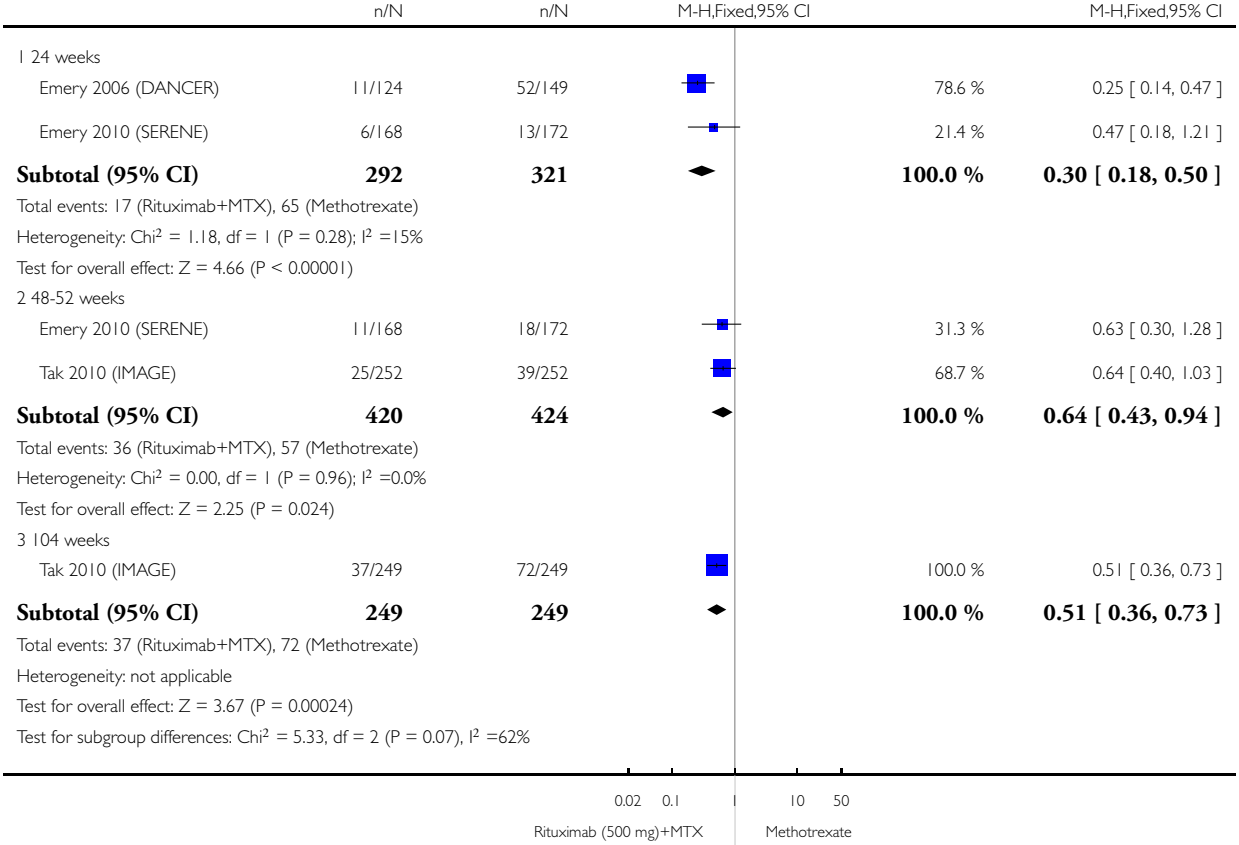
Analysis 8.1. Comparison 8 Withdrawals - RTX (2 x 500 mg) + MTX versus MTX, Outcome 1 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 8 Withdrawals - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 1 Total discontinuations

Study or subgroup	Rituximab+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	11/124	52/149		78.6 %	0.25 [0.14, 0.47]
Emery 2010 (SERENE)	6/168	13/172		21.4 %	0.47 [0.18, 1.21]
Subtotal (95% CI)	**292**	**321**		**100.0 %**	**0.30 [0.18, 0.50]**
Total events: 17 (Rituximab+MTX), 65 (Methotrexate)					
Heterogeneity: Chi² = 1.18, df = 1 (P = 0.28); I² =15%					
Test for overall effect: Z = 4.66 (P < 0.00001)					
2 48-52 weeks					
Emery 2010 (SERENE)	11/168	18/172		31.3 %	0.63 [0.30, 1.28]
Tak 2010 (IMAGE)	25/252	39/252		68.7 %	0.64 [0.40, 1.03]
Subtotal (95% CI)	**420**	**424**		**100.0 %**	**0.64 [0.43, 0.94]**
Total events: 36 (Rituximab+MTX), 57 (Methotrexate)					
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² =0.0%					
Test for overall effect: Z = 2.25 (P = 0.024)					
3 104 weeks					
Tak 2010 (IMAGE)	37/249	72/249		100.0 %	0.51 [0.36, 0.73]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**0.51 [0.36, 0.73]**
Total events: 37 (Rituximab+MTX), 72 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.67 (P = 0.00024)					
Test for subgroup differences: Chi² = 5.33, df = 2 (P = 0.07), I² =62%					



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Analysis 8.2. Comparison 8 Withdrawals - RTX (2 x 500 mg) + MTX versus MTX, Outcome 2 Lack of efficacy.

Review: Rituximab for rheumatoid arthritis

Comparison: 8 Withdrawals - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 2 Lack of efficacy

Study or subgroup	Rituximab+MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	8/124	46/149		85.8 %	0.21 [0.10, 0.43]
Emery 2010 (SERENE)	1/168	7/172		14.2 %	0.15 [0.02, 1.18]
Subtotal (95% CI)	**292**	**321**		**100.0 %**	**0.20 [0.10, 0.39]**
Total events: 9 (Rituximab+MTX), 53 (Methotrexate)					
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 4.68 (P < 0.00001)					
2 48-52 weeks					
Emery 2010 (SERENE)	2/168	11/172		36.4 %	0.19 [0.04, 0.83]
Tak 2010 (IMAGE)	9/252	19/252		63.6 %	0.47 [0.22, 1.03]
Subtotal (95% CI)	**420**	**424**		**100.0 %**	**0.37 [0.19, 0.73]**
Total events: 11 (Rituximab+MTX), 30 (Methotrexate)					
Heterogeneity: Chi^2 = 1.21, df = 1 (P = 0.27); I^2 =17%					
Test for overall effect: Z = 2.88 (P = 0.0039)					
Test for subgroup differences: Chi^2 = 1.58, df = 1 (P = 0.21), I^2 =37%					

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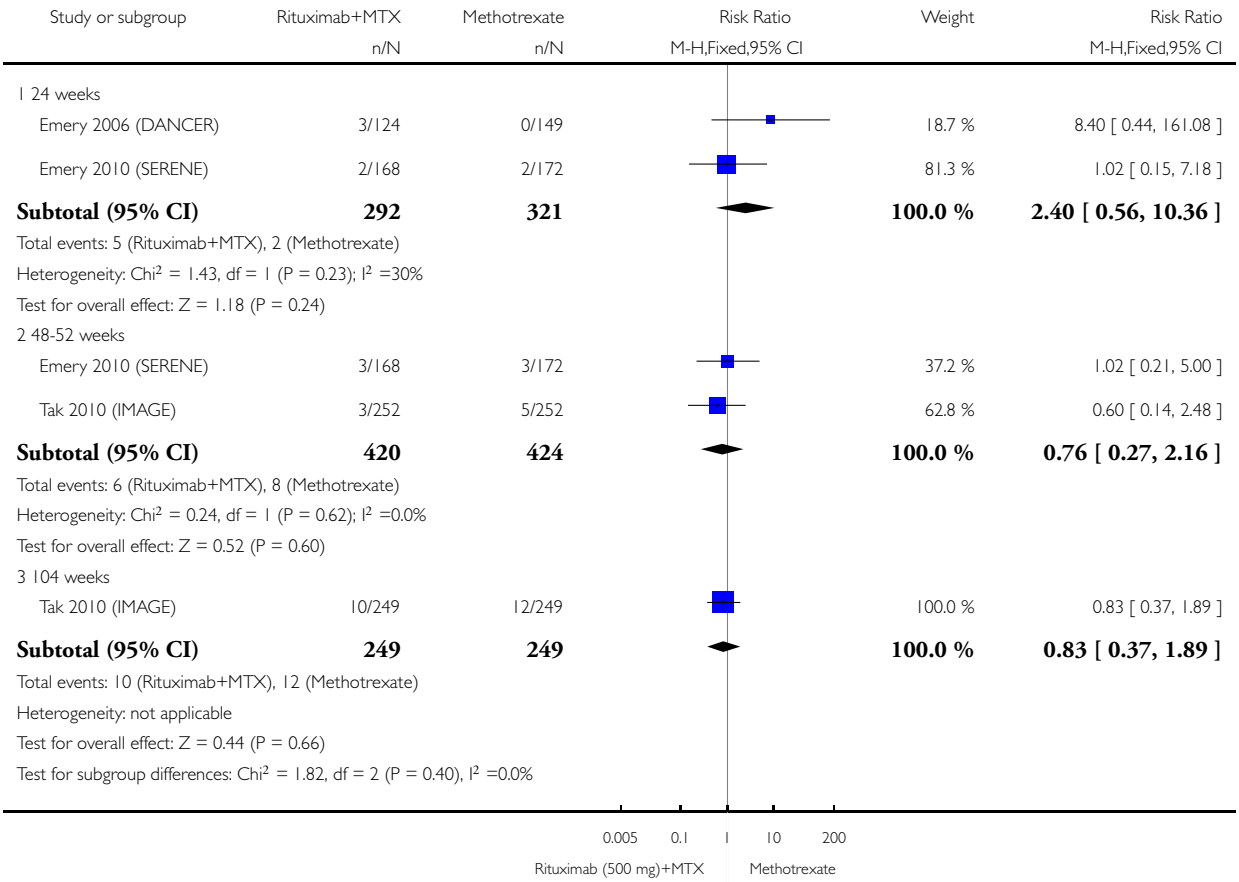
Analysis 8.3. Comparison 8 Withdrawals - RTX (2 x 500 mg) + MTX versus MTX, Outcome 3 Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 8 Withdrawals - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 3 Adverse Events



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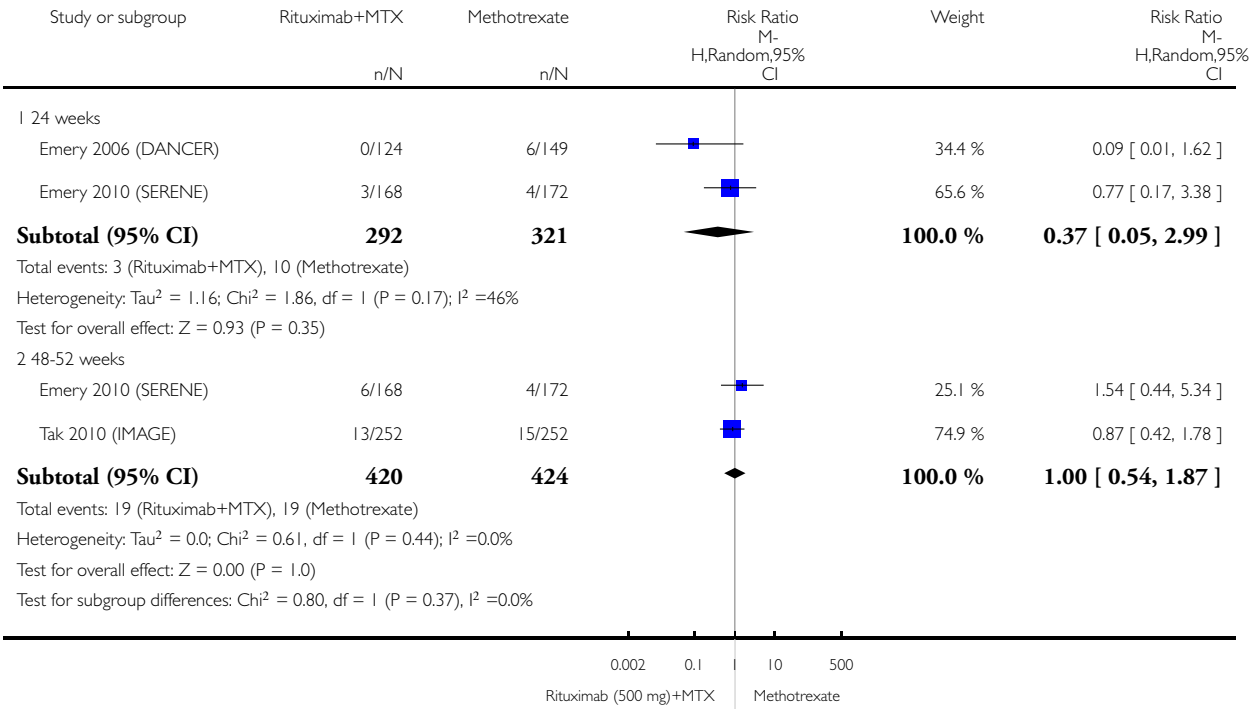
Analysis 8.4. Comparison 8 Withdrawals - RTX (2 x 500 mg) + MTX versus MTX, Outcome 4 Other reasons.

Review: Rituximab for rheumatoid arthritis

Comparison: 8 Withdrawals - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 4 Other reasons



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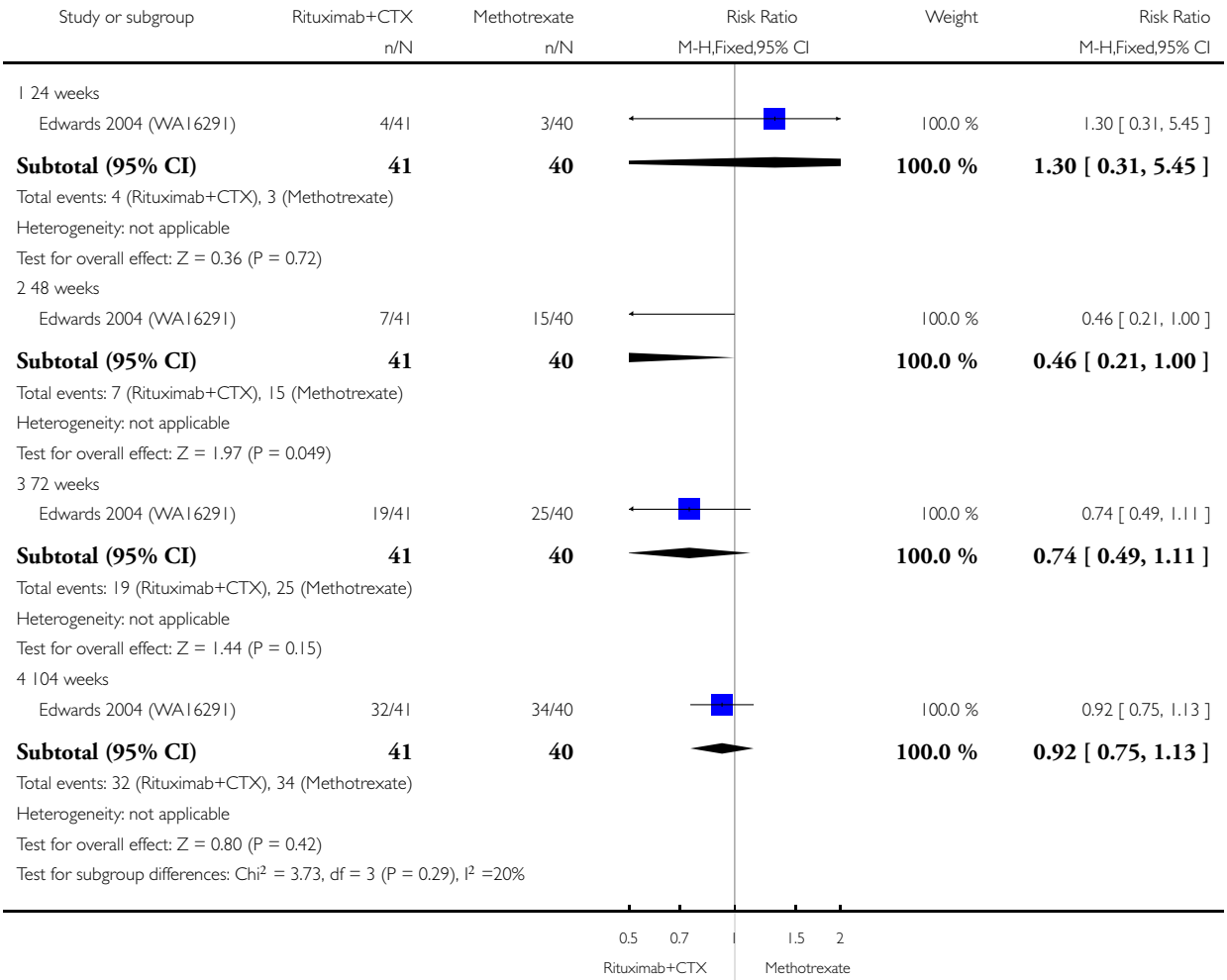
Analysis 9.1. Comparison 9 Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 1 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 9 Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 1 Total discontinuations



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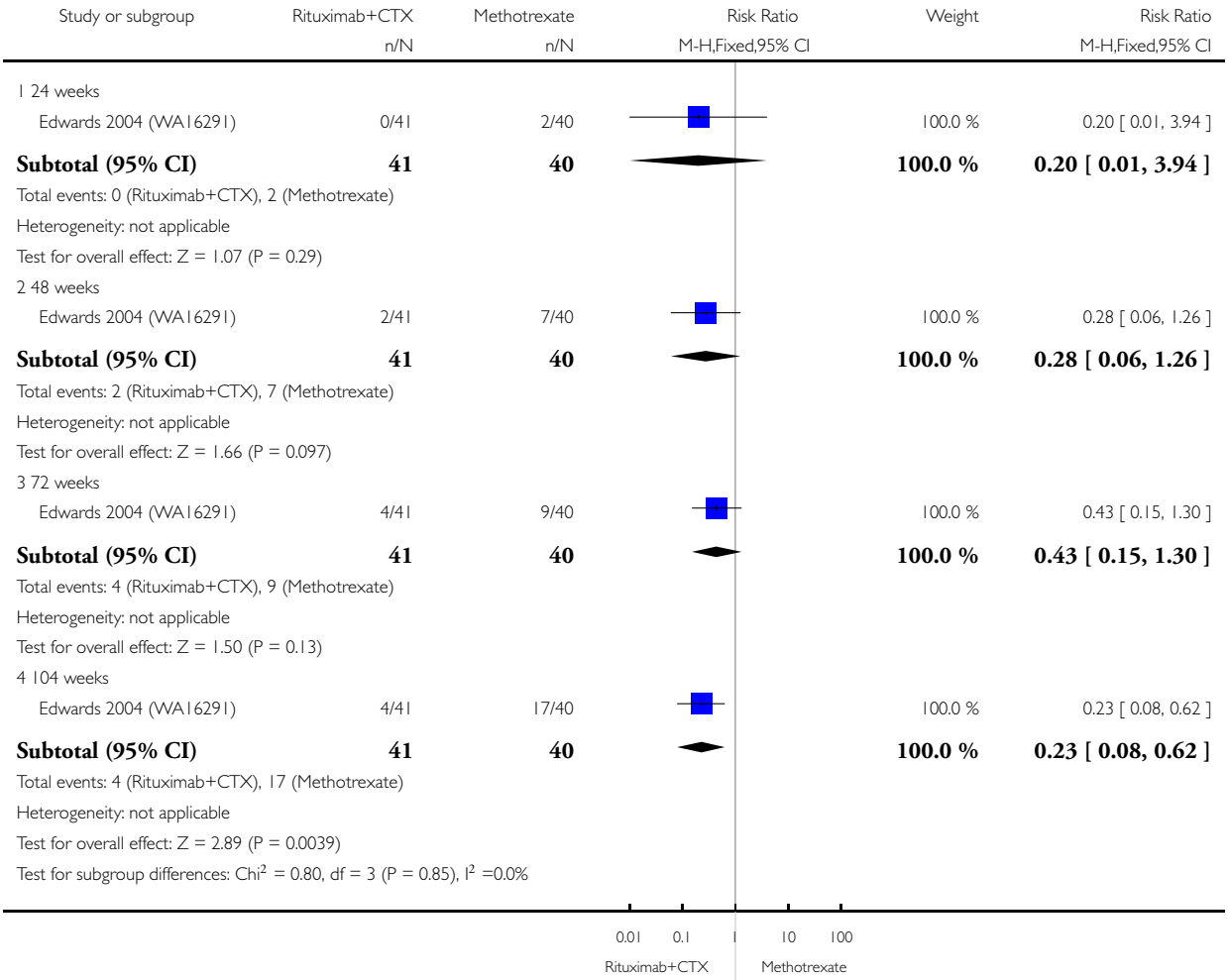
Analysis 9.2. Comparison 9 Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 2 Lack of efficacy.

Review: Rituximab for rheumatoid arthritis

Comparison: 9 Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 2 Lack of efficacy



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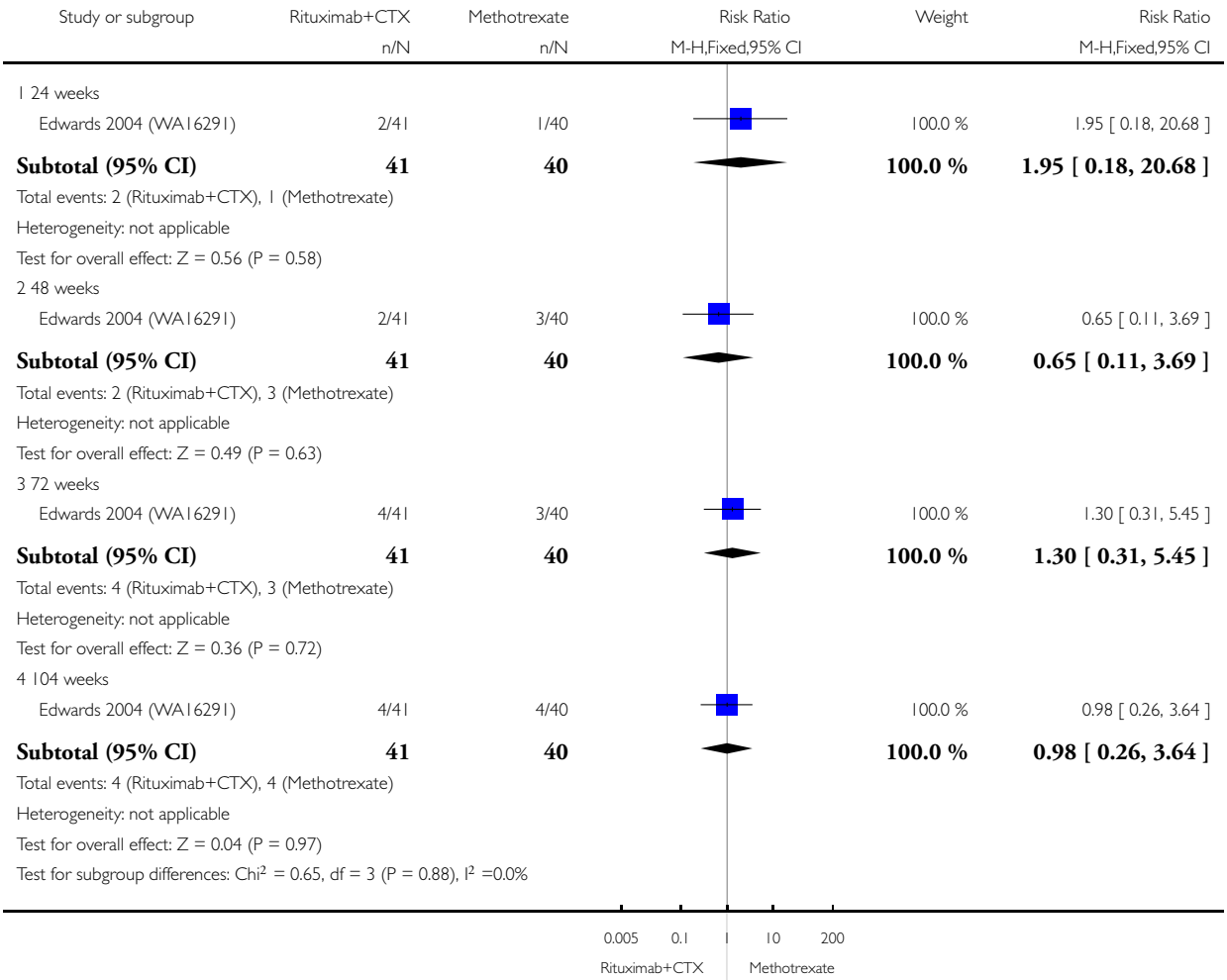
Analysis 9.3. Comparison 9 Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 3 Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 9 Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 3 Adverse Events



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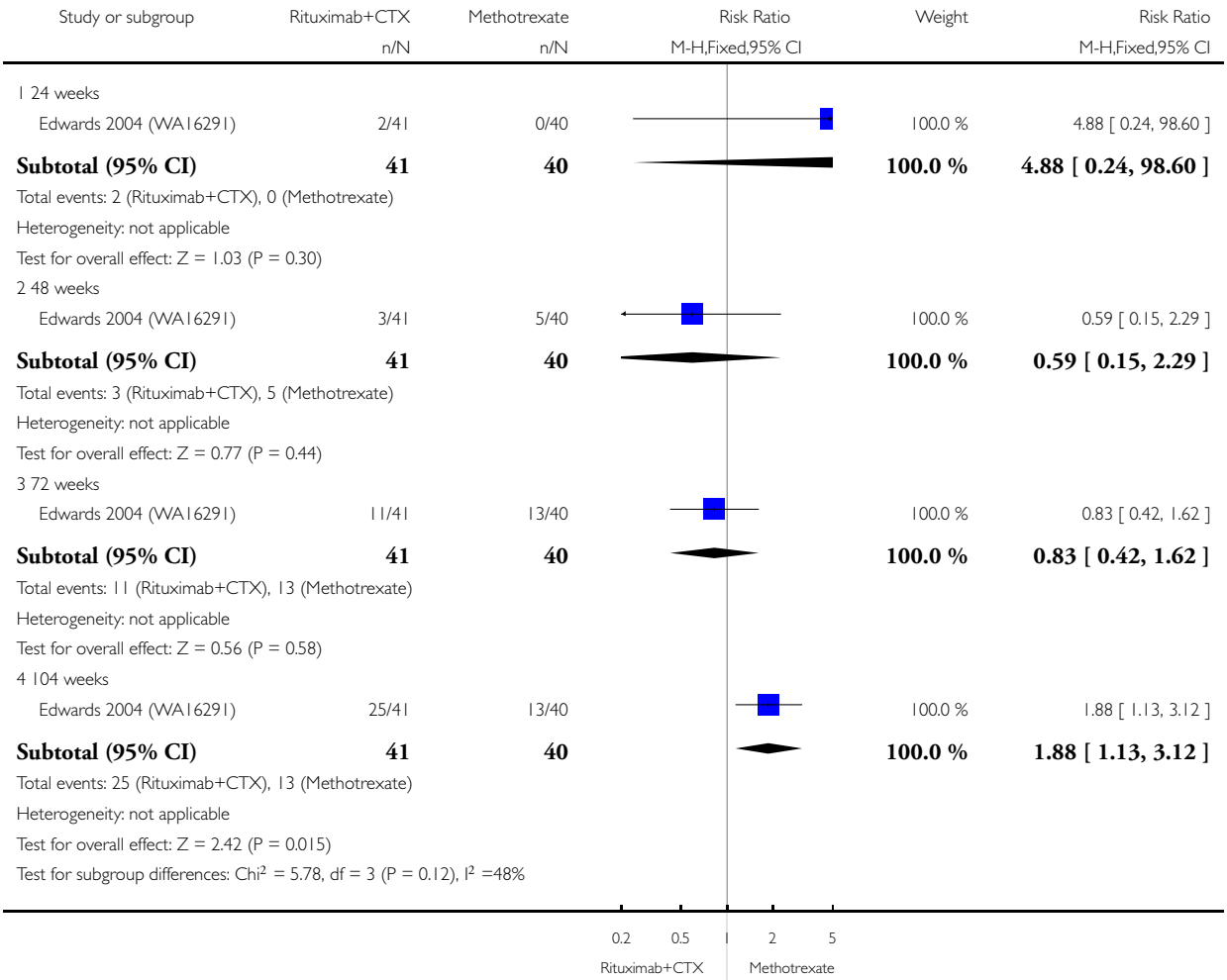
Analysis 9.4. Comparison 9 Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 4 Other reasons.

Review: Rituximab for rheumatoid arthritis

Comparison: 9 Withdrawals - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 4 Other reasons



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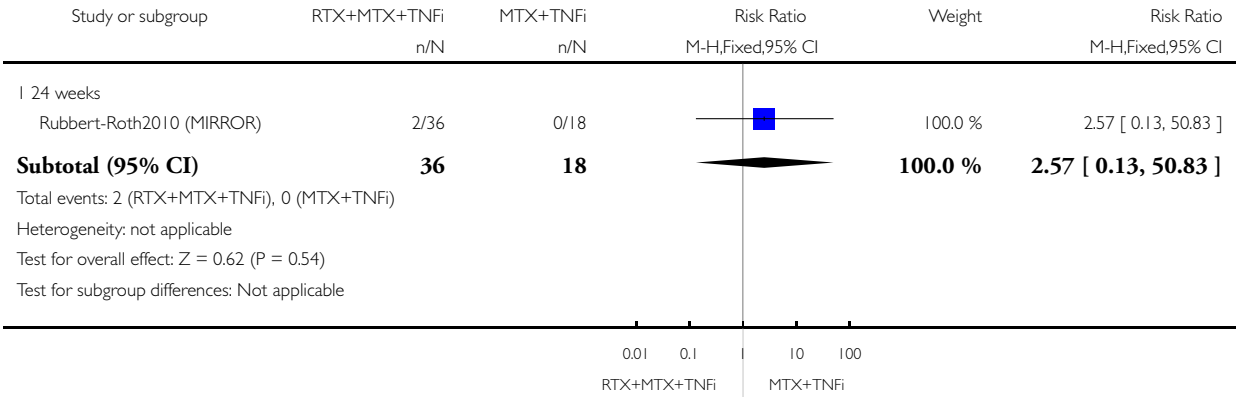
Analysis 10.1. Comparison 10 Withdrawals - RTX + MTX + TNFi versus MTX + TNFi, Outcome 1 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 10 Withdrawals - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 1 Total discontinuations

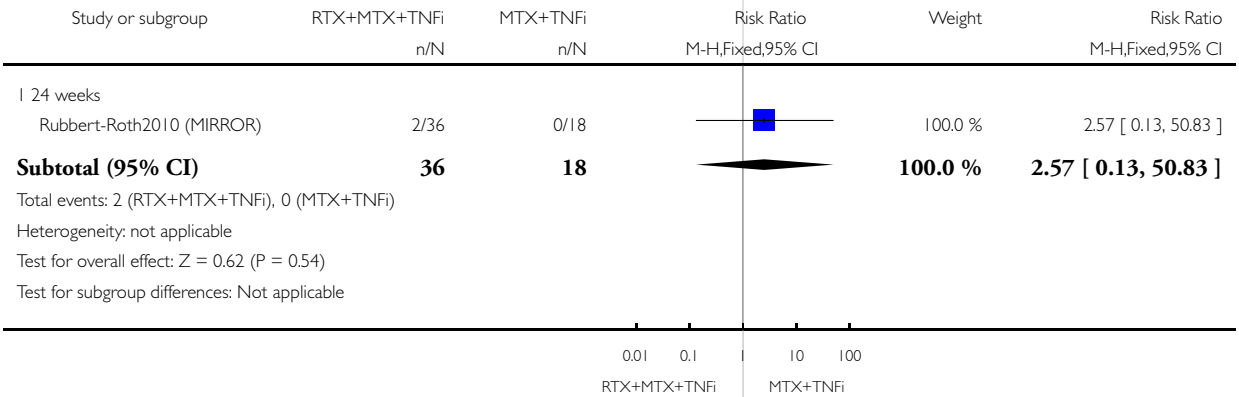


Analysis 10.2. Comparison 10 Withdrawals - RTX + MTX + TNFi versus MTX + TNFi, Outcome 2 Adverse events.

Review: Rituximab for rheumatoid arthritis

Comparison: 10 Withdrawals - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 2 Adverse events



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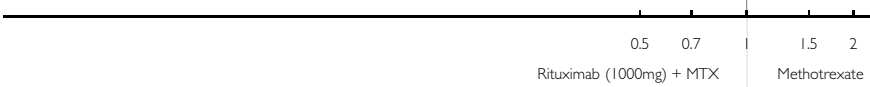
Analysis 11.1. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 1 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 1 Any Adverse Event

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	261/308	183/209		31.9 %	0.97 [0.90, 1.04]
Edwards 2004 (WA16291)	34/40	32/40		16.7 %	1.06 [0.87, 1.30]
Emery 2006 (DANCER)	164/192	105/149		25.8 %	1.21 [1.08, 1.37]
Emery 2010 (SERENE)	130/170	128/172		25.6 %	1.03 [0.91, 1.16]
Subtotal (95% CI)	**710**	**570**		**100.0 %**	**1.06 [0.95, 1.18]**
Total events: 589 (Rituximab + MTX), 448 (Methotrexate)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 10.83, df = 3 (P = 0.01); I^2 =72%					
Test for overall effect: Z = 0.98 (P = 0.33)					
2 48-56 weeks					
Edwards 2004 (WA16291)	35/40	34/40		19.9 %	1.03 [0.86, 1.23]
Tak 2010 (IMAGE)	197/249	203/250		80.1 %	0.97 [0.89, 1.06]
Subtotal (95% CI)	**289**	**290**		**100.0 %**	**0.99 [0.91, 1.07]**
Total events: 232 (Rituximab + MTX), 237 (Methotrexate)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 0.38 (P = 0.71)					
3 104 weeks					
Tak 2010 (IMAGE)	217/250	215/249		100.0 %	1.01 [0.94, 1.08]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**1.01 [0.94, 1.08]**
Total events: 217 (Rituximab + MTX), 215 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.15 (P = 0.88)					
Test for subgroup differences: Chi^2 = 1.05, df = 2 (P = 0.59), I^2 =0.0%					



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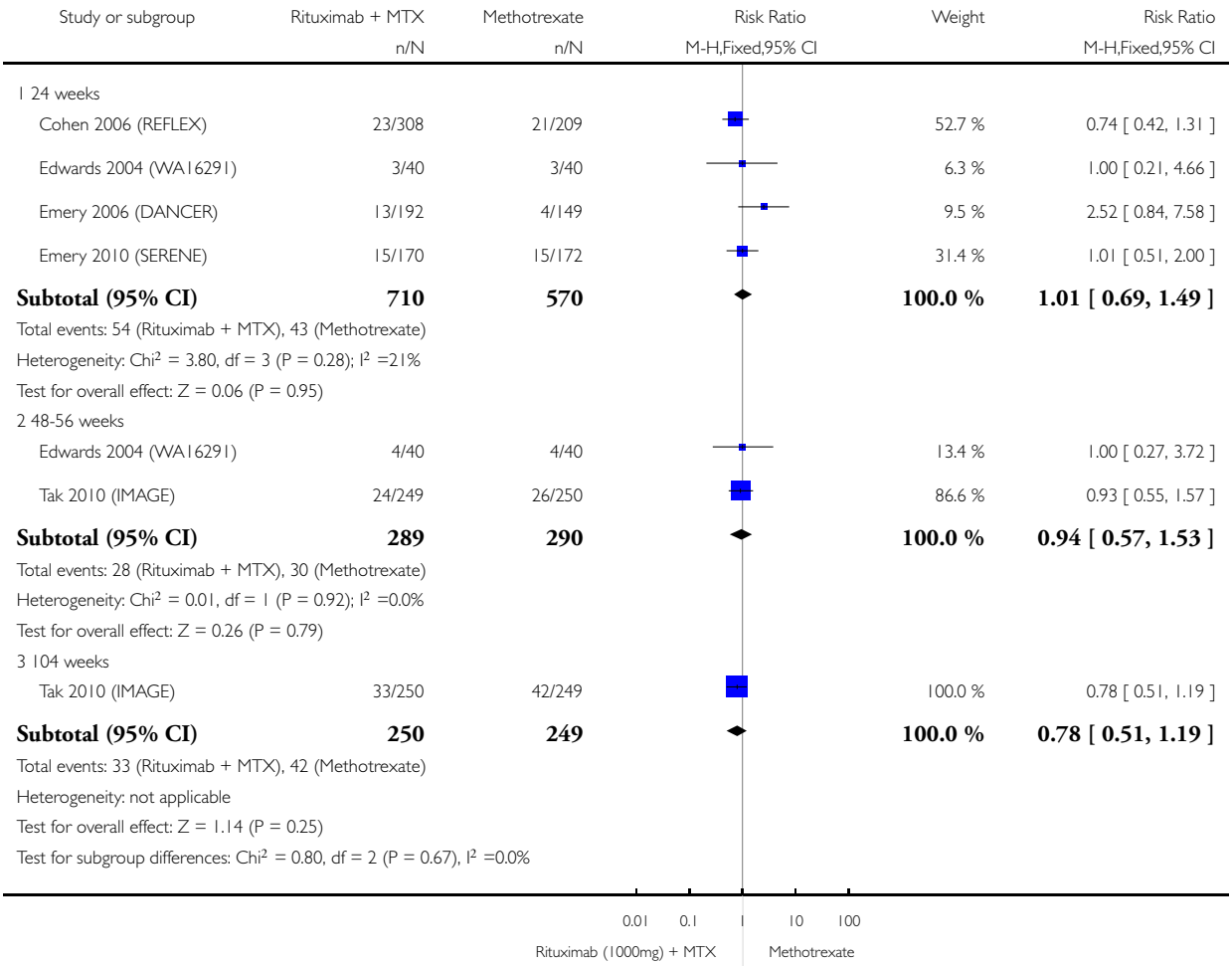
Analysis 11.2. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 2 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 2 Serious Adverse Events



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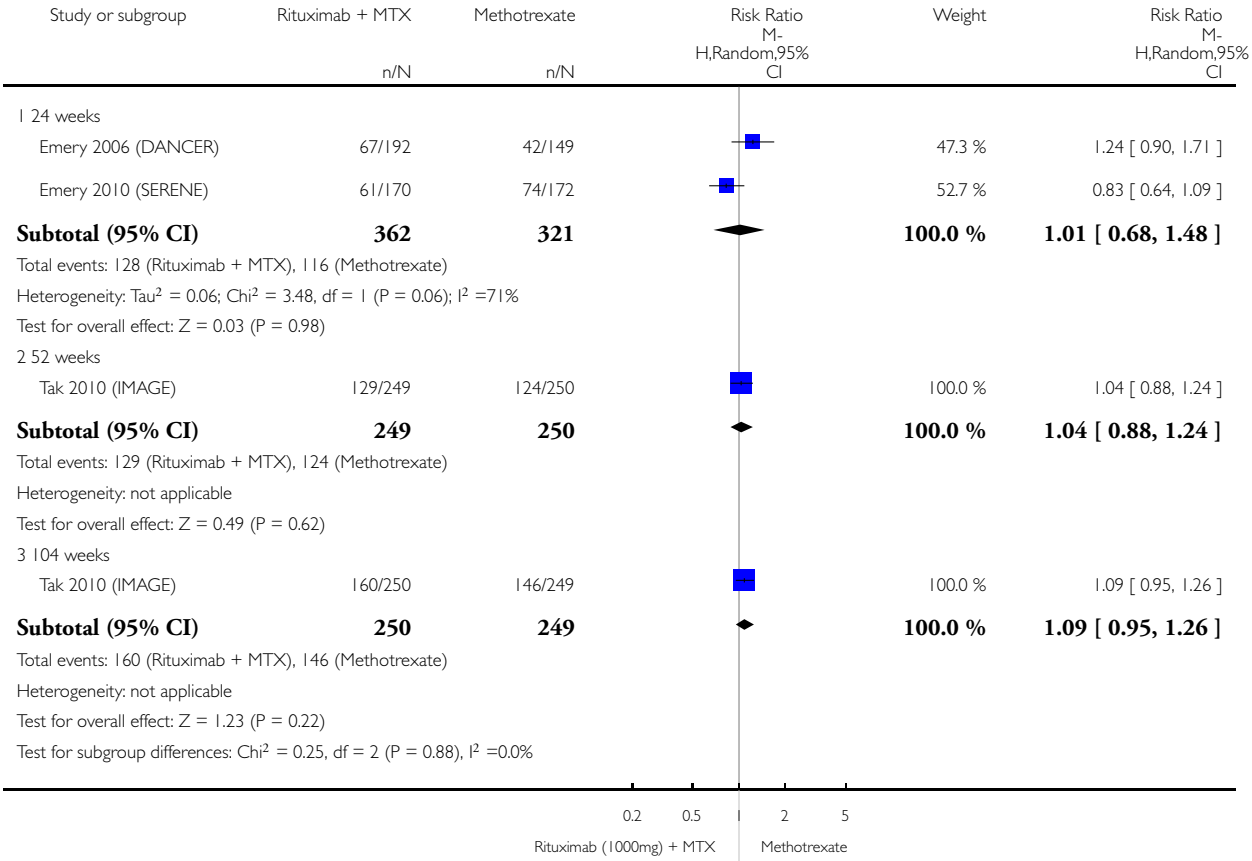
Analysis 11.3. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 3 Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 3 Infections



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Analysis 11.4. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 4 Serious infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 4 Serious infections

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/40	1/40		3.7 %	0.33 [0.01, 7.95]
Emery 2006 (DANCER)	4/192	2/149		5.6 %	1.55 [0.29, 8.36]
Emery 2010 (SERENE)	2/170	4/172		9.9 %	0.51 [0.09, 2.73]
Subtotal (95% CI)	**402**	**361**		**19.2 %**	**0.78 [0.27, 2.25]**
Total events: 6 (Rituximab + MTX), 7 (Methotrexate)					
Heterogeneity: Chi^2 = 1.17, df = 2 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 0.46 (P = 0.64)					
2 48-56 weeks					
Edwards 2004 (WA16291)	1/40	0/40		1.2 %	3.00 [0.13, 71.51]
Tak 2010 (IMAGE)	8/249	13/250		32.2 %	0.62 [0.26, 1.46]
Subtotal (95% CI)	**289**	**290**		**33.5 %**	**0.71 [0.31, 1.59]**
Total events: 9 (Rituximab + MTX), 13 (Methotrexate)					
Heterogeneity: Chi^2 = 0.89, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 0.84 (P = 0.40)					
3 104 weeks					
Tak 2010 (IMAGE)	12/250	19/249		47.3 %	0.63 [0.31, 1.27]
Subtotal (95% CI)	**250**	**249**		**47.3 %**	**0.63 [0.31, 1.27]**
Total events: 12 (Rituximab + MTX), 19 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.20)					
Total (95% CI)	**941**	**900**		**100.0 %**	**0.68 [0.42, 1.10]**
Total events: 27 (Rituximab + MTX), 39 (Methotrexate)					
Heterogeneity: Chi^2 = 2.17, df = 5 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 1.57 (P = 0.12)					
Test for subgroup differences: Chi^2 = 0.12, df = 2 (P = 0.94), I^2 =0.0%					

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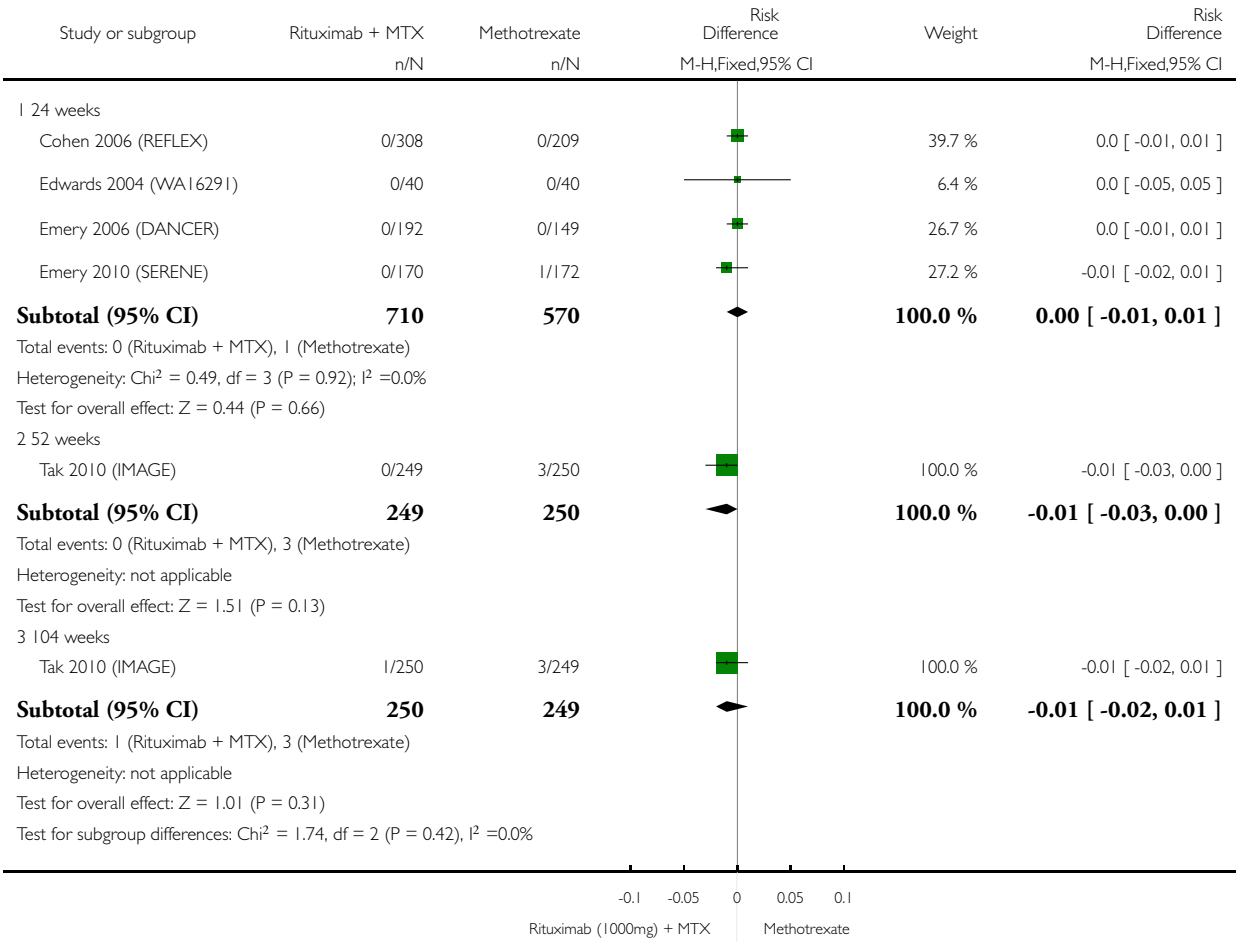
Analysis 11.5. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 5 Death.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 5 Death



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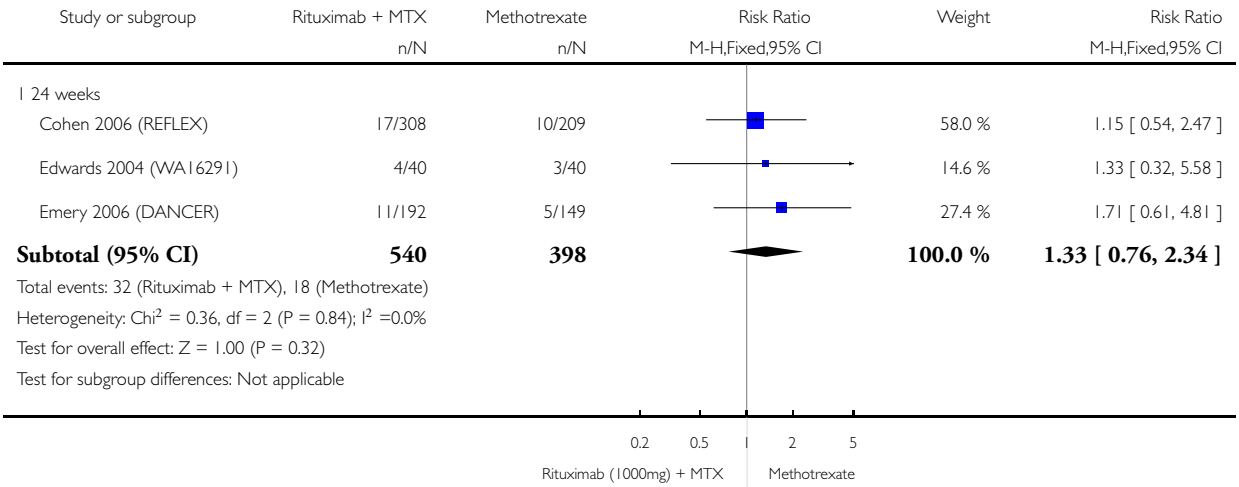
Analysis 11.6. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 6 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 6 Arthralgia



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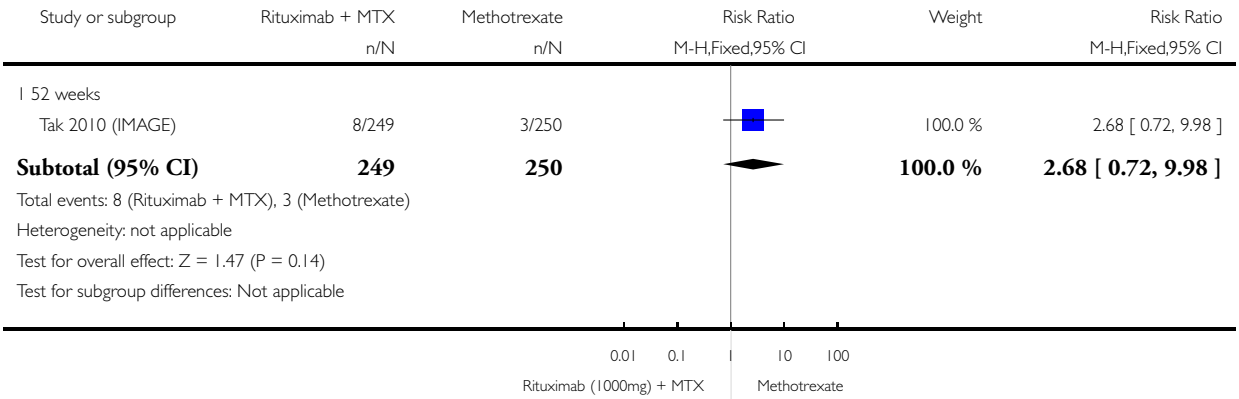
Analysis 11.7. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 7 Cardiac event (any).

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 7 Cardiac event (any)

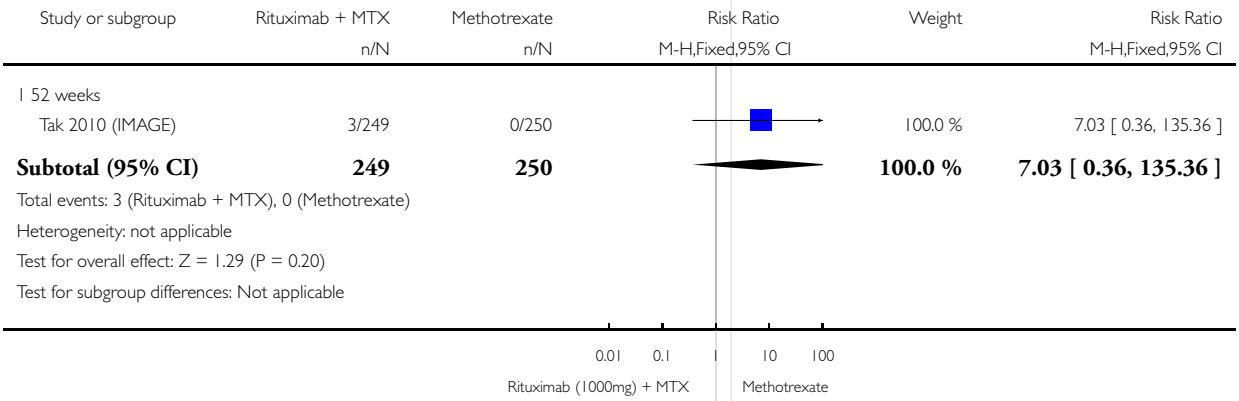


Analysis 11.8. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 8 Cardiac event (serious).

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 8 Cardiac event (serious)



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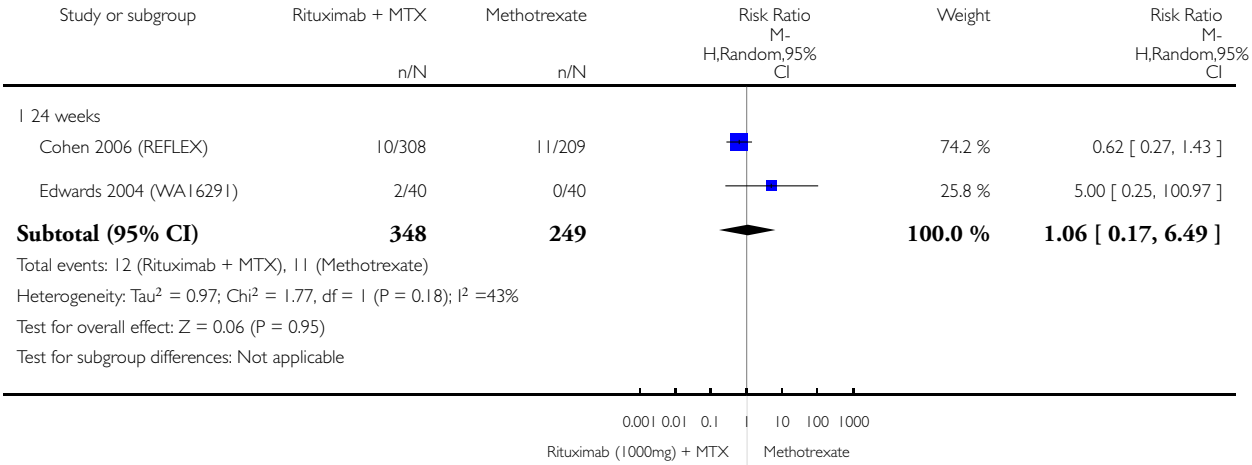
Analysis 11.9. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 9 Cough.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 9 Cough



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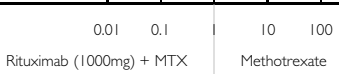
Analysis 11.10. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 10 Diarrhea.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 10 Diarrhea

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	18/308	16/209		67.9 %	0.76 [0.40, 1.46]
Emery 2006 (DANCER)	6/192	8/149		32.1 %	0.58 [0.21, 1.64]
Subtotal (95% CI)	**500**	**358**		**100.0 %**	**0.71 [0.41, 1.22]**
Total events: 24 (Rituximab + MTX), 24 (Methotrexate)					
Heterogeneity: Chi^2 = 0.19, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Not applicable					



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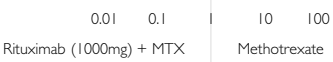
Analysis 11.11. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 11 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 11 Exacerbation of RA

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	65/308	87/209		61.3 %	0.51 [0.39, 0.66]
Edwards 2004 (WA16291)	2/40	16/40		9.5 %	0.13 [0.03, 0.51]
Emery 2006 (DANCER)	27/192	44/149		29.3 %	0.48 [0.31, 0.73]
Subtotal (95% CI)	**540**	**398**		**100.0 %**	**0.46 [0.37, 0.58]**
Total events: 94 (Rituximab + MTX), 147 (Methotrexate)					
Heterogeneity: Chi^2 = 3.81, df = 2 (P = 0.15); I^2 =48%					
Test for overall effect: Z = 6.72 (P < 0.00001)					
2 48-56 weeks					
Edwards 2004 (WA16291)	0/40	0/40			Not estimable
Tak 2010 (IMAGE)	2/249	1/250		100.0 %	2.01 [0.18, 22.00]
Subtotal (95% CI)	**289**	**290**		**100.0 %**	**2.01 [0.18, 22.00]**
Total events: 2 (Rituximab + MTX), 1 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Chi^2 = 1.43, df = 1 (P = 0.23), I^2 =30%					



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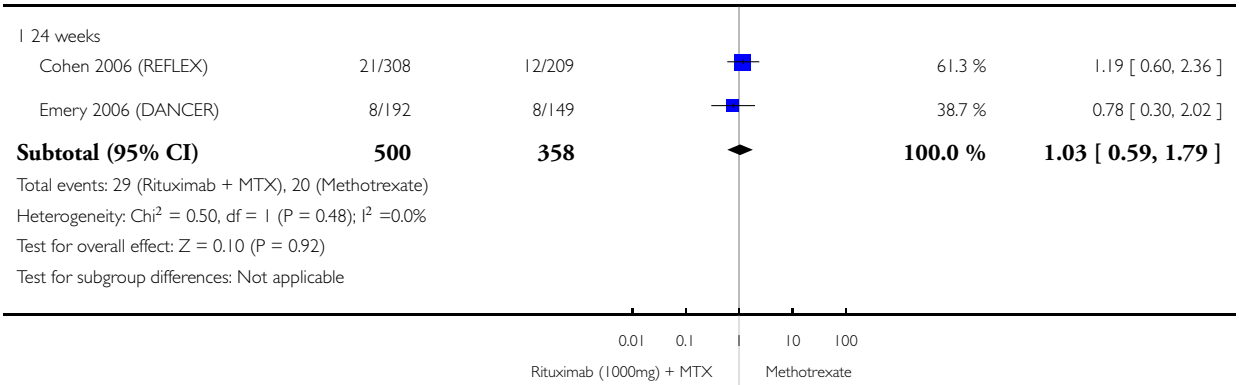
Analysis 11.12. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 12 Fatigue.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 12 Fatigue

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	21/308	12/209		61.3 %	1.19 [0.60, 2.36]
Emery 2006 (DANCER)	8/192	8/149		38.7 %	0.78 [0.30, 2.02]
Subtotal (95% CI)	**500**	**358**		**100.0 %**	**1.03 [0.59, 1.79]**
Total events: 29 (Rituximab + MTX), 20 (Methotrexate)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 0.10 (P = 0.92)					
Test for subgroup differences: Not applicable					



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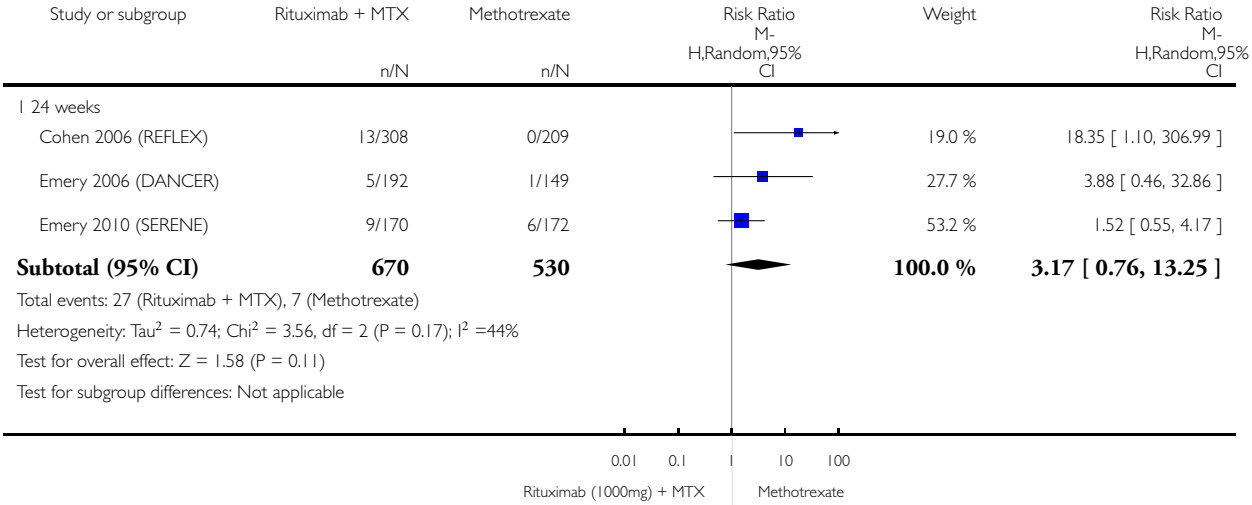
Analysis 11.13. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 13 HACA.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 13 HACA



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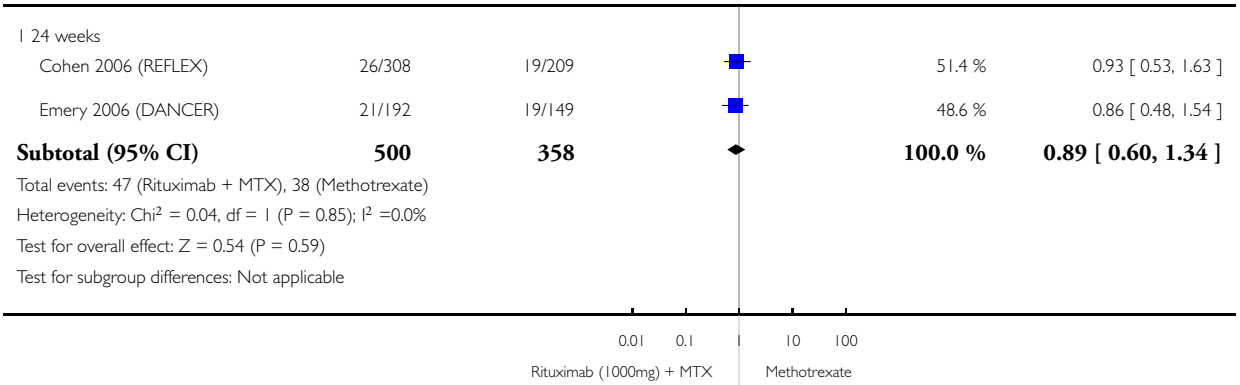
Analysis 11.14. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 14 Headache.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 14 Headache

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	26/308	19/209		51.4 %	0.93 [0.53, 1.63]
Emery 2006 (DANCER)	21/192	19/149		48.6 %	0.86 [0.48, 1.54]
Subtotal (95% CI)	**500**	**358**		**100.0 %**	**0.89 [0.60, 1.34]**
Total events: 47 (Rituximab + MTX), 38 (Methotrexate)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 0.54 (P = 0.59)					
Test for subgroup differences: Not applicable					



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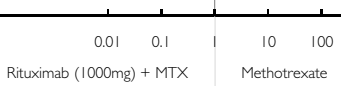
Analysis 11.15. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 15 Hypertension.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 15 Hypertension

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	21/308	11/209		55.5 %	1.30 [0.64, 2.63]
Edwards 2004 (WA16291)	10/40	6/40		25.4 %	1.67 [0.67, 4.15]
Emery 2006 (DANCER)	12/192	4/149		19.1 %	2.33 [0.77, 7.07]
Subtotal (95% CI)	**540**	**398**		**100.0 %**	**1.59 [0.96, 2.61]**
Total events: 43 (Rituximab + MTX), 21 (Methotrexate)					
Heterogeneity: Chi^2 = 0.78, df = 2 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 1.82 (P = 0.069)					
Test for subgroup differences: Not applicable					



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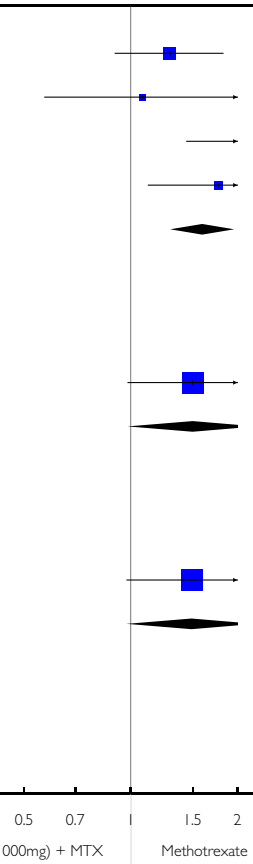
Analysis 11.16. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 16 Infusion-related reactions (1st course -1st infusion).

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 16 Infusion-related reactions (1st course -1st infusion)

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	72/308	38/209		40.6 %	1.29 [0.90, 1.83]
Edwards 2004 (WA16291)	13/40	12/40		10.8 %	1.08 [0.57, 2.08]
Emery 2006 (DANCER)	73/192	27/149		27.3 %	2.10 [1.43, 3.09]
Emery 2010 (SERENE)	42/170	24/172		21.4 %	1.77 [1.12, 2.79]
Subtotal (95% CI)	**710**	**570**		**100.0 %**	**1.59 [1.29, 1.96]**
Total events: 200 (Rituximab + MTX), 101 (Methotrexate)					
Heterogeneity: Chi^2 = 4.93, df = 3 (P = 0.18); I^2 =39%					
Test for overall effect: Z = 4.28 (P = 0.000019)					
2 52 weeks					
Tak 2010 (IMAGE)	46/249	31/250		100.0 %	1.49 [0.98, 2.27]
Subtotal (95% CI)	**249**	**250**		**100.0 %**	**1.49 [0.98, 2.27]**
Total events: 46 (Rituximab + MTX), 31 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.86 (P = 0.063)					
3 104 weeks					
Tak 2010 (IMAGE)	46/250	31/249		100.0 %	1.48 [0.97, 2.25]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**1.48 [0.97, 2.25]**
Total events: 46 (Rituximab + MTX), 31 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.82 (P = 0.068)					
Test for subgroup differences: Chi^2 = 0.14, df = 2 (P = 0.93), I^2 =0.0%					



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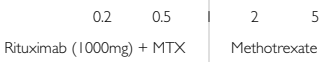
Analysis 11.17. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 17 Infusion-related reaction (1st course -2nd infusion).

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 17 Infusion-related reaction (1st course -2nd infusion)

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	26/308	24/209		68.7 %	0.74 [0.43, 1.24]
Emery 2006 (DANCER)	12/122	13/122		31.3 %	0.92 [0.44, 1.94]
Subtotal (95% CI)	**430**	**331**		**100.0 %**	**0.79 [0.52, 1.22]**
Total events: 38 (Rituximab + MTX), 37 (Methotrexate)					
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.05 (P = 0.29)					
Test for subgroup differences: Not applicable					



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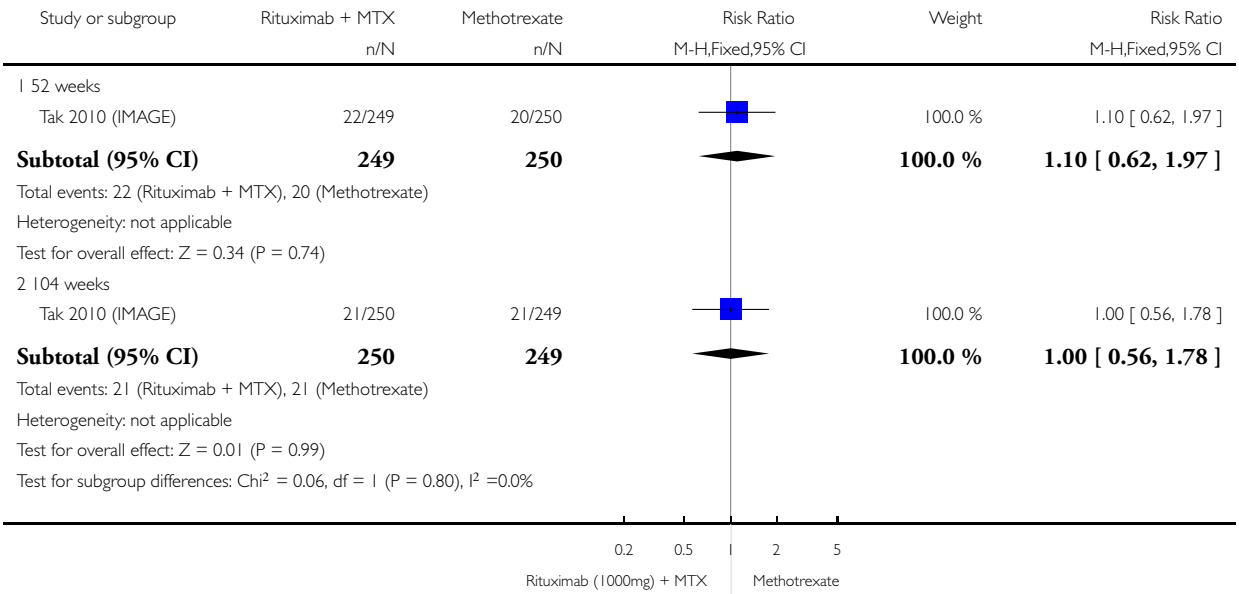
Analysis 11.18. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 18 Infusion-related reaction (2nd course).

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 18 Infusion-related reaction (2nd course)



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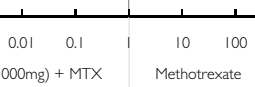
Analysis 11.19. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 19 Infusion-related reaction (3rd course).

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 19 Infusion-related reaction (3rd course)

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 52 weeks					
Tak 2010 (IMAGE)	9/249	7/250		100.0 %	1.29 [0.49, 3.41]
Subtotal (95% CI)	**249**	**250**		**100.0 %**	**1.29 [0.49, 3.41]**
Total events: 9 (Rituximab + MTX), 7 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					
2 104 weeks					
Tak 2010 (IMAGE)	12/250	10/249		100.0 %	1.20 [0.53, 2.72]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**1.20 [0.53, 2.72]**
Total events: 12 (Rituximab + MTX), 10 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.91), I^2 =0.0%					



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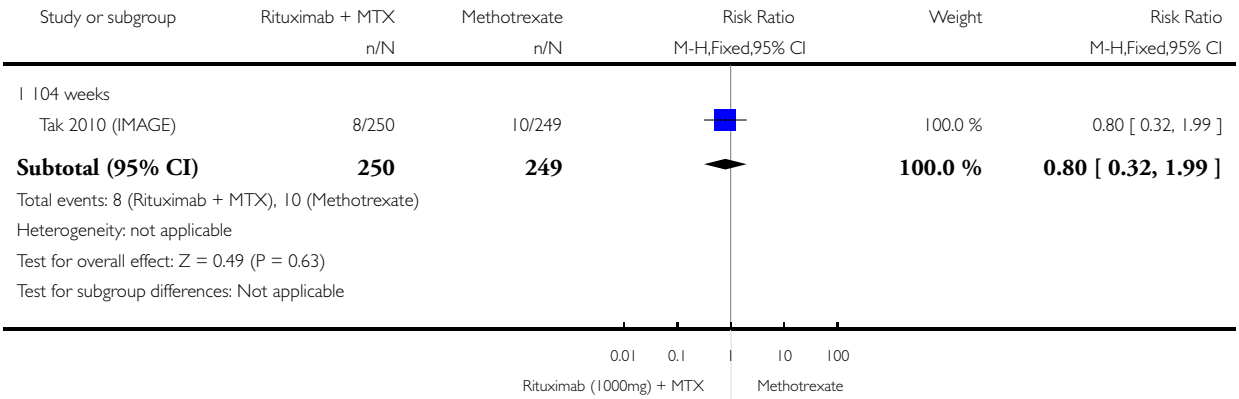
Analysis 11.20. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 20 Infusion-related reaction (4th course).

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 20 Infusion-related reaction (4th course)

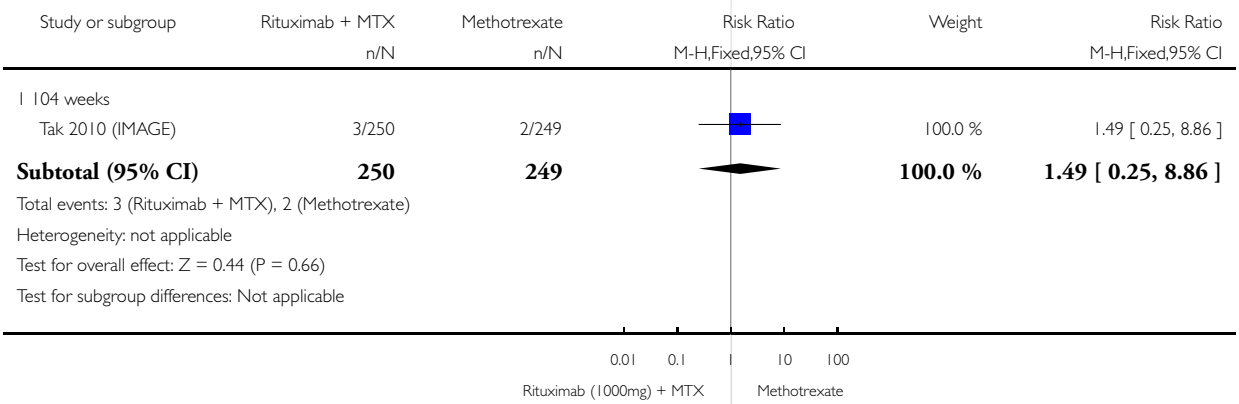


Analysis 11.21. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 21 Infusion-related reaction (5th course).

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 21 Infusion-related reaction (5th course)



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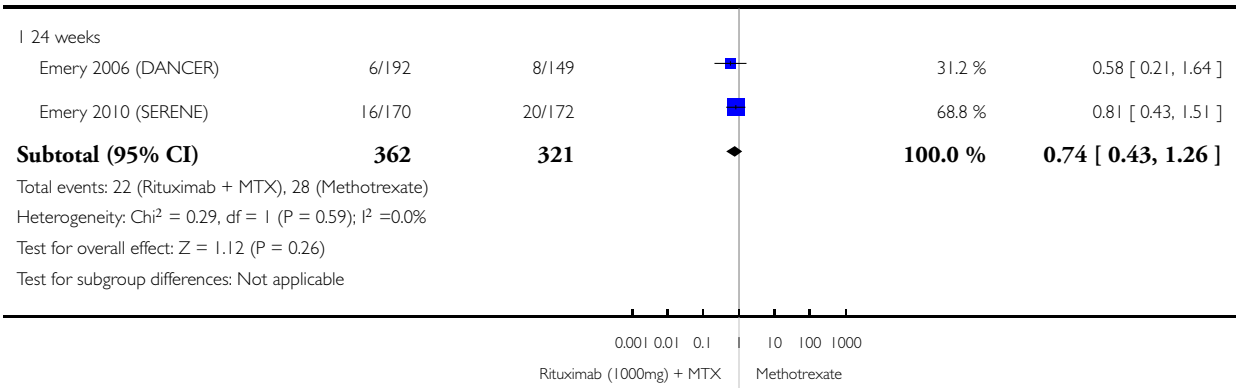
Analysis 11.22. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 22 Lower gastrointestinal events.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 22 Lower gastrointestinal events

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	6/192	8/149		31.2 %	0.58 [0.21, 1.64]
Emery 2010 (SERENE)	16/170	20/172		68.8 %	0.81 [0.43, 1.51]
Subtotal (95% CI)	**362**	**321**		**100.0 %**	**0.74 [0.43, 1.26]**
Total events: 22 (Rituximab + MTX), 28 (Methotrexate)					
Heterogeneity: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 1.12 (P = 0.26)					
Test for subgroup differences: Not applicable					



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Analysis 11.23. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 23 Malignancy.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 23 Malignancy

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	0/308	1/209		64.2 %	0.23 [0.01, 5.53]
Emery 2006 (DANCER)	0/192	0/124			Not estimable
Emery 2010 (SERENE)	2/170	1/172		35.8 %	2.02 [0.19, 22.11]
Subtotal (95% CI)	**670**	**505**		**100.0 %**	**0.87 [0.16, 4.63]**
Total events: 2 (Rituximab + MTX), 2 (Methotrexate)					
Heterogeneity: Chi^2 = 1.16, df = 1 (P = 0.28); I^2 =14%					
Test for overall effect: Z = 0.16 (P = 0.87)					
2 48-56 weeks					
Edwards 2004 (WA16291)	0/40	0/40			Not estimable
Tak 2010 (IMAGE)	1/249	5/250		100.0 %	0.20 [0.02, 1.71]
Subtotal (95% CI)	**289**	**290**		**100.0 %**	**0.20 [0.02, 1.71]**
Total events: 1 (Rituximab + MTX), 5 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					
3 104 weeks					
Tak 2010 (IMAGE)	3/250	7/249		100.0 %	0.43 [0.11, 1.63]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**0.43 [0.11, 1.63]**
Total events: 3 (Rituximab + MTX), 7 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.21)					
Test for subgroup differences: Chi^2 = 1.14, df = 2 (P = 0.56), I^2 =0.0%					

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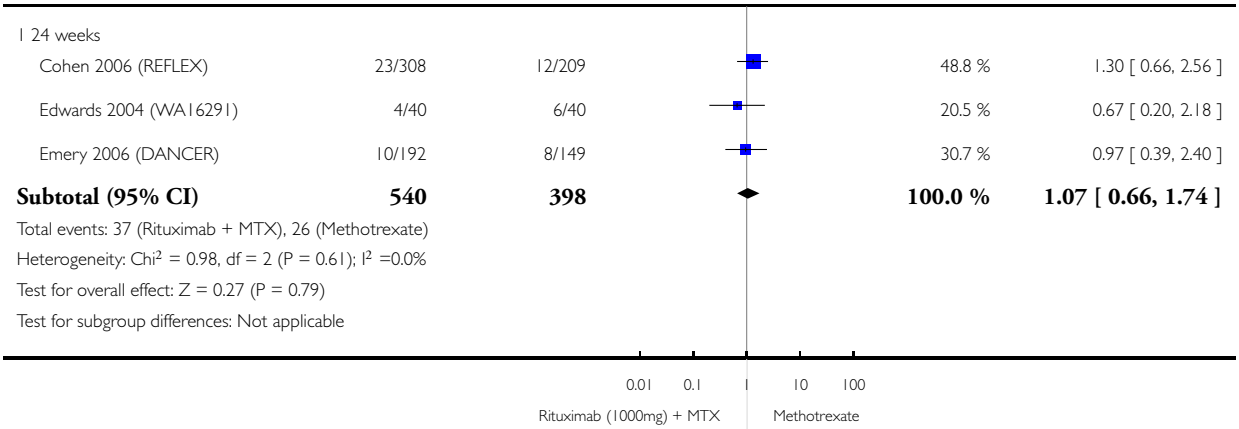
Analysis 11.24. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 24 Nasopharyngitis.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 24 Nasopharyngitis

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	23/308	12/209		48.8 %	1.30 [0.66, 2.56]
Edwards 2004 (WA16291)	4/40	6/40		20.5 %	0.67 [0.20, 2.18]
Emery 2006 (DANCER)	10/192	8/149		30.7 %	0.97 [0.39, 2.40]
Subtotal (95% CI)	**540**	**398**		**100.0 %**	**1.07 [0.66, 1.74]**
Total events: 37 (Rituximab + MTX), 26 (Methotrexate)					
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 0.27 (P = 0.79)					
Test for subgroup differences: Not applicable					



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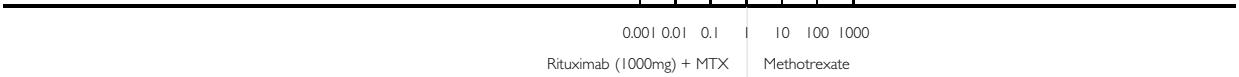
Analysis 11.25. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 25 Nausea.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 25 Nausea

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	10/308	11/209		44.8 %	0.62 [0.27, 1.43]
Edwards 2004 (WA16291)	0/40	1/40		5.1 %	0.33 [0.01, 7.95]
Emery 2006 (DANCER)	19/192	13/149		50.1 %	1.13 [0.58, 2.22]
Subtotal (95% CI)	**540**	**398**		**100.0 %**	**0.86 [0.52, 1.43]**
Total events: 29 (Rituximab + MTX), 25 (Methotrexate)					
Heterogeneity: Chi^2 = 1.60, df = 2 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Not applicable					



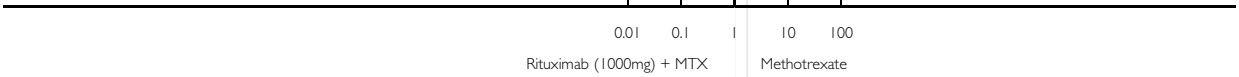
Analysis 11.26. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 26 Pyrexia.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 26 Pyrexia

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	15/308	7/209		100.0 %	1.45 [0.60, 3.50]
Subtotal (95% CI)	**308**	**209**		**100.0 %**	**1.45 [0.60, 3.50]**
Total events: 15 (Rituximab + MTX), 7 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.40)					
Test for subgroup differences: Not applicable					



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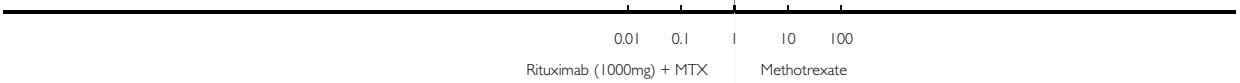
Analysis 11.27. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 27 Upper respiratory tract infection.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 27 Upper respiratory tract infection

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	24/308	14/209		84.8 %	1.16 [0.62, 2.20]
Subtotal (95% CI)	**308**	**209**		**84.8 %**	**1.16 [0.62, 2.20]**
Total events: 24 (Rituximab + MTX), 14 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					
2 52 weeks					
Tak 2010 (IMAGE)	2/249	3/250		15.2 %	0.67 [0.11, 3.97]
Subtotal (95% CI)	**249**	**250**		**15.2 %**	**0.67 [0.11, 3.97]**
Total events: 2 (Rituximab + MTX), 3 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
Total (95% CI)	**557**	**459**		**100.0 %**	**1.09 [0.60, 1.97]**
Total events: 26 (Rituximab + MTX), 17 (Methotrexate)					
Heterogeneity: Chi^2 = 0.33, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 0.28 (P = 0.78)					
Test for subgroup differences: Chi^2 = 0.33, df = 1 (P = 0.57), I^2 =0.0%					



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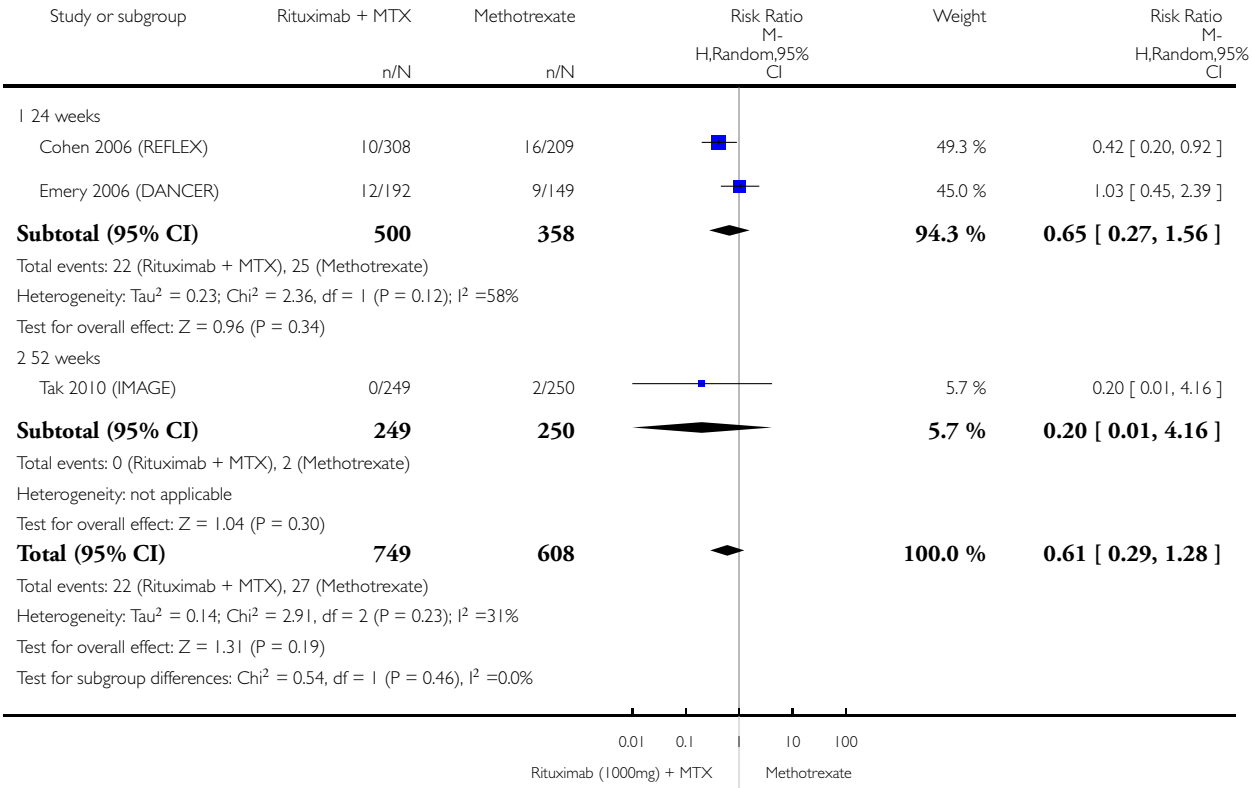
Analysis 11.28. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 28 Urinary tract infection.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 28 Urinary tract infection



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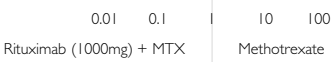
Analysis 11.29. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 29 Vascular disorders.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 29 Vascular disorders

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	10/40	6/40		19.1 %	1.67 [0.67, 4.15]
Emery 2006 (DANCER)	12/192	4/149		14.3 %	2.33 [0.77, 7.07]
Emery 2010 (SERENE)	7/170	4/172		12.6 %	1.77 [0.53, 5.94]
Subtotal (95% CI)	**402**	**361**		**46.0 %**	**1.90 [1.03, 3.51]**
Total events: 29 (Rituximab + MTX), 14 (Methotrexate)					
Heterogeneity: Chi^2 = 0.22, df = 2 (P = 0.90); I^2 =0.0%					
Test for overall effect: Z = 2.06 (P = 0.040)					
2 52 weeks					
Tak 2010 (IMAGE)	21/249	17/250		54.0 %	1.24 [0.67, 2.29]
Subtotal (95% CI)	**249**	**250**		**54.0 %**	**1.24 [0.67, 2.29]**
Total events: 21 (Rituximab + MTX), 17 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Total (95% CI)	**651**	**611**		**100.0 %**	**1.54 [1.00, 2.38]**
Total events: 50 (Rituximab + MTX), 31 (Methotrexate)					
Heterogeneity: Chi^2 = 1.09, df = 3 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 1.98 (P = 0.048)					
Test for subgroup differences: Chi^2 = 0.93, df = 1 (P = 0.33), I^2 =0.0%					



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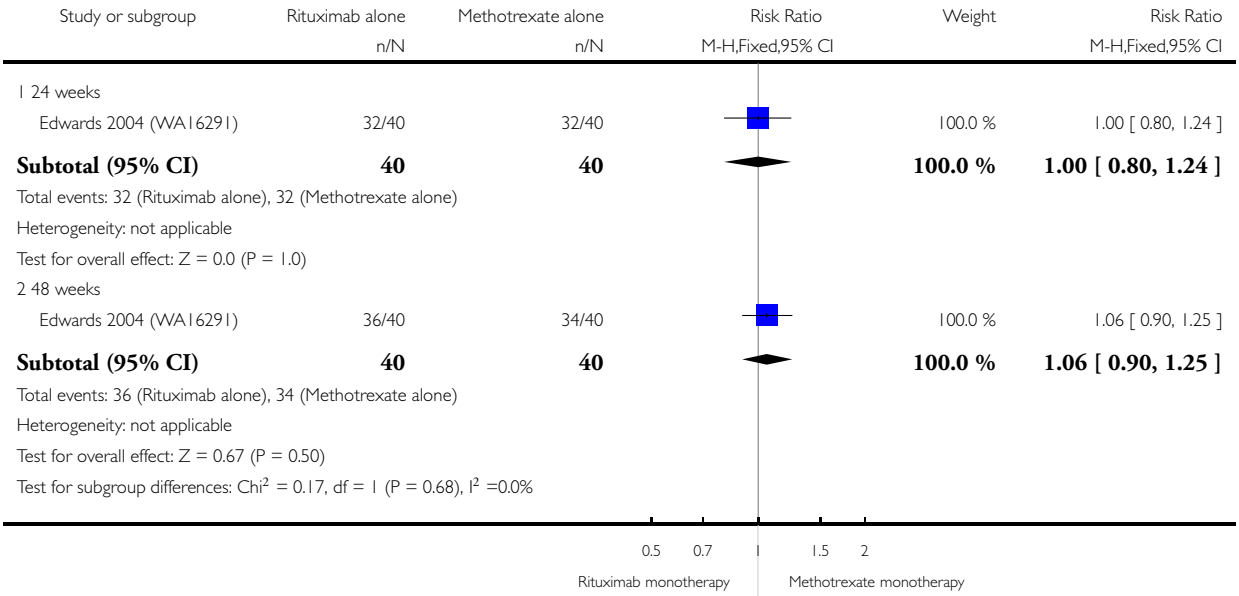
Analysis 12.1. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 1 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 1 Any Adverse Event



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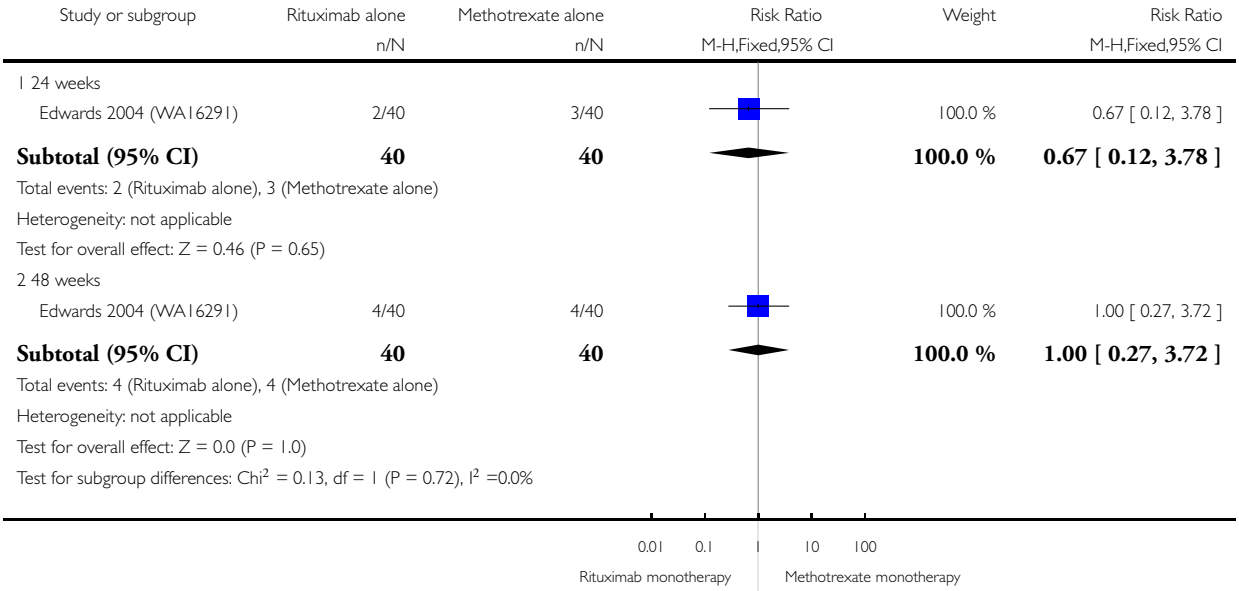
Analysis 12.2. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 2 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 2 Serious Adverse Events



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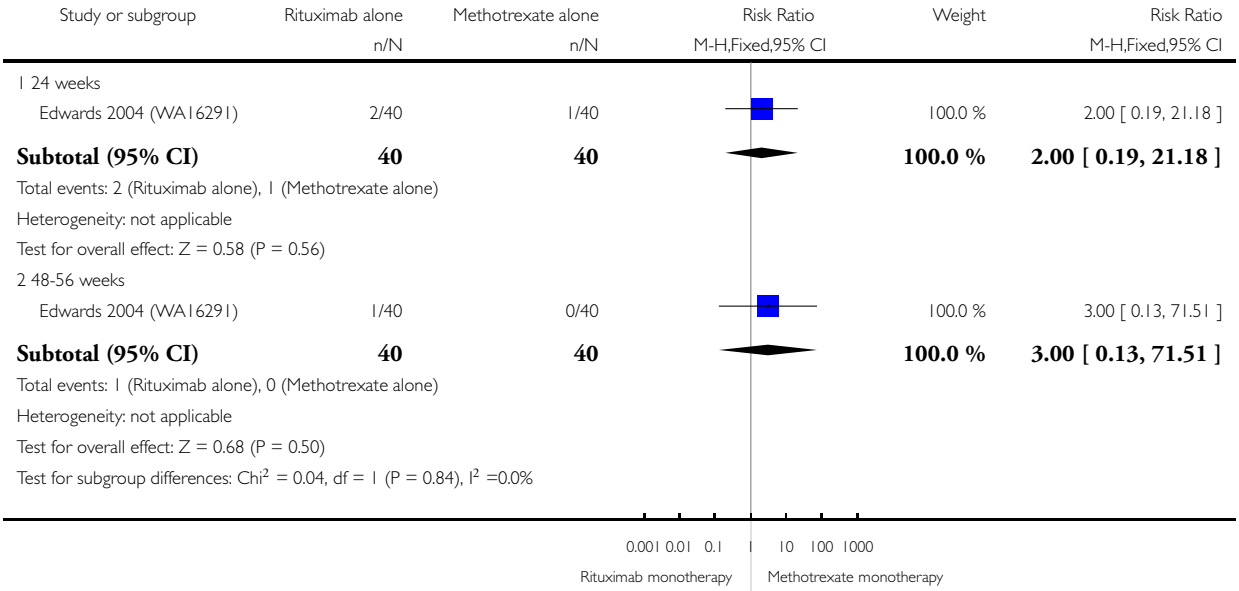
Analysis 12.3. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 3 Serious Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 3 Serious Infections



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Analysis 12.4. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 4 Death.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 4 Death

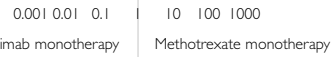
Study or subgroup	Rituximab alone n/N	Methotrexate alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	1/40	0/40		100.0 %	3.00 [0.13, 71.51]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**3.00 [0.13, 71.51]**

Total events: 1 (Rituximab alone), 0 (Methotrexate alone)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable



Analysis 12.5. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 5 Any Event Associated with 1st Infusion.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

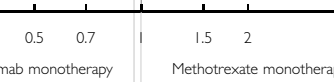
Outcome: 5 Any Event Associated with 1st Infusion

Study or subgroup	Rituximab alone n/N	Methotrexate alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	18/40	12/40		100.0 %	1.50 [0.84, 2.69]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**1.50 [0.84, 2.69]**

Total events: 18 (Rituximab alone), 12 (Methotrexate alone)

Heterogeneity: not applicable

Test for overall effect: Z = 1.36 (P = 0.17)



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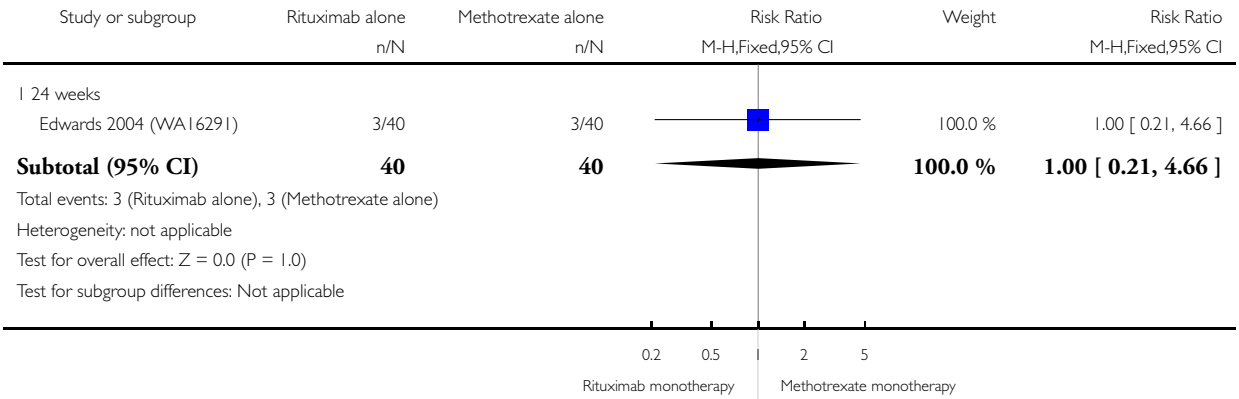
Analysis 12.6. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 6 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 6 Arthralgia

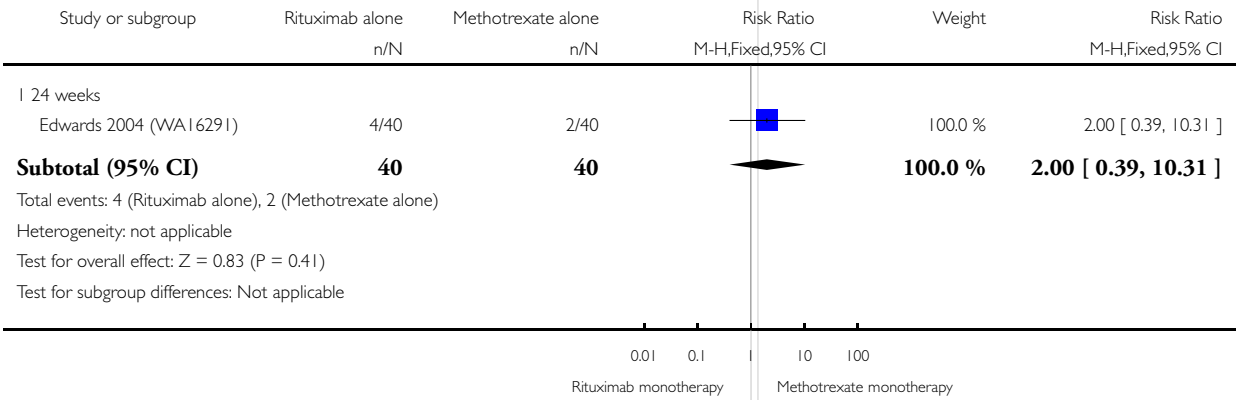


Analysis 12.7. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 7 Back pain.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 7 Back pain



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Analysis 12.8. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 8 Cough.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 8 Cough

Study or subgroup	Rituximab alone n/N	Methotrexate alone n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	5/40	0/40		100.0 %	8.22 [1.36, 49.69]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**8.22 [1.36, 49.69]**
Total events: 5 (Rituximab alone), 0 (Methotrexate alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.29 (P = 0.022)					

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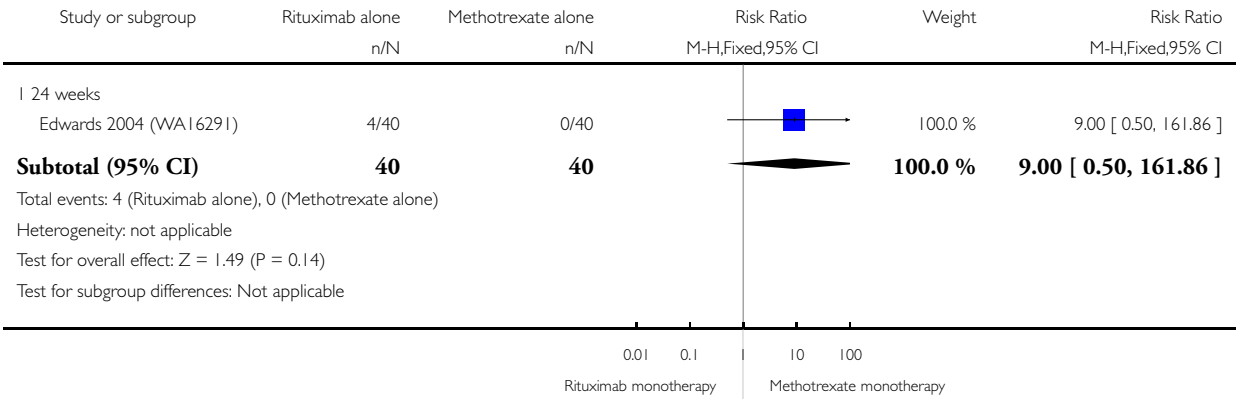
Analysis 12.9. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 9 Dyspnea.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 9 Dyspnea



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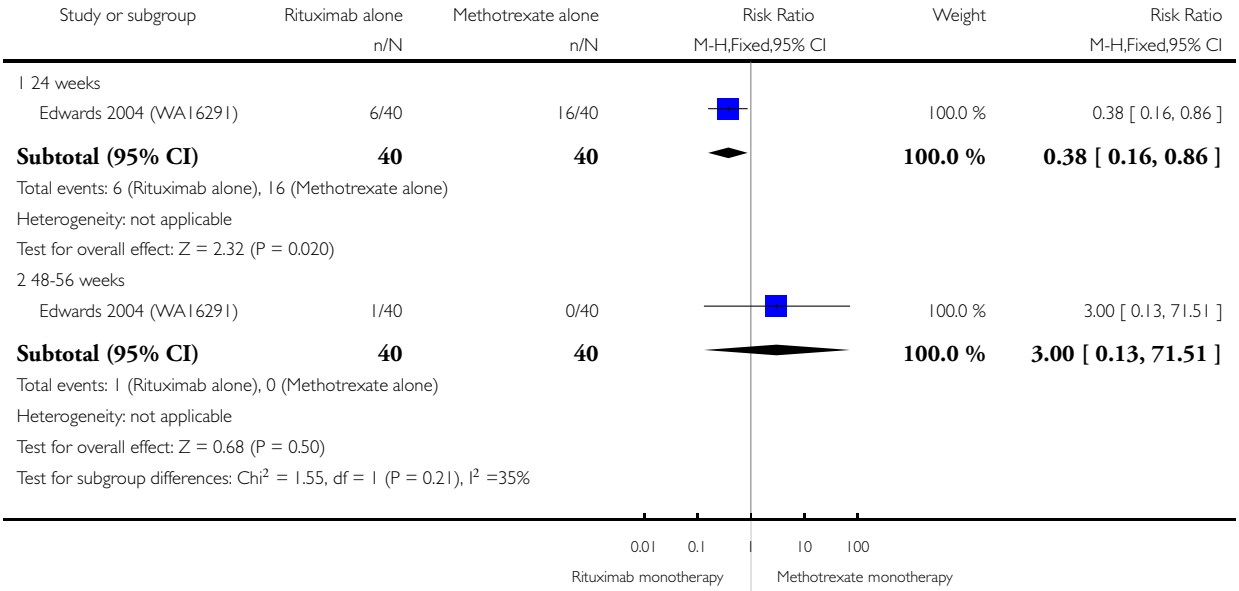
Analysis 12.10. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 10 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 10 Exacerbation of RA



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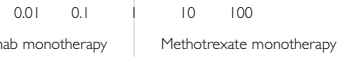
Analysis 12.11. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 11 Hypertension.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 11 Hypertension

Study or subgroup	Rituximab alone n/N	Methotrexate alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	6/40	6/40		100.0 %	1.00 [0.35, 2.84]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**1.00 [0.35, 2.84]**
Total events: 6 (Rituximab alone), 6 (Methotrexate alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					



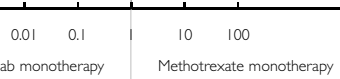
Analysis 12.12. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 12 Hypotension.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 12 Hypotension

Study or subgroup	Rituximab alone n/N	Methotrexate alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	12/40	7/40		100.0 %	1.71 [0.75, 3.90]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**1.71 [0.75, 3.90]**
Total events: 12 (Rituximab alone), 7 (Methotrexate alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					



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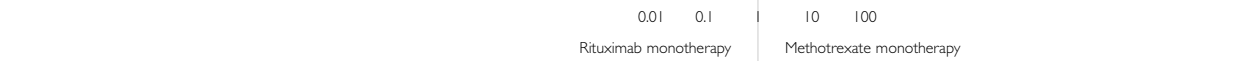
Analysis 12.13. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 13 Nasopharyngitis.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 13 Nasopharyngitis

Study or subgroup	Rituximab alone n/N	Methotrexate alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	4/40	6/40		100.0 %	0.67 [0.20, 2.18]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.67 [0.20, 2.18]**
Total events: 4 (Rituximab alone), 6 (Methotrexate alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
Test for subgroup differences: Not applicable					



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Analysis 12.14. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 14 Nausea.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 14 Nausea

Study or subgroup	Rituximab alone n/N	Methotrexate alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	2/40	1/40		100.0 %	2.00 [0.19, 21.18]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**2.00 [0.19, 21.18]**
Total events: 2 (Rituximab alone), 1 (Methotrexate alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Not applicable					

Analysis 12.15. Comparison 12 Harms - RTX monotherapy versus MTX monotherapy, Outcome 15 Rash.

Review: Rituximab for rheumatoid arthritis

Comparison: 12 Harms - RTX monotherapy versus MTX monotherapy

Outcome: 15 Rash

Study or subgroup	Rituximab alone n/N	Methotrexate alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	4/40	1/40		100.0 %	4.00 [0.47, 34.24]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**4.00 [0.47, 34.24]**
Total events: 4 (Rituximab alone), 1 (Methotrexate alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.27 (P = 0.21)					

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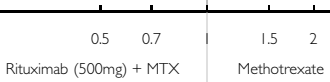
Analysis 13.1. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 1 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 1 Any Adverse Event

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	100/124	105/149		43.1 %	1.14 [1.00, 1.31]
Emery 2010 (SERENE)	128/167	128/172		56.9 %	1.03 [0.91, 1.16]
Subtotal (95% CI)	**291**	**321**		**100.0 %**	**1.08 [0.99, 1.18]**
Total events: 228 (Rituximab + MTX), 233 (Methotrexate)					
Heterogeneity: Chi^2 = 1.30, df = 1 (P = 0.26); I^2 =23%					
Test for overall effect: Z = 1.66 (P = 0.097)					
2 52 weeks					
Tak 2010 (IMAGE)	189/249	203/250		100.0 %	0.93 [0.85, 1.02]
Subtotal (95% CI)	**249**	**250**		**100.0 %**	**0.93 [0.85, 1.02]**
Total events: 189 (Rituximab + MTX), 203 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					
3 104 weeks					
Tak 2010 (IMAGE)	206/249	215/249		100.0 %	0.96 [0.89, 1.03]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**0.96 [0.89, 1.03]**
Total events: 206 (Rituximab + MTX), 215 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
Test for subgroup differences: Chi^2 = 5.71, df = 2 (P = 0.06), I^2 =65%					



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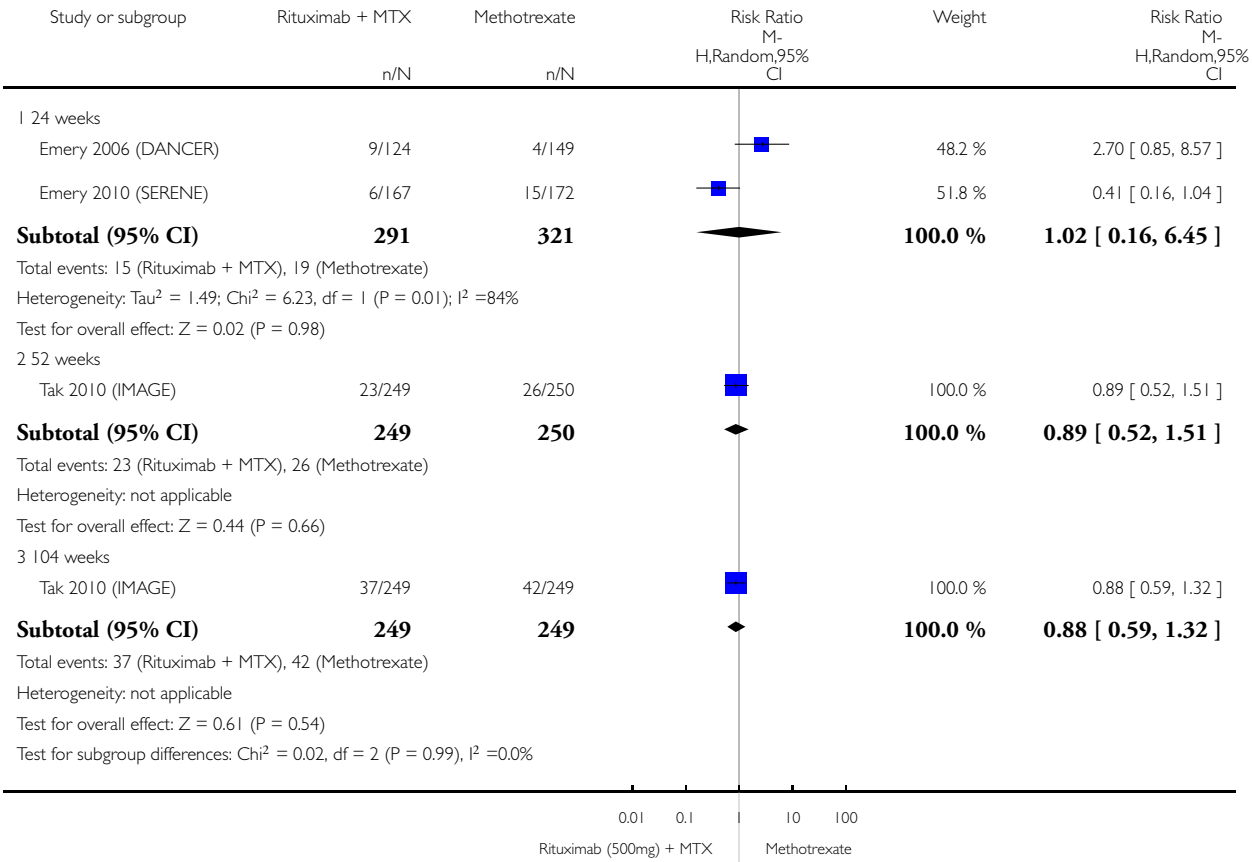
Analysis 13.2. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 2 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 2 Serious Adverse Events



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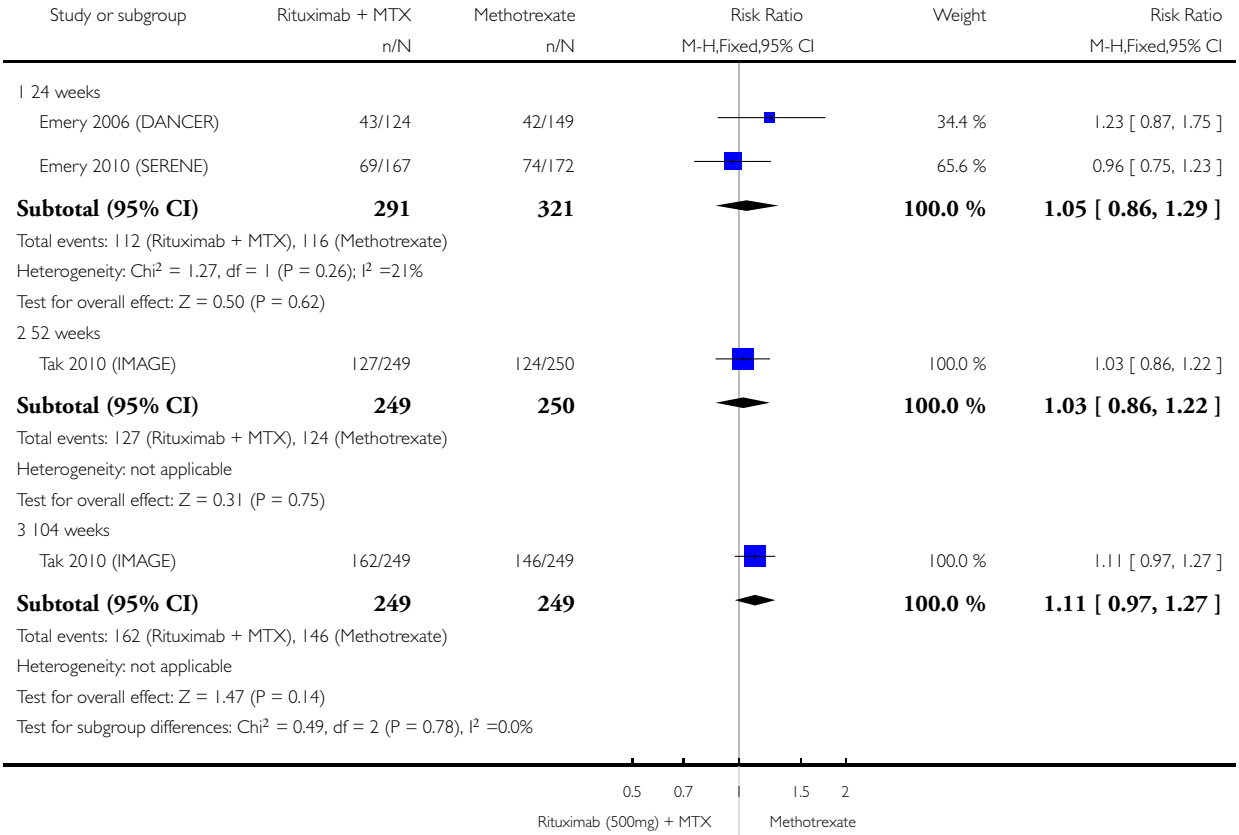
Analysis 13.3. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 3 Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 3 Infections



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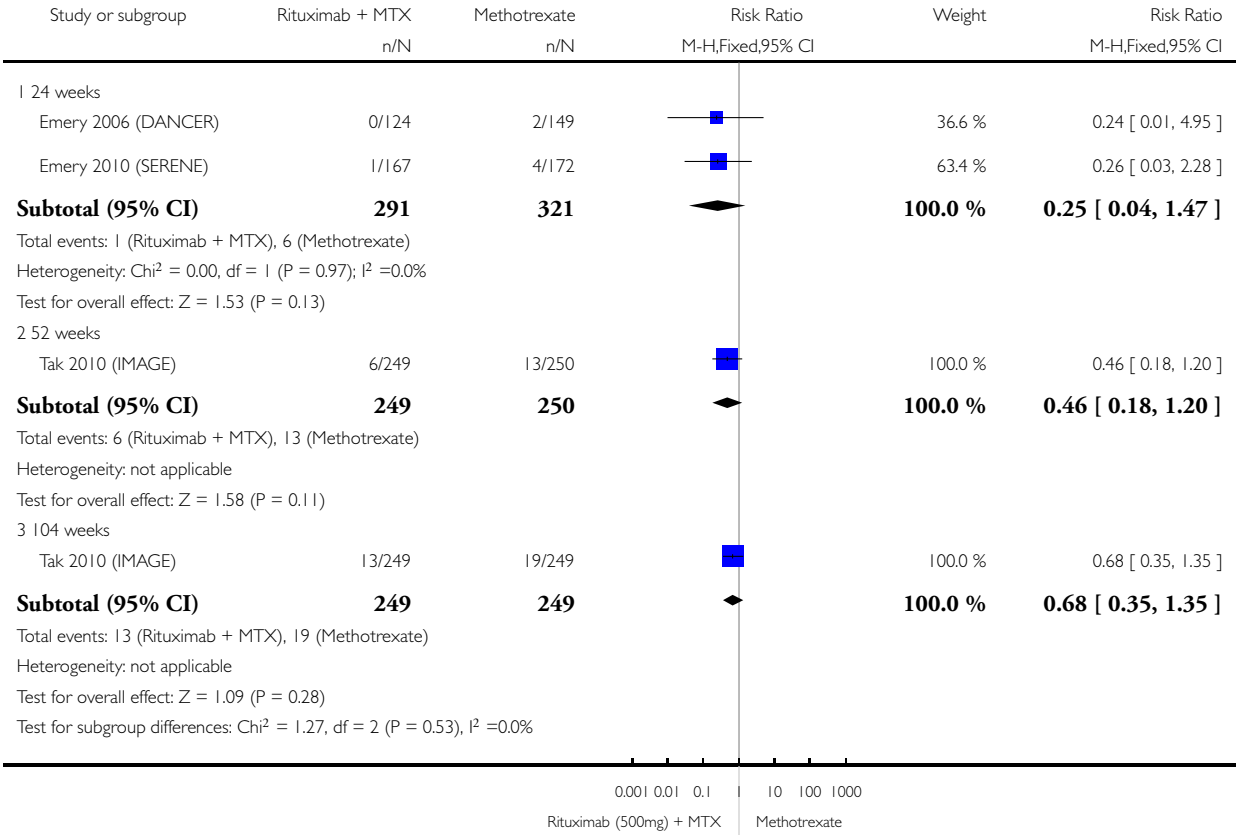
Analysis 13.4. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 4 Serious Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 4 Serious Infections



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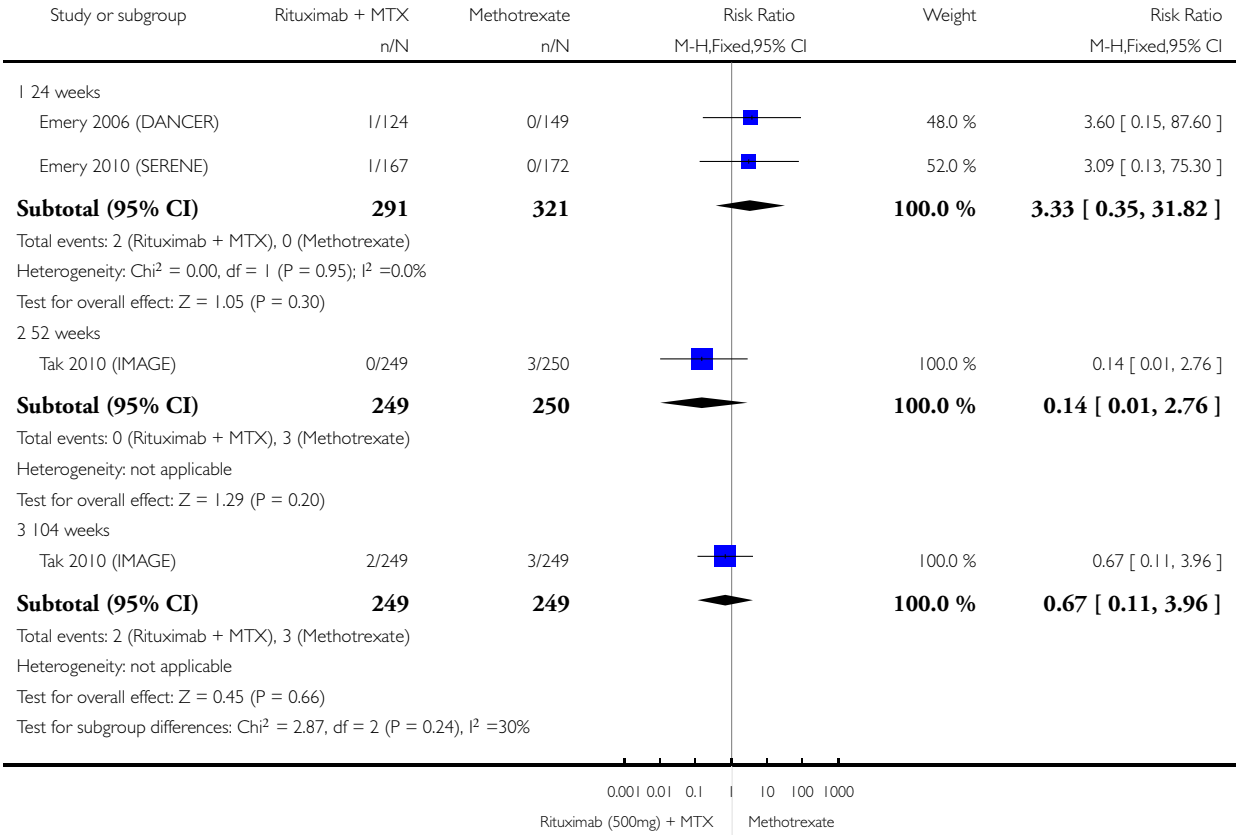
Analysis 13.5. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 5 Death.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 5 Death



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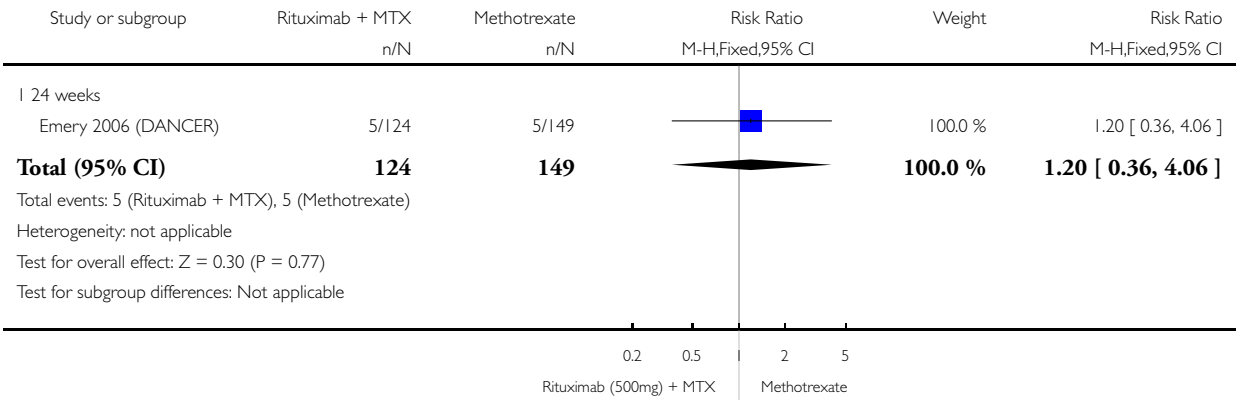
Analysis 13.6. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 6 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 6 Arthralgia

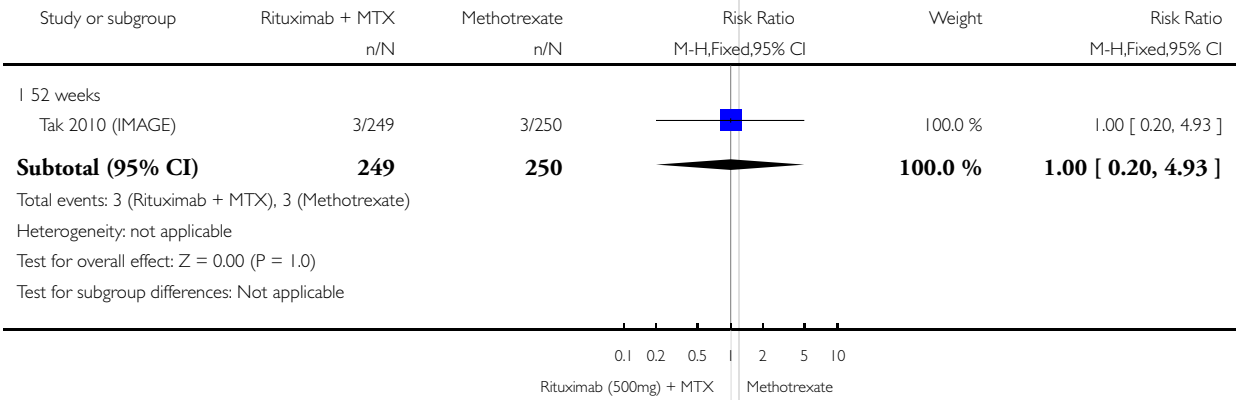


Analysis 13.7. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 7 Cardiac event (any).

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 7 Cardiac event (any)



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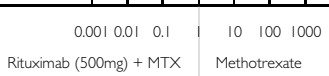
Analysis 13.8. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 8 Cardiac event (serious).

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 8 Cardiac event (serious)

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 52 weeks					
Tak 2010 (IMAGE)	2/249	0/250		100.0 %	5.02 [0.24, 104.04]
Subtotal (95% CI)	**249**	**250**		**100.0 %**	**5.02 [0.24, 104.04]**
Total events: 2 (Rituximab + MTX), 0 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
Test for subgroup differences: Not applicable					



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Analysis 13.9. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 9 Diarrhea.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 9 Diarrhea

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	7/124	8/149		100.0 %	1.05 [0.39, 2.82]
Subtotal (95% CI)	**124**	**149**		**100.0 %**	**1.05 [0.39, 2.82]**
Total events: 7 (Rituximab + MTX), 8 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					
Test for subgroup differences: Not applicable					

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Analysis 13.10. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 10 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 10 Exacerbation of RA

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 MTX vs RTX 500 mg + MTX					
Emery 2006 (DANCER)	21/124	44/149		96.4 %	0.57 [0.36, 0.91]
Subtotal (95% CI)	**124**	**149**		**96.4 %**	**0.57 [0.36, 0.91]**
Total events: 21 (Rituximab + MTX), 44 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					
2 52 weeks					
Tak 2010 (IMAGE)	0/249	1/250		3.6 %	0.33 [0.01, 8.18]
Subtotal (95% CI)	**249**	**250**		**3.6 %**	**0.33 [0.01, 8.18]**
Total events: 0 (Rituximab + MTX), 1 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
Total (95% CI)	**373**	**399**		**100.0 %**	**0.56 [0.36, 0.89]**
Total events: 21 (Rituximab + MTX), 45 (Methotrexate)					
Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 2.45 (P = 0.014)					
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 =0.0%					

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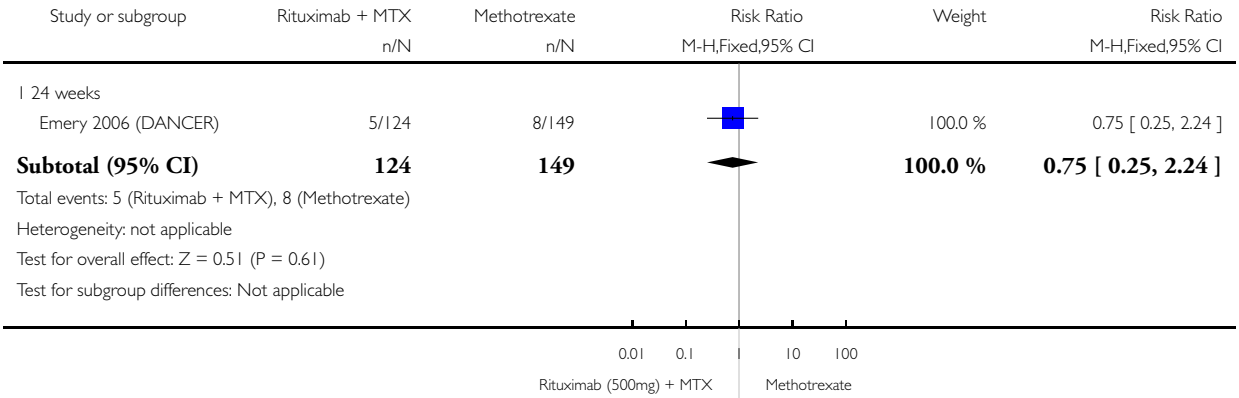
Analysis 13.11. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 11 Fatigue.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 11 Fatigue

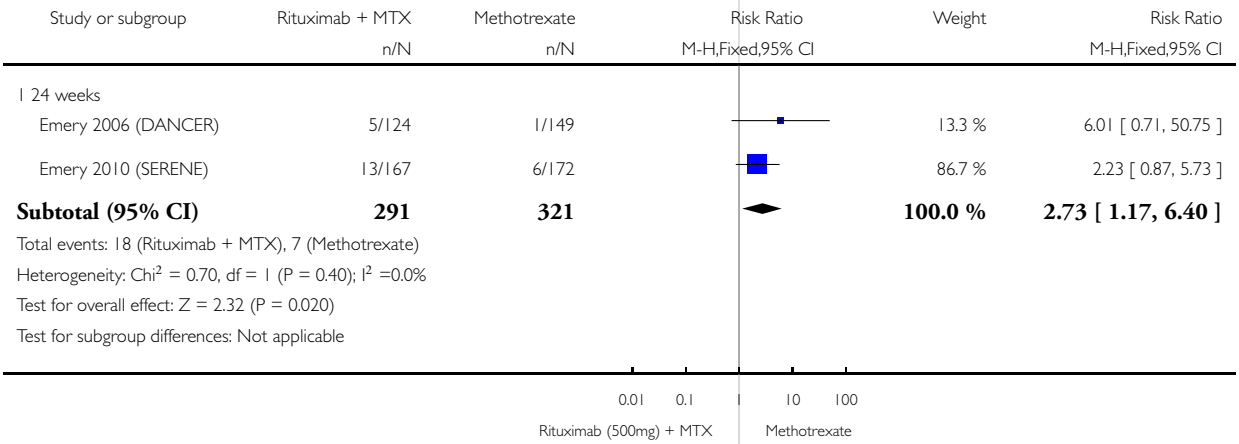


Analysis 13.12. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 12 HACA.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 12 HACA



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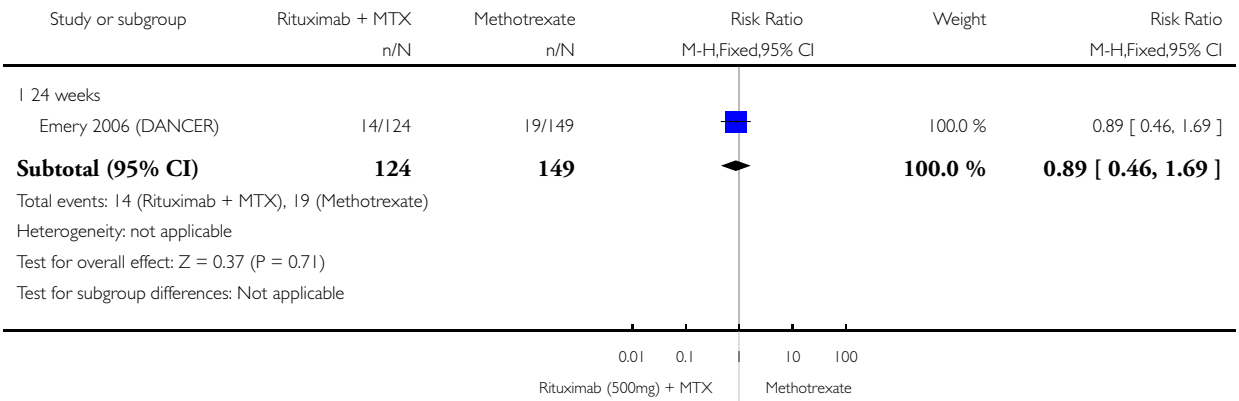
Analysis 13.13. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 13 Headache.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 13 Headache



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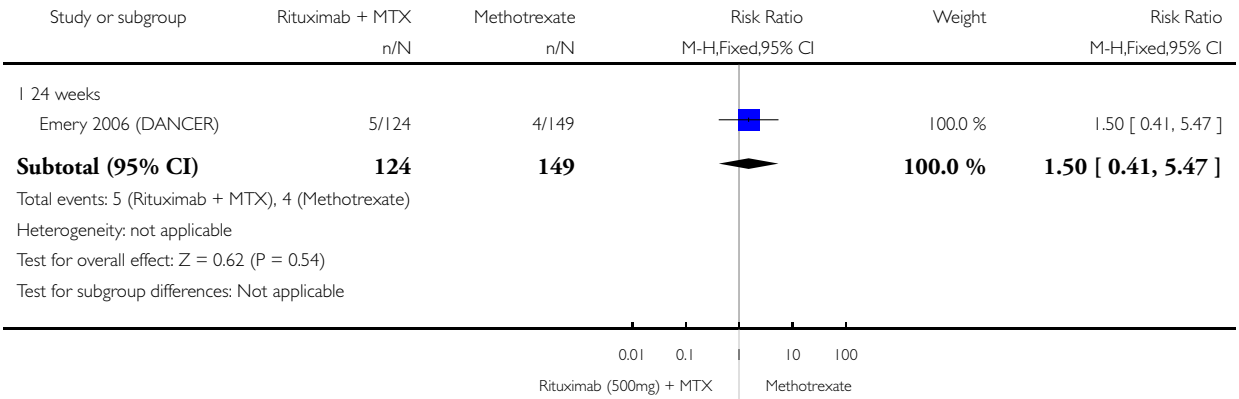
Analysis 13.14. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 14 Hypertension.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 14 Hypertension



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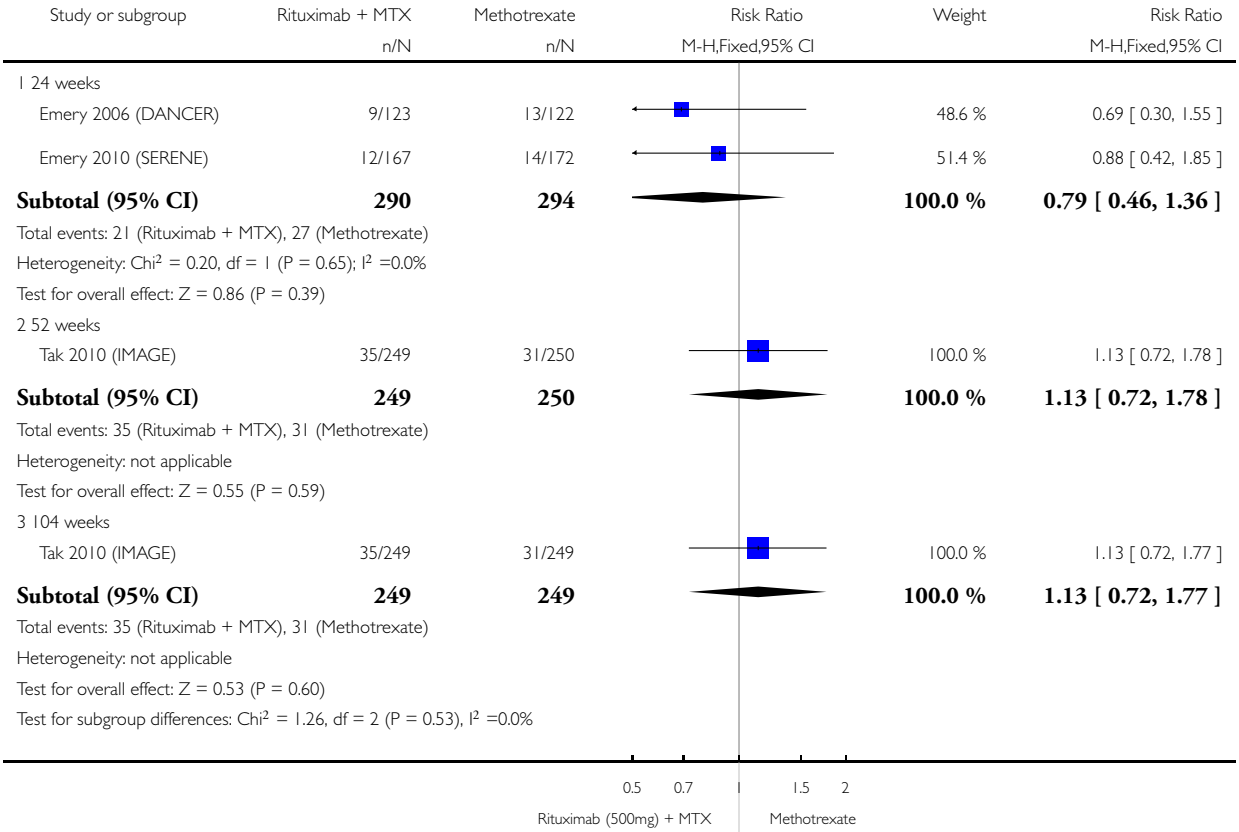
Analysis 13.15. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 15 Infusion-related reactions (1st course - 1st infusion).

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 15 Infusion-related reactions (1st course - 1st infusion)



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Analysis 13.16. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 16 Infusion related reaction (1st course -2nd infusion).

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 16 Infusion related reaction (1st course -2nd infusion)

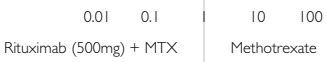
Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	38/124	27/149		50.9 %	1.69 [1.10, 2.60]
Emery 2010 (SERENE)	31/167	24/172		49.1 %	1.33 [0.82, 2.17]
Subtotal (95% CI)	**291**	**321**		**100.0 %**	**1.51 [1.10, 2.09]**

Total events: 69 (Rituximab + MTX), 51 (Methotrexate)

Heterogeneity: $Chi^2 = 0.52$, df = 1 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 2.51 (P = 0.012)

Test for subgroup differences: Not applicable



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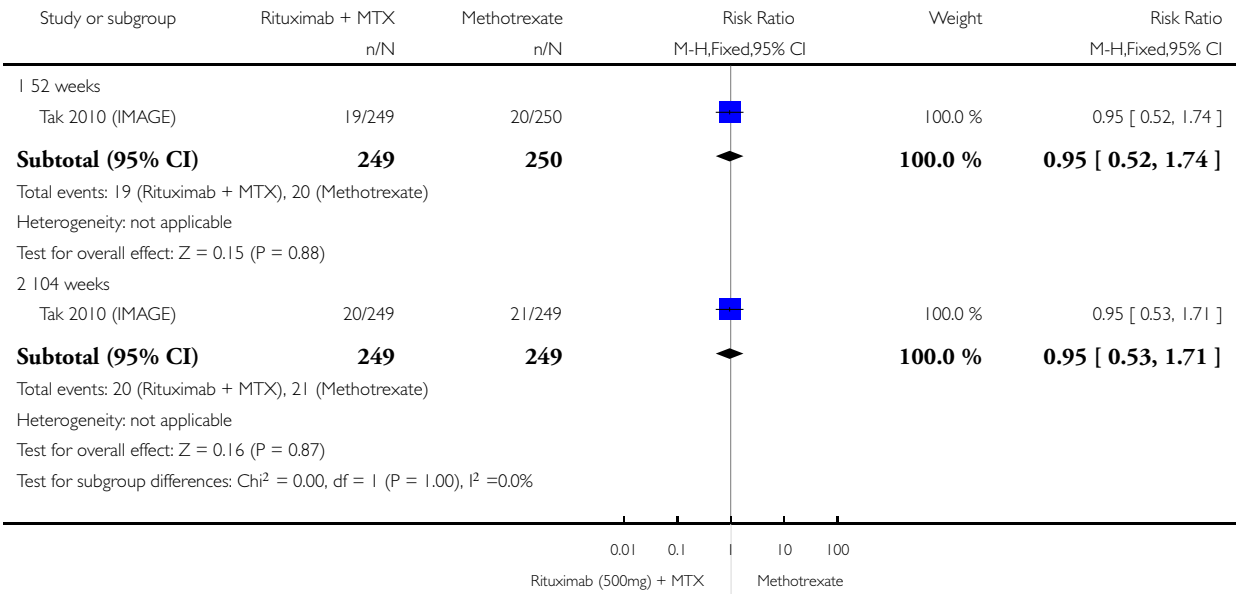
Analysis 13.17. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 17 Infusion related reaction (2nd course).

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 17 Infusion related reaction (2nd course)



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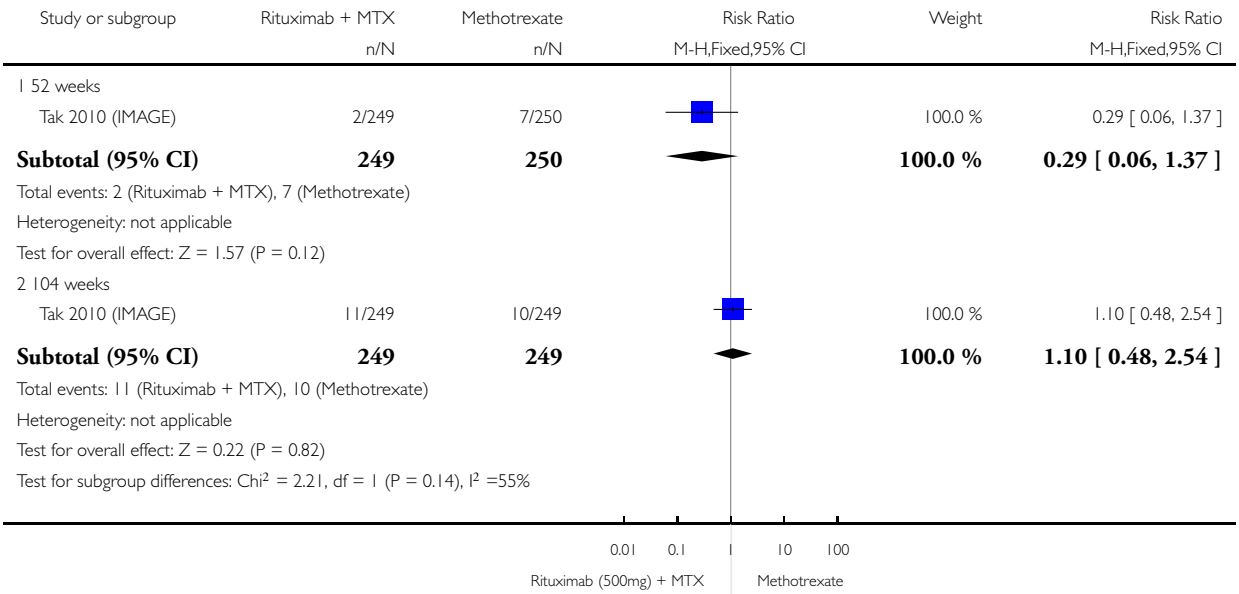
Analysis 13.18. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 18 Infusion related reaction (3rd course).

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 18 Infusion related reaction (3rd course)



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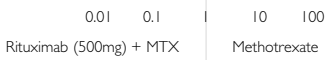
Analysis 13.19. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 19 Infusion related reaction (4th course).

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 19 Infusion related reaction (4th course)

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 104 weeks					
Tak 2010 (IMAGE)	10/249	10/249		100.0 %	1.00 [0.42, 2.36]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**1.00 [0.42, 2.36]**
Total events: 10 (Rituximab + MTX), 10 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					



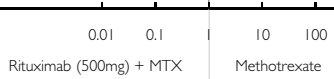
Analysis 13.20. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 20 Infusion related reaction (5th course).

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 20 Infusion related reaction (5th course)

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 104 weeks					
Tak 2010 (IMAGE)	1/249	2/249		100.0 %	0.50 [0.05, 5.48]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**0.50 [0.05, 5.48]**
Total events: 1 (Rituximab + MTX), 2 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Not applicable					



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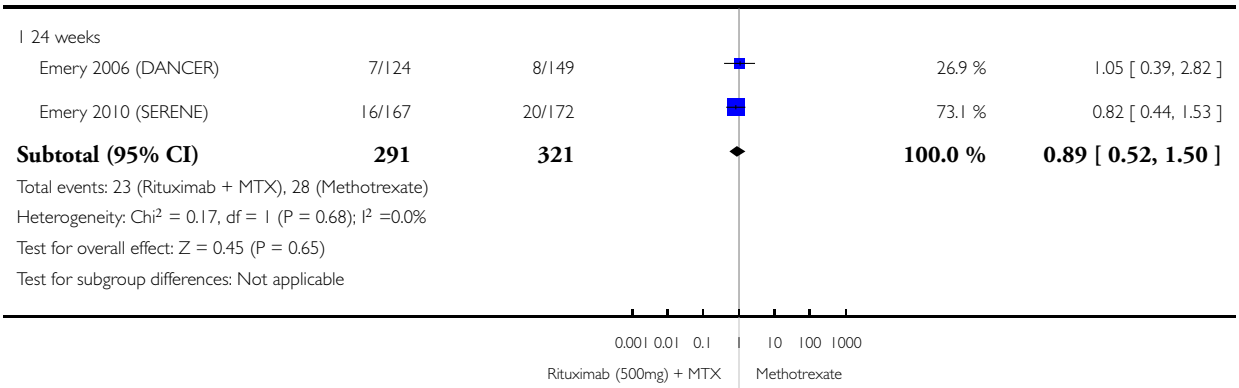
Analysis 13.21. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 21 Lower gastrointestinal events.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 21 Lower gastrointestinal events

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	7/124	8/149		26.9 %	1.05 [0.39, 2.82]
Emery 2010 (SERENE)	16/167	20/172		73.1 %	0.82 [0.44, 1.53]
Subtotal (95% CI)	**291**	**321**		**100.0 %**	**0.89 [0.52, 1.50]**
Total events: 23 (Rituximab + MTX), 28 (Methotrexate)					
Heterogeneity: Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 0.45 (P = 0.65)					
Test for subgroup differences: Not applicable					



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Analysis 13.22. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 22 Malignancy.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 22 Malignancy

Study or subgroup	Rituximab + MTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	0/124	0/149			Not estimable
Emery 2010 (SERENE)	1/167	1/172		100.0 %	1.03 [0.06, 16.33]
Subtotal (95% CI)	**291**	**321**		**100.0 %**	**1.03 [0.06, 16.33]**
Total events: 1 (Rituximab + MTX), 1 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
2 52 weeks					
Tak 2010 (IMAGE)	2/249	5/250		100.0 %	0.40 [0.08, 2.05]
Subtotal (95% CI)	**249**	**250**		**100.0 %**	**0.40 [0.08, 2.05]**
Total events: 2 (Rituximab + MTX), 5 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
3 104 weeks					
Tak 2010 (IMAGE)	6/249	7/249		100.0 %	0.86 [0.29, 2.51]
Subtotal (95% CI)	**249**	**249**		**100.0 %**	**0.86 [0.29, 2.51]**
Total events: 6 (Rituximab + MTX), 7 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.28 (P = 0.78)					
Test for subgroup differences: Chi^2 = 0.66, df = 2 (P = 0.72), I^2 =0.0%					

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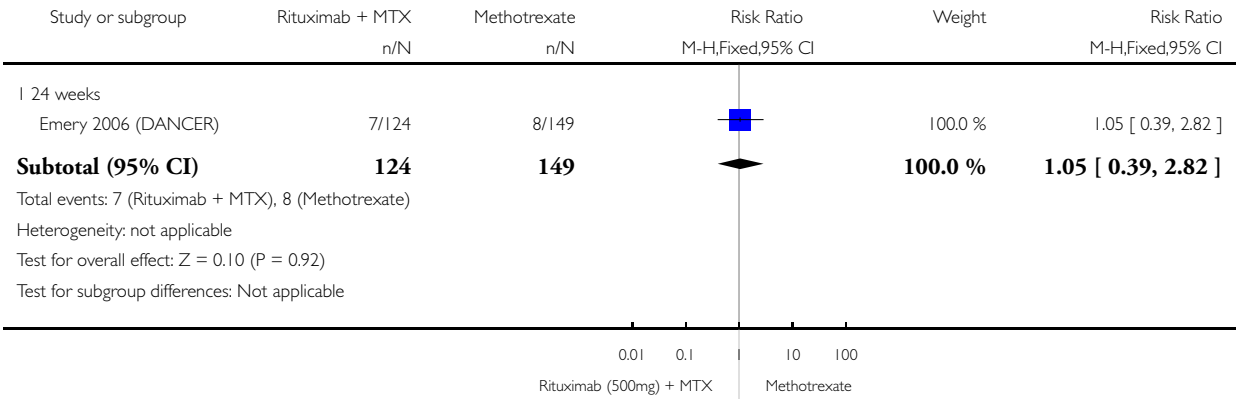
Analysis 13.23. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 23 Nasopharyngitis.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 23 Nasopharyngitis

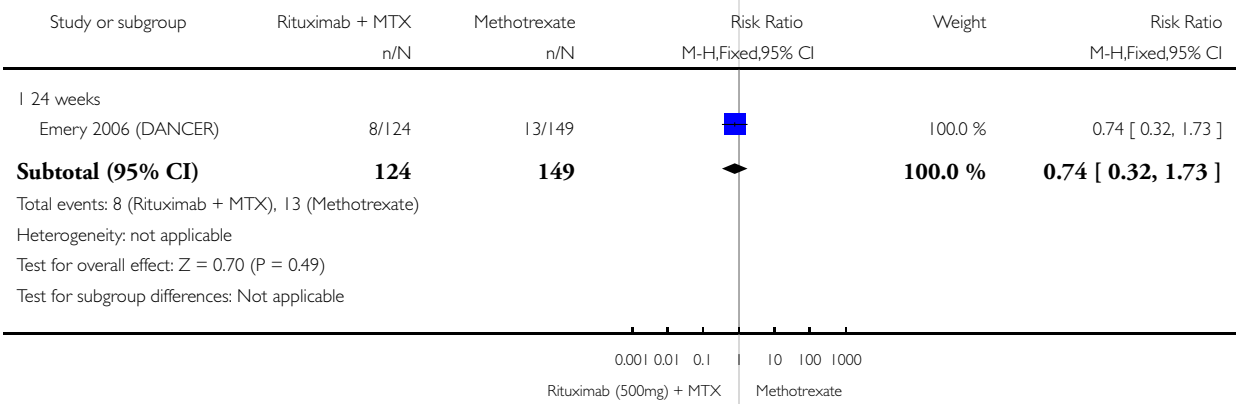


Analysis 13.24. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 24 Nausea.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 24 Nausea



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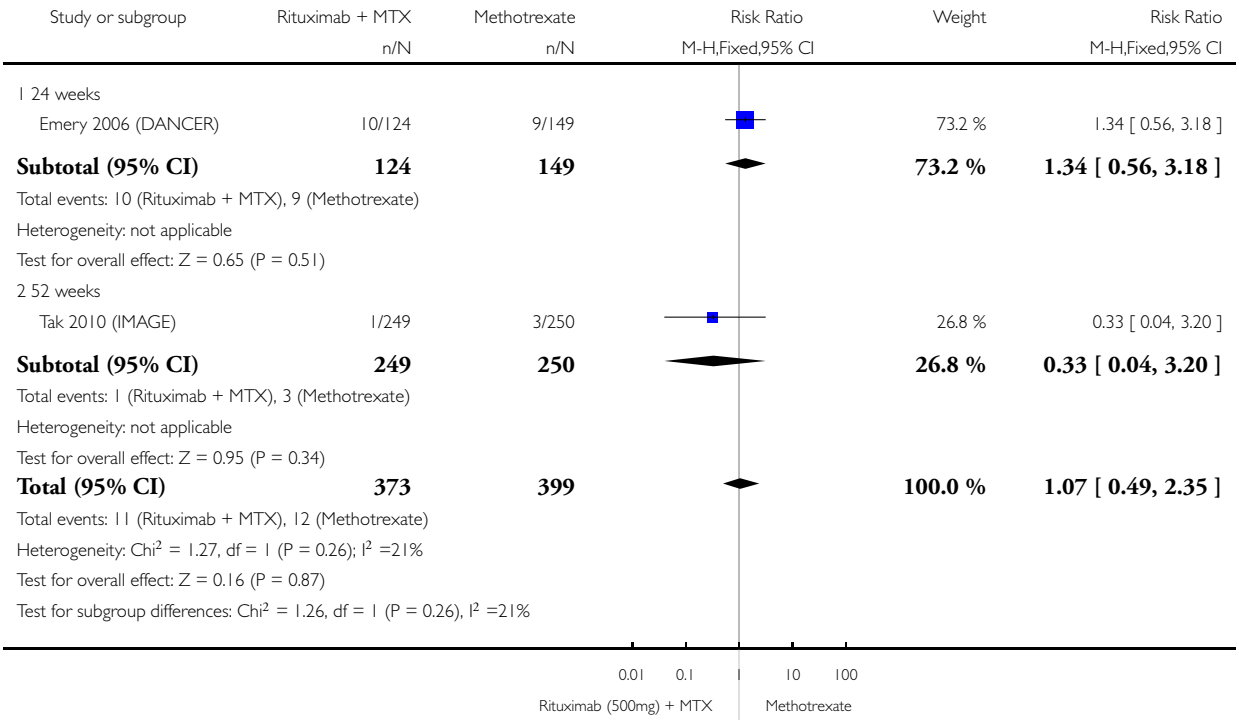
Analysis 13.25. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 25 Upper respiratory tract infection.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 25 Upper respiratory tract infection



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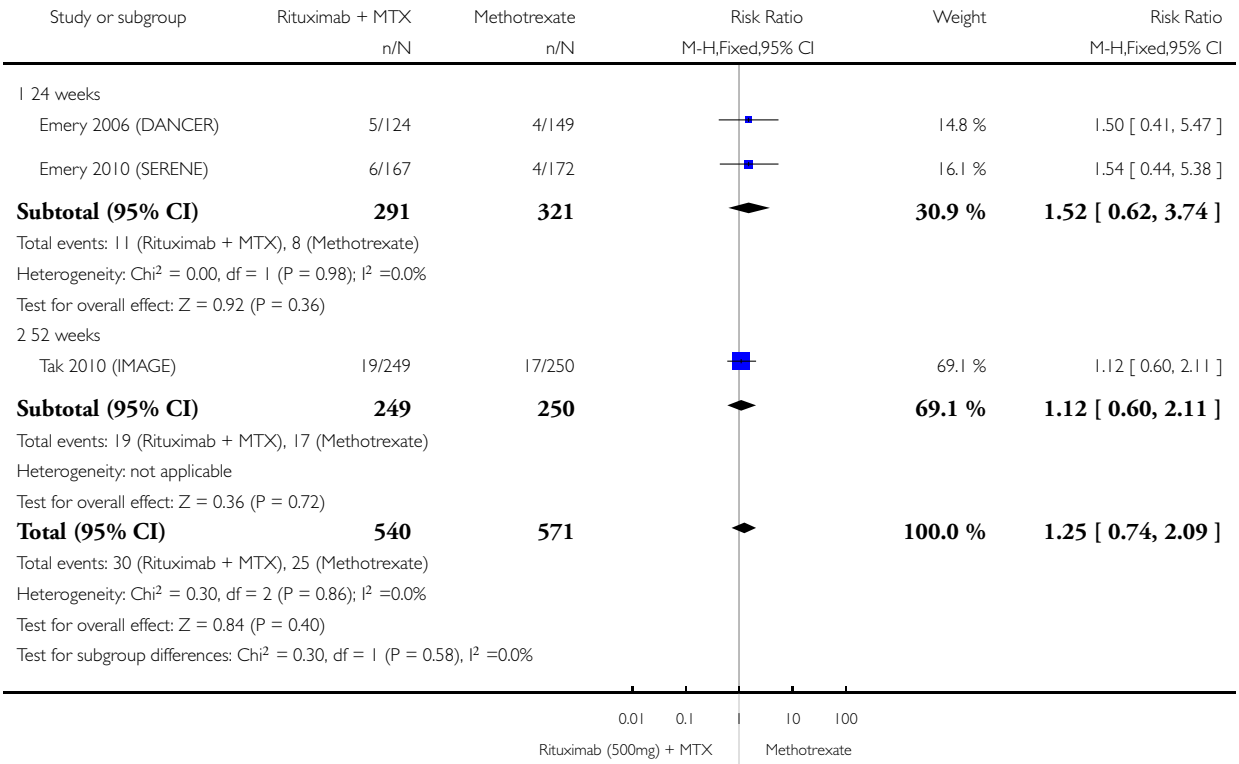
Analysis 13.26. Comparison 13 Harms - RTX (2 x 500 mg) + MTX versus MTX, Outcome 26 Vascular disorders.

Review: Rituximab for rheumatoid arthritis

Comparison: 13 Harms - RTX (2 x 500 mg) + MTX versus MTX

Outcome: 26 Vascular disorders



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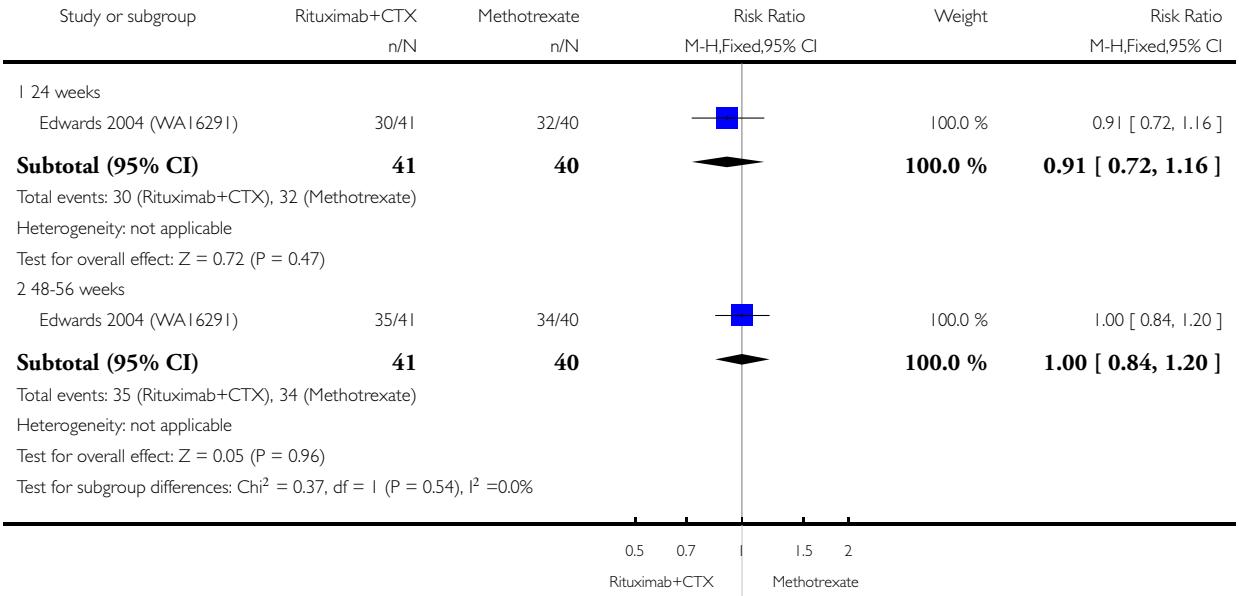
Analysis 14.1. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 1 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 1 Any Adverse Event



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Analysis 14.2. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 2 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 2 Serious Adverse Events

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	6/41	3/40		100.0 %	1.95 [0.52, 7.27]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**1.95 [0.52, 7.27]**
Total events: 6 (Rituximab+CTX), 3 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
2 48-56 weeks					
Edwards 2004 (WA16291)	7/41	4/40		100.0 %	1.71 [0.54, 5.38]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**1.71 [0.54, 5.38]**
Total events: 7 (Rituximab+CTX), 4 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.36)					
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%					

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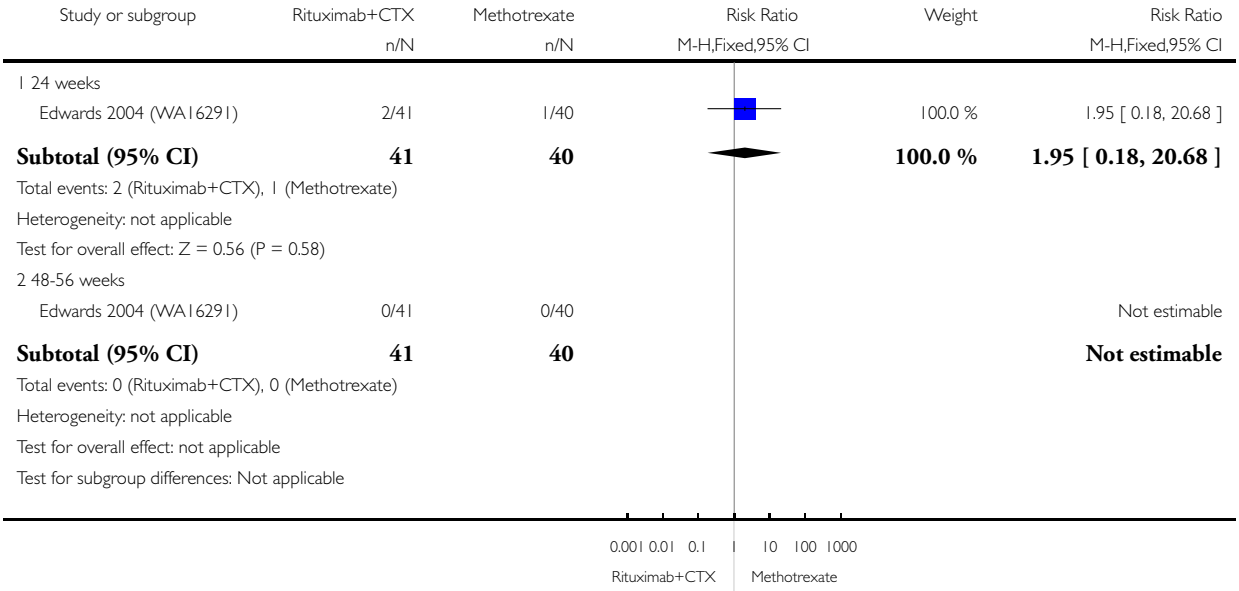
Analysis 14.3. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 3 Serious Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 3 Serious Infections



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Analysis 14.4. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 4 Death.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 4 Death

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/41	0/40		100.0 %	0.0 [-0.05, 0.05]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.0 [-0.05, 0.05]**
Total events: 0 (Rituximab+CTX), 0 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

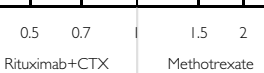
Analysis 14.5. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 5 Any Event Associated with 1st Infusion.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 5 Any Event Associated with 1st Infusion

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	13/41	12/40		100.0 %	1.06 [0.55, 2.03]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**1.06 [0.55, 2.03]**
Total events: 13 (Rituximab+CTX), 12 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					
Test for subgroup differences: Not applicable					



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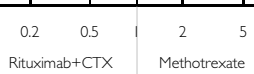
Analysis 14.6. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 6 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 6 Arthralgia

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	1/41	3/40		100.0 %	0.33 [0.04, 3.00]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.33 [0.04, 3.00]**
Total events: 1 (Rituximab+CTX), 3 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					
Test for subgroup differences: Not applicable					



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Analysis 14.7. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 7 Back pain.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 7 Back pain

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	3/41	2/40		100.0 %	1.46 [0.26, 8.30]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**1.46 [0.26, 8.30]**
Total events: 3 (Rituximab+CTX), 2 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Not applicable					

Analysis 14.8. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 8 Cough.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 8 Cough

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	1/41	0/40		100.0 %	2.93 [0.12, 69.83]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**2.93 [0.12, 69.83]**
Total events: 1 (Rituximab+CTX), 0 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Test for subgroup differences: Not applicable					

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Analysis 14.9. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 9 Dyspnea.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 9 Dyspnea

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/41	0/40		100.0 %	0.0 [-0.05, 0.05]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.0 [-0.05, 0.05]**
Total events: 0 (Rituximab+CTX), 0 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

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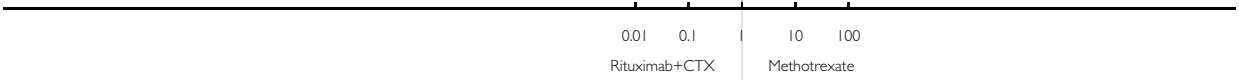
Analysis 14.10. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 10 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 10 Exacerbation of RA

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	6/41	16/40		100.0 %	0.37 [0.16, 0.84]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.37 [0.16, 0.84]**
Total events: 6 (Rituximab+CTX), 16 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.37 (P = 0.018)					
2 48-56 weeks					
Edwards 2004 (WA16291)	0/41	0/40			Not estimable
Subtotal (95% CI)	**41**	**40**			**Not estimable**
Total events: 0 (Rituximab+CTX), 0 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



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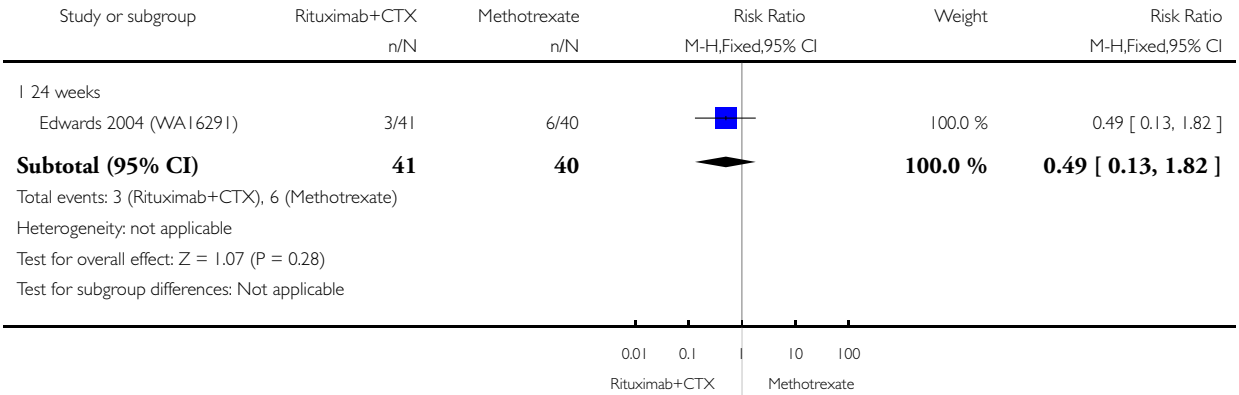
Analysis 14.11. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 11 Hypertension.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 11 Hypertension

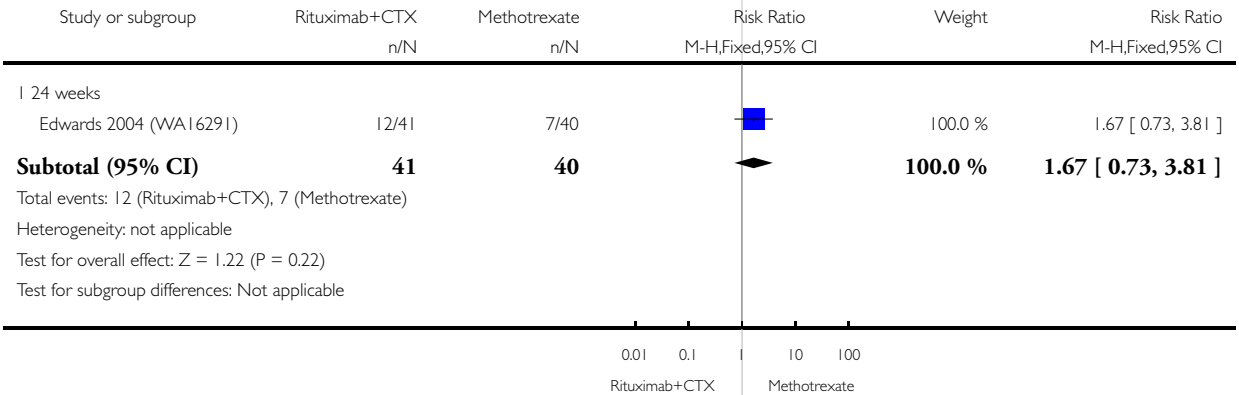


Analysis 14.12. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 12 Hypotension.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 12 Hypotension



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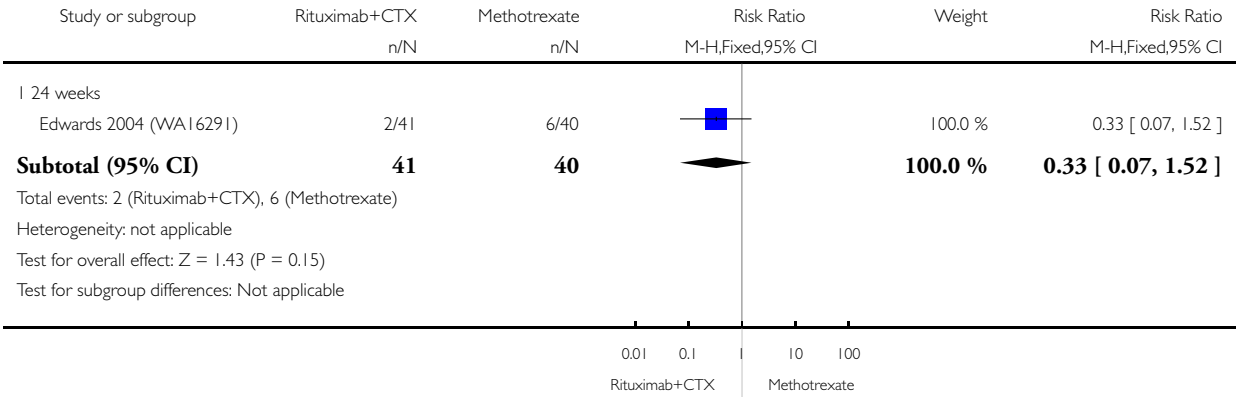
Analysis 14.13. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 13 Nasopharyngitis.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 13 Nasopharyngitis

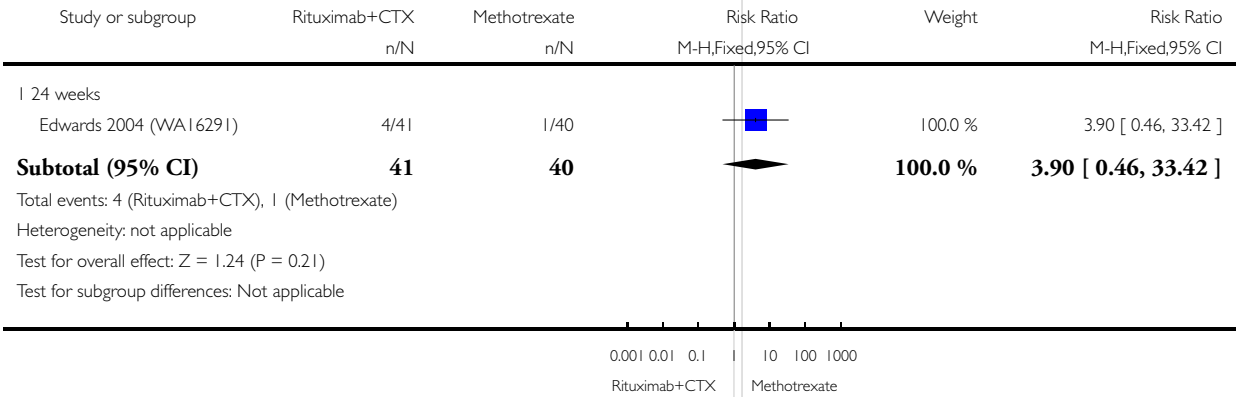


Analysis 14.14. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 14 Nausea.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 14 Nausea



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Analysis 14.15. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 15 Pruritus.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 15 Pruritus

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	4/41	0/40		100.0 %	8.79 [0.49, 158.07]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**8.79 [0.49, 158.07]**
Total events: 4 (Rituximab+CTX), 0 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					
Test for subgroup differences: Not applicable					

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Analysis 14.16. Comparison 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX, Outcome 16 Rash.

Review: Rituximab for rheumatoid arthritis

Comparison: 14 Harms - RTX (2 x 1000 mg) + CTX versus MTX

Outcome: 16 Rash

Study or subgroup	Rituximab+CTX n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	4/41	1/40		100.0 %	3.90 [0.46, 33.42]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**3.90 [0.46, 33.42]**
Total events: 4 (Rituximab+CTX), 1 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.21)					
2 48 weeks					
Edwards 2004 (WA16291)	0/40	0/40			Not estimable
Subtotal (95% CI)	**40**	**40**			**Not estimable**
Total events: 0 (Rituximab+CTX), 0 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

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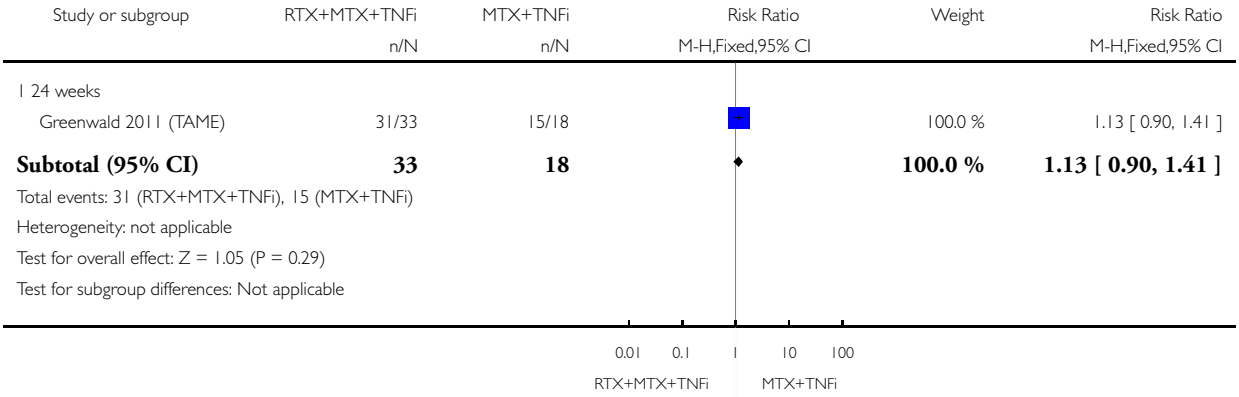
Analysis 15.1. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 1 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 1 Any Adverse Event

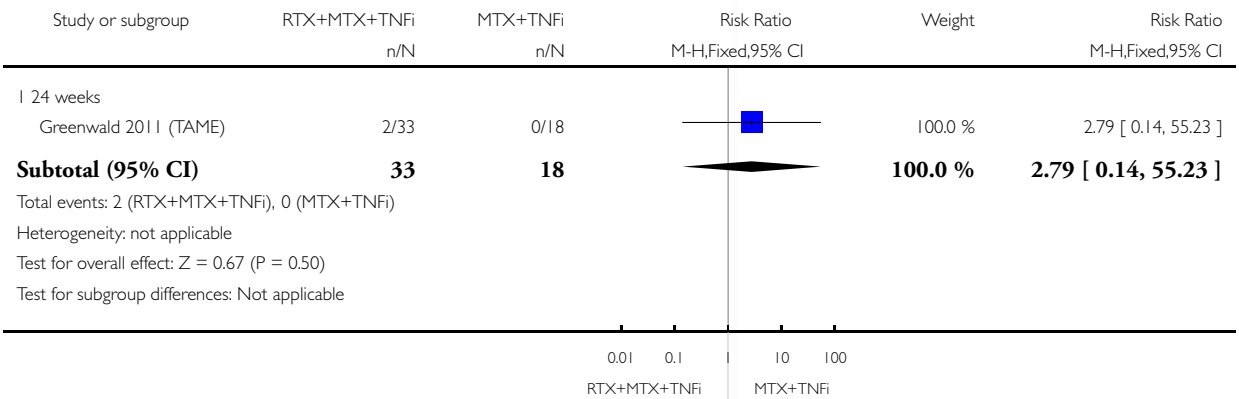


Analysis 15.2. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 2 Serious adverse events.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 2 Serious adverse events



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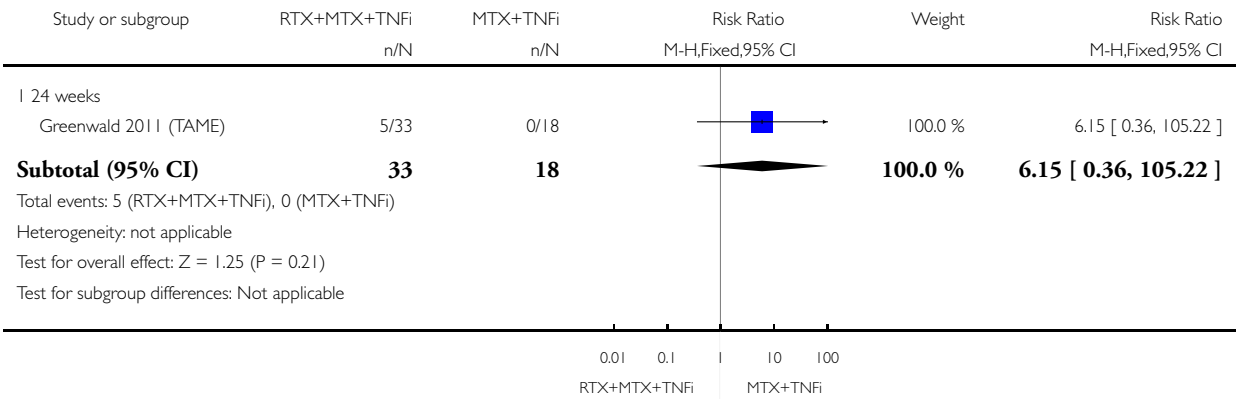
Analysis 15.3. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 3 Grade 3 adverse events.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 3 Grade 3 adverse events



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Analysis 15.4. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 4 All infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 4 All infections

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	18/33	11/18		100.0 %	0.89 [0.55, 1.45]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**0.89 [0.55, 1.45]**
Total events: 18 (RTX+MTX+TNFi), 11 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.64)					
Test for subgroup differences: Not applicable					

Analysis 15.5. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 5 Grade 3 infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 5 Grade 3 infections

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	3/33	0/18		100.0 %	3.91 [0.21, 71.77]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**3.91 [0.21, 71.77]**
Total events: 3 (RTX+MTX+TNFi), 0 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					
Test for subgroup differences: Not applicable					

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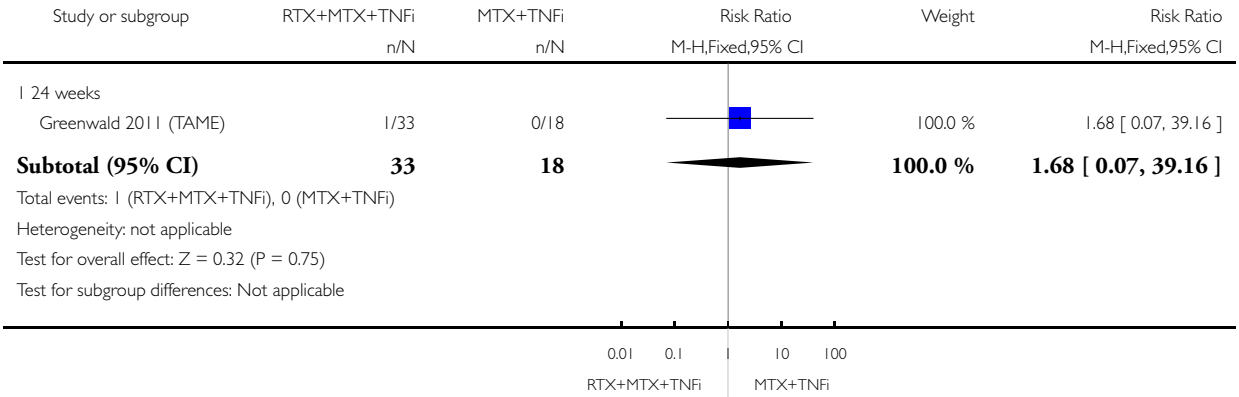
Analysis 15.6. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 6 Serious infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 6 Serious infections

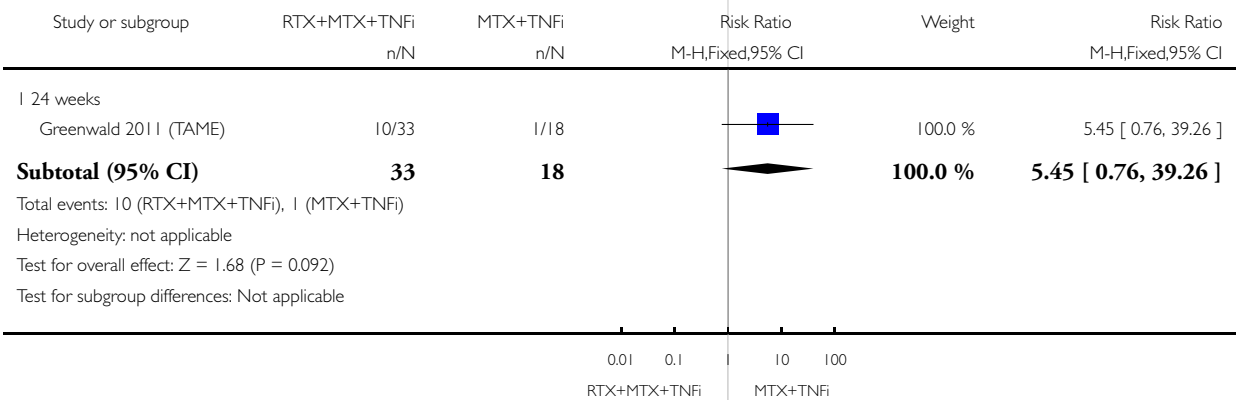


Analysis 15.7. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 7 Any Event Associated with 1st infusion.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 7 Any Event Associated with 1st infusion



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Analysis 15.8. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 8 Any Event Associated with 2nd infusion.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 8 Any Event Associated with 2nd infusion

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	3/33	2/18		100.0 %	0.82 [0.15, 4.45]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**0.82 [0.15, 4.45]**
Total events: 3 (RTX+MTX+TNFi), 2 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
Test for subgroup differences: Not applicable					

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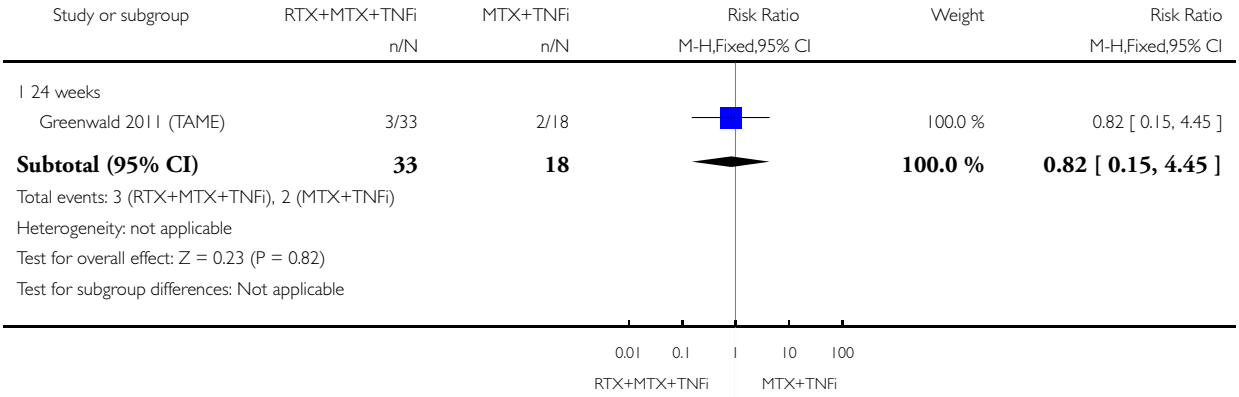
Analysis 15.9. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 9 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 9 Arthralgia

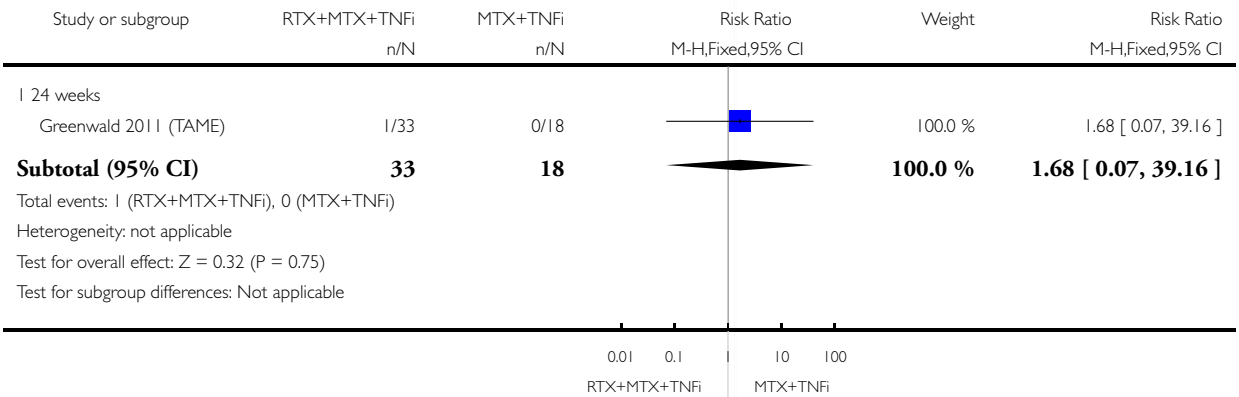


Analysis 15.10. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 10 Coronary artery occlusion.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 10 Coronary artery occlusion



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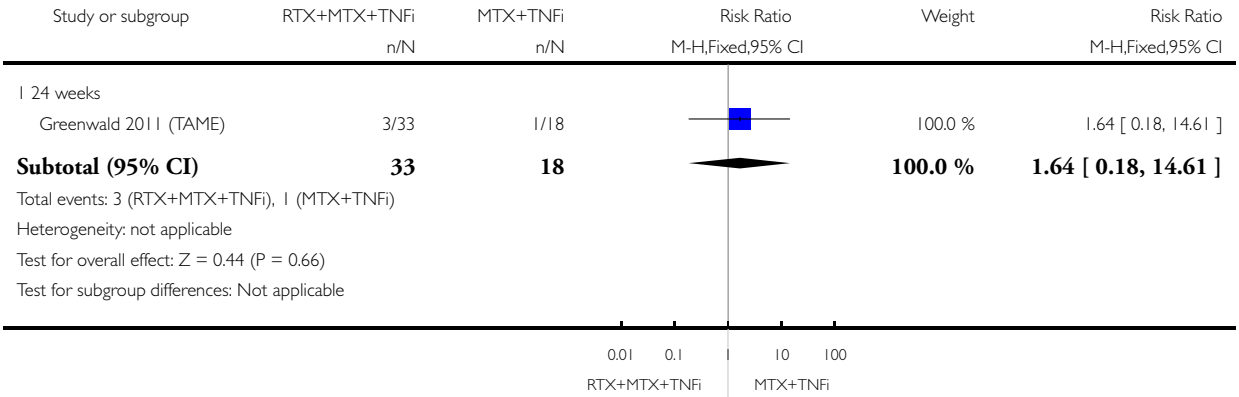
Analysis 15.11. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 11 Diarrhea.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 11 Diarrhea

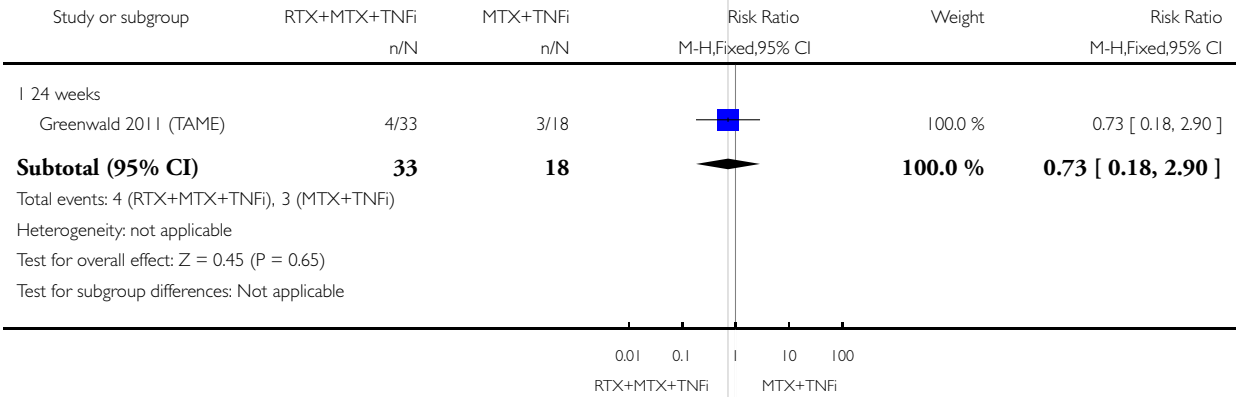


Analysis 15.12. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 12 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 12 Exacerbation of RA



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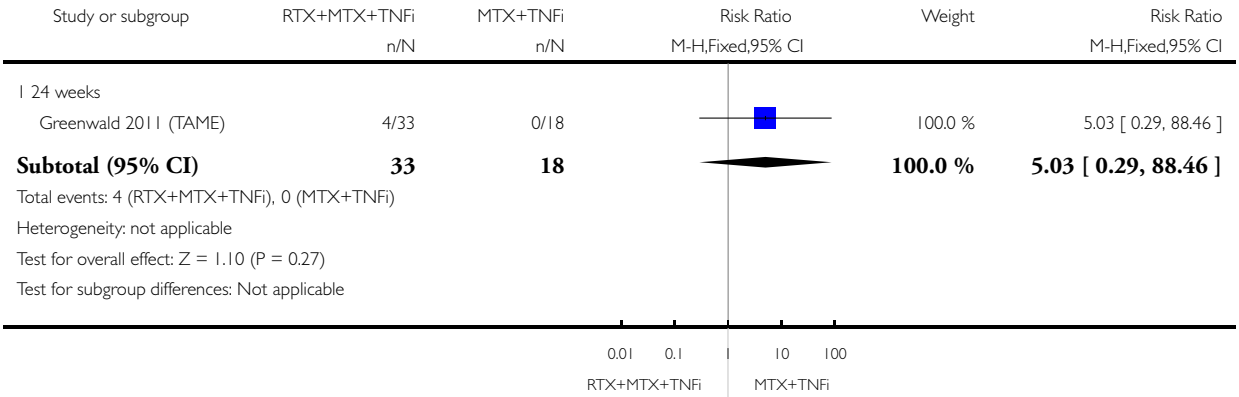
Analysis 15.13. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 13 Fatigue.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 13 Fatigue

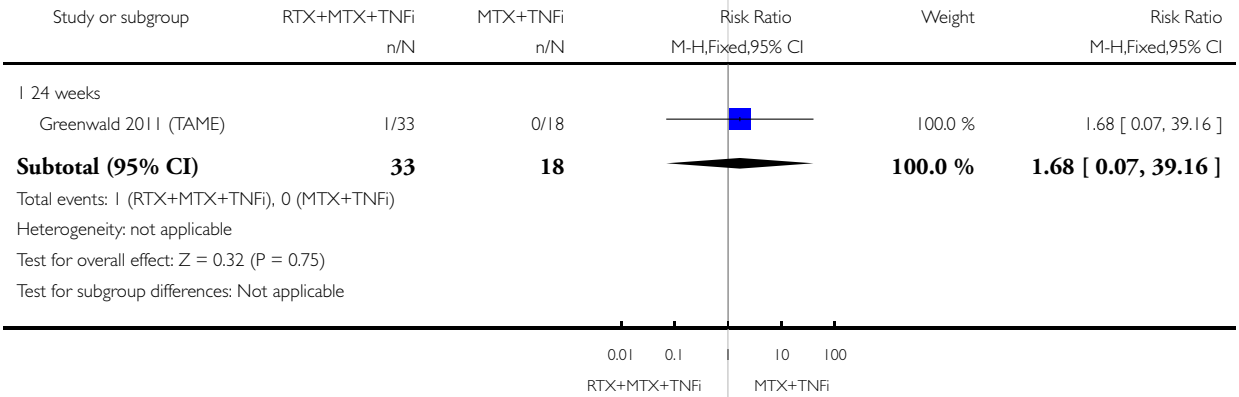


Analysis 15.14. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 14 HACA.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 14 HACA



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Analysis 15.15. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 15 Headache.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 15 Headache

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	3/33	2/18		100.0 %	0.82 [0.15, 4.45]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**0.82 [0.15, 4.45]**
Total events: 3 (RTX+MTX+TNFi), 2 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
Test for subgroup differences: Not applicable					

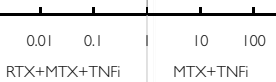
Analysis 15.16. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 16 Influenza.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 16 Influenza

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	1/33	0/18		100.0 %	1.68 [0.07, 39.16]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**1.68 [0.07, 39.16]**
Total events: 1 (RTX+MTX+TNFi), 0 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
Test for subgroup differences: Not applicable					



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Analysis 15.17. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 17 Muscle spasms.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 17 Muscle spasms

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	1/33	2/18		100.0 %	0.27 [0.03, 2.81]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**0.27 [0.03, 2.81]**
Total events: 1 (RTX+MTX+TNFi), 2 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.27)					
Test for subgroup differences: Not applicable					

Analysis 15.18. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 18 Nasopharyngitis.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 18 Nasopharyngitis

Study or subgroup	RTX+MTX+TNFi n/N	MTX+TNFi n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Greenwald 2011 (TAME)	2/33	1/18		100.0 %	1.09 [0.11, 11.22]
Subtotal (95% CI)	**33**	**18**		**100.0 %**	**1.09 [0.11, 11.22]**
Total events: 2 (RTX+MTX+TNFi), 1 (MTX+TNFi)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.07 (P = 0.94)					
Test for subgroup differences: Not applicable					

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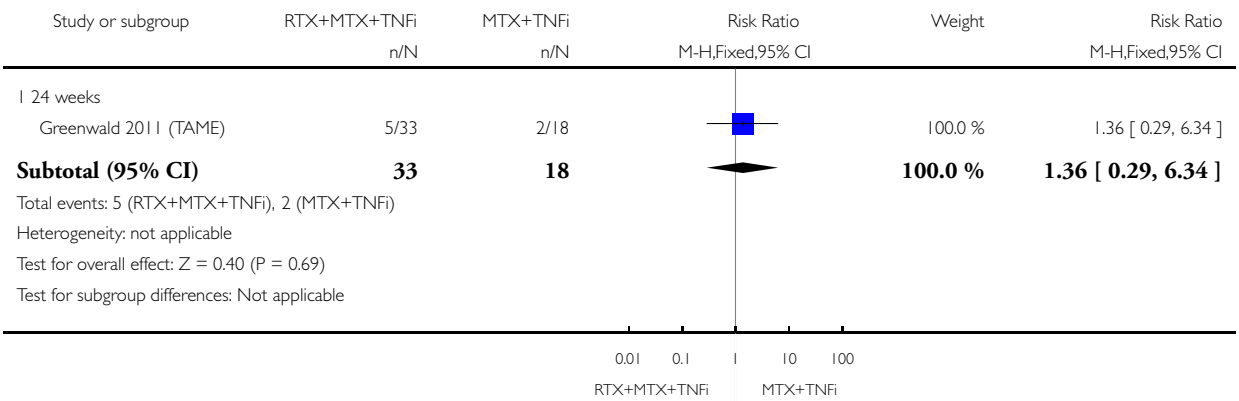
Analysis 15.19. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 19 Nausea.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 19 Nausea



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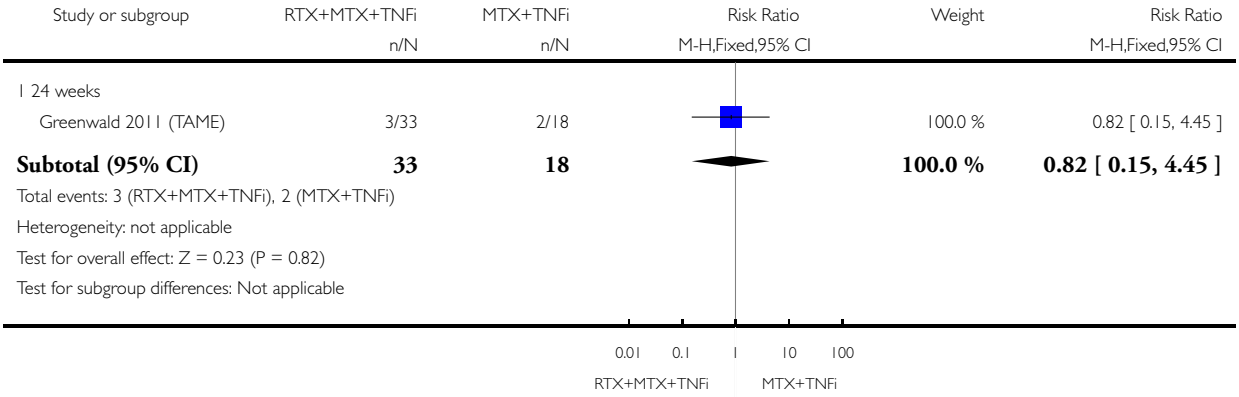
Analysis 15.20. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 20 Peripheral edema.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 20 Peripheral edema

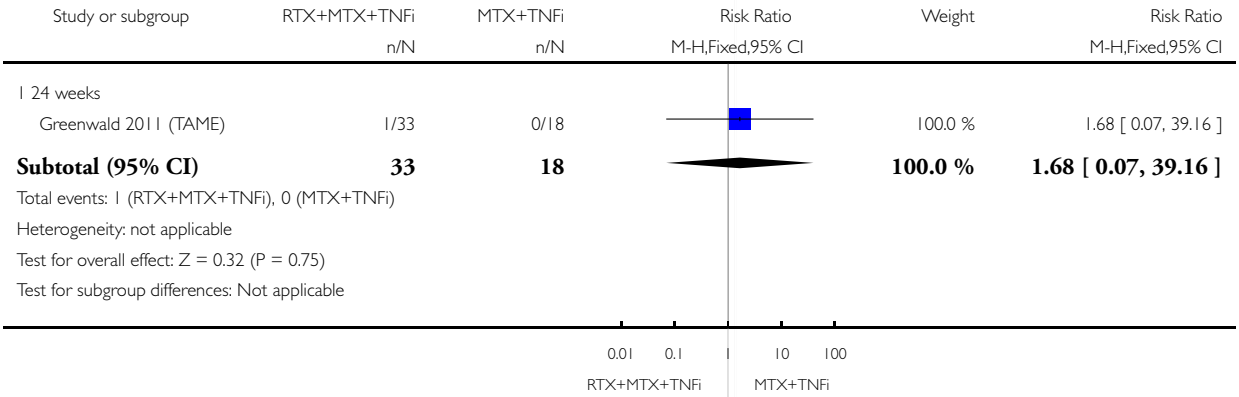


Analysis 15.21. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 21 Pneumonia.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 21 Pneumonia



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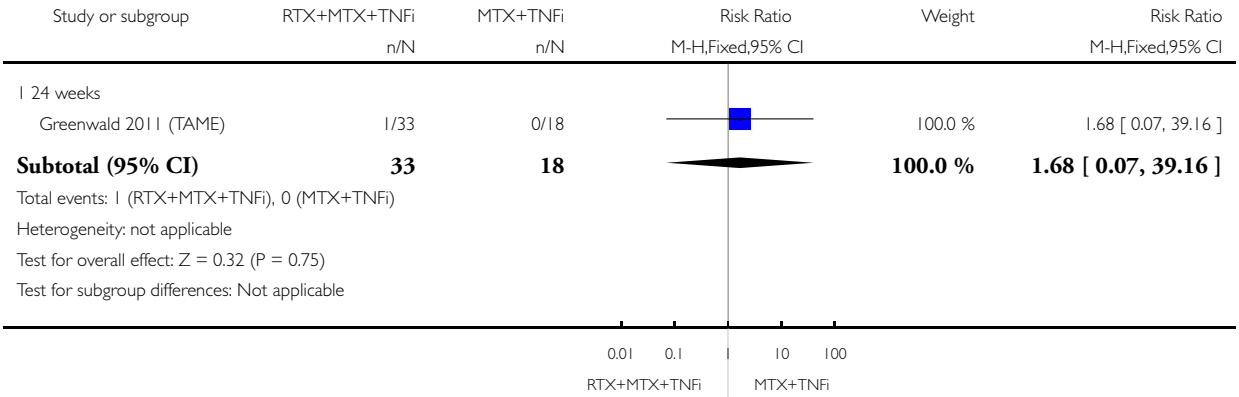
Analysis 15.22. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 22 Postoperative infection.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 22 Postoperative infection

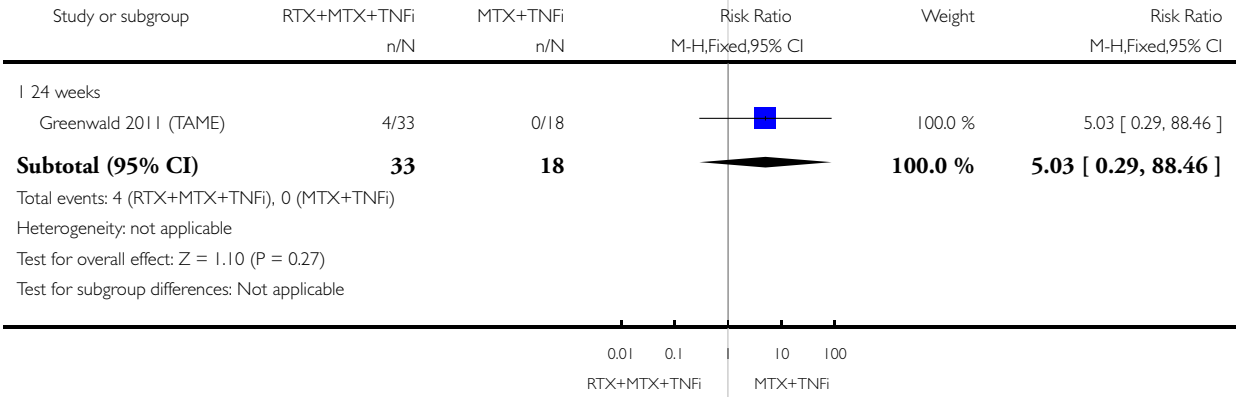


Analysis 15.23. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 23 Pruritus.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 23 Pruritus



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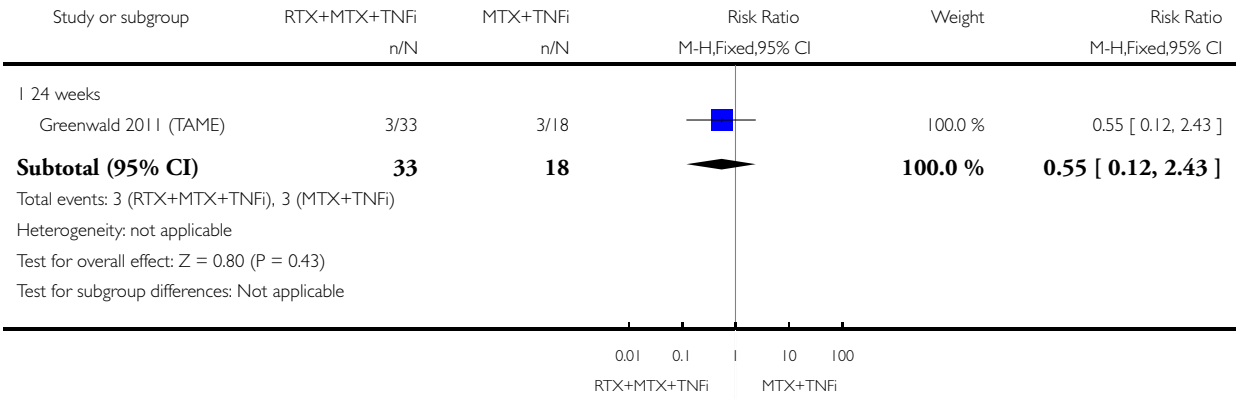
Analysis 15.24. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 24 Sinusitits.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 24 Sinusitits

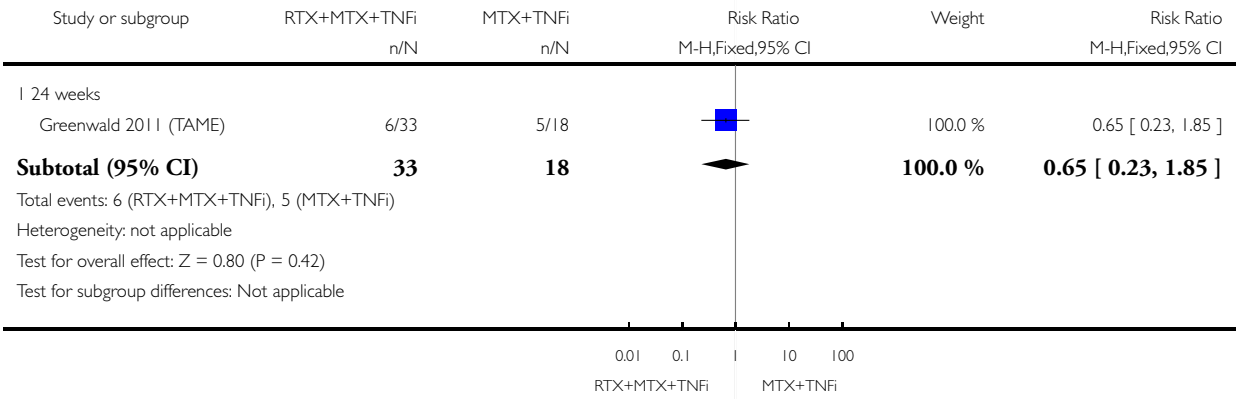


Analysis 15.25. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 25 Upper respiratory tract infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 25 Upper respiratory tract infections



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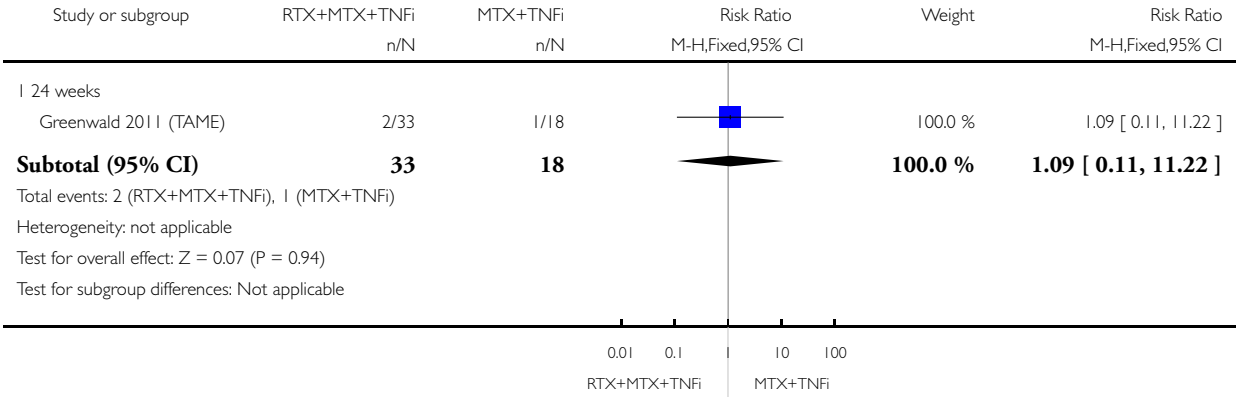
Analysis 15.26. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 26 Urinary tract infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 26 Urinary tract infections

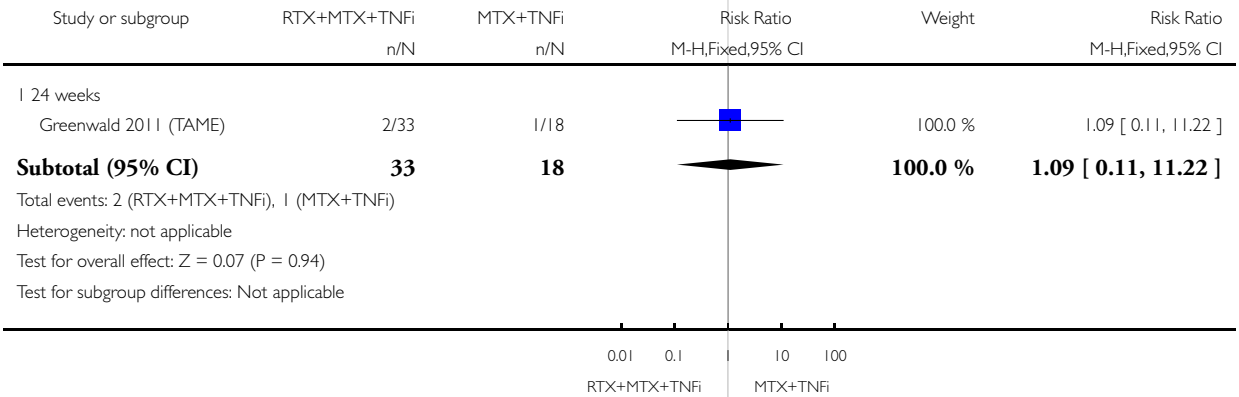


Analysis 15.27. Comparison 15 Harms - RTX + MTX + TNFi versus MTX + TNFi, Outcome 27 Vaginal Mycosis.

Review: Rituximab for rheumatoid arthritis

Comparison: 15 Harms - RTX + MTX + TNFi versus MTX + TNFi

Outcome: 27 Vaginal Mycosis



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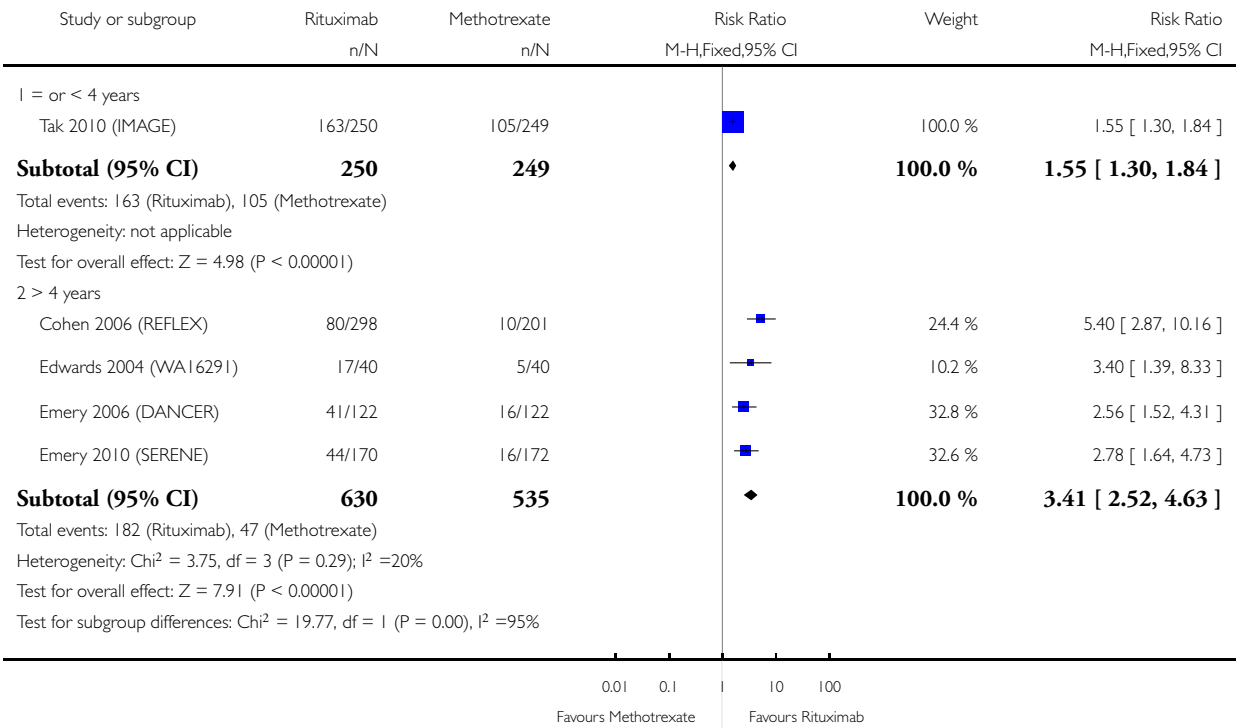
Analysis 16.1. Comparison 16 Disease duration (subgroup analysis), Outcome 1 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 16 Disease duration (subgroup analysis)

Outcome: 1 ACR 50



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Analysis 17.1. Comparison 17 Previous treatment (subgroup analysis), Outcome 1 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 17 Previous treatment (subgroup analysis)

Outcome: 1 ACR 50

Study or subgroup	Rituximab n/N	Methotrexate n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Methotrexate-naive					
Tak 2010 (IMAGE)	163/250	105/249		100.0 %	1.55 [1.30, 1.84]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**1.55 [1.30, 1.84]**
Total events: 163 (Rituximab), 105 (Methotrexate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.98 (P < 0.00001)					
2 DMARDs failure					
Edwards 2004 (WA16291)	17/40	5/40		23.9 %	3.40 [1.39, 8.33]
Emery 2010 (SERENE)	44/170	16/172		76.1 %	2.78 [1.64, 4.73]
Subtotal (95% CI)	**210**	**212**		**100.0 %**	**2.93 [1.86, 4.63]**
Total events: 61 (Rituximab), 21 (Methotrexate)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 4.61 (P < 0.00001)					
3 DMARD and TNFi failure					
Cohen 2006 (REFLEX)	80/298	10/201		42.7 %	5.40 [2.87, 10.16]
Emery 2006 (DANCER)	41/122	16/122		57.3 %	2.56 [1.52, 4.31]
Subtotal (95% CI)	**420**	**323**		**100.0 %**	**3.77 [2.51, 5.66]**
Total events: 121 (Rituximab), 26 (Methotrexate)					
Heterogeneity: Chi^2 = 3.35, df = 1 (P = 0.07); I^2 =70%					
Test for overall effect: Z = 6.41 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 19.93, df = 2 (P = 0.00), I^2 =90%					

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Analysis 18.1. Comparison 18 Study quality (subgroup analysis), Outcome 1 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 18 Study quality (subgroup analysis)

Outcome: 1 ACR 50

Study or subgroup	Rituximab n/N	Methotrexate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Edwards 2004 (WA16291)	17/40	5/40		34.3 %	3.40 [1.39, 8.33]
Tak 2010 (IMAGE)	163/250	105/249		65.7 %	1.55 [1.30, 1.84]
Subtotal (95% CI)	**290**	**289**		**100.0 %**	**2.03 [0.96, 4.26]**
Total events: 180 (Rituximab), 110 (Methotrexate)					
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 2.95$, df = 1 (P = 0.09); $I^2 = 66\%$					
Test for overall effect: Z = 1.86 (P = 0.063)					
2 High risk of bias					
Cohen 2006 (REFLEX)	80/298	10/201		29.0 %	5.40 [2.87, 10.16]
Emery 2006 (DANCER)	41/122	16/122		35.9 %	2.56 [1.52, 4.31]
Emery 2010 (SERENE)	44/170	16/172		35.1 %	2.78 [1.64, 4.73]
Subtotal (95% CI)	**590**	**495**		**100.0 %**	**3.27 [2.10, 5.09]**
Total events: 165 (Rituximab), 42 (Methotrexate)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.75$, df = 2 (P = 0.15); $I^2 = 47\%$					
Test for overall effect: Z = 5.26 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 1.18$, df = 1 (P = 0.28), $I^2 = 15\%$					

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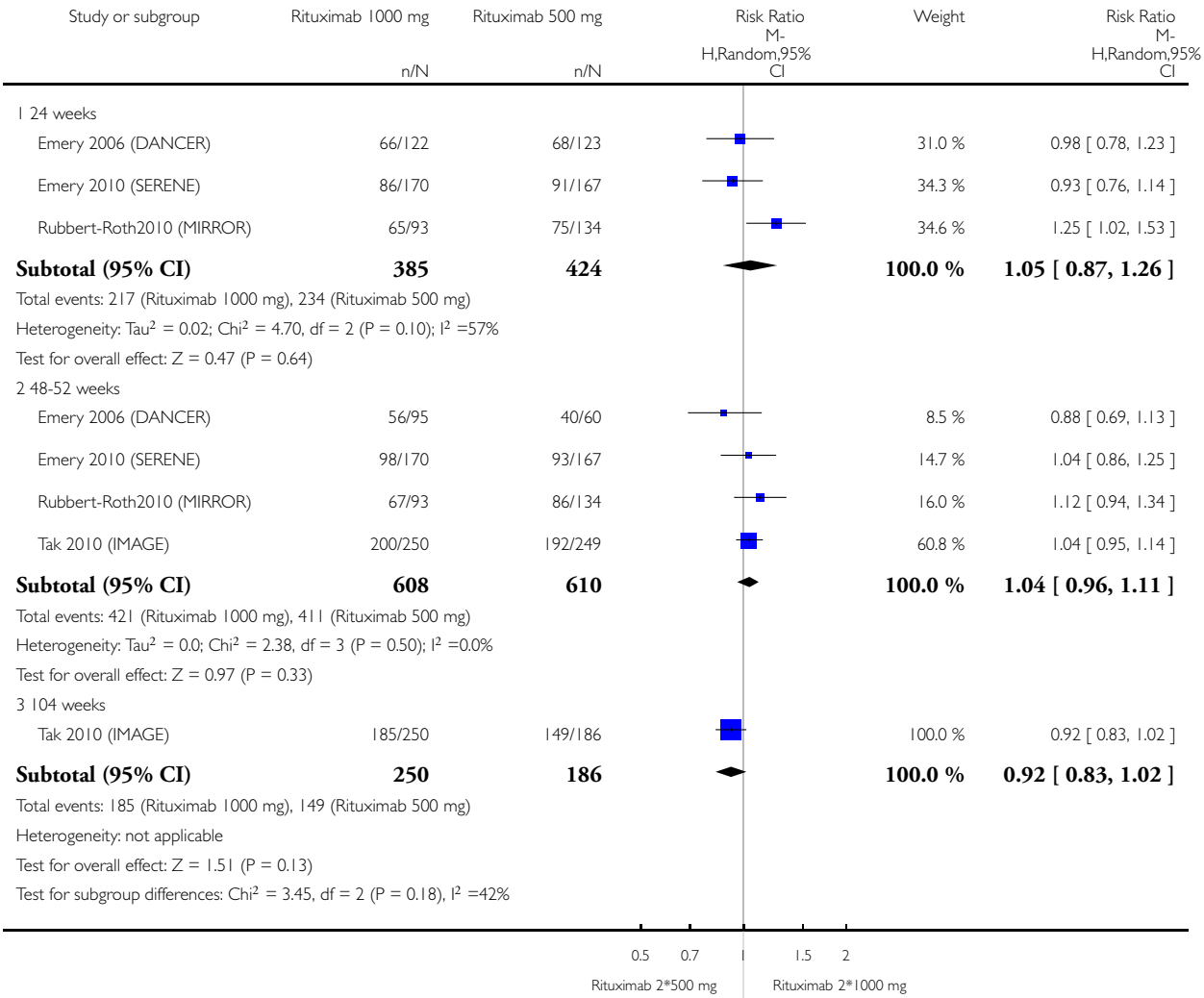
Analysis 19.1. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 1 ACR 20.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 1 ACR 20



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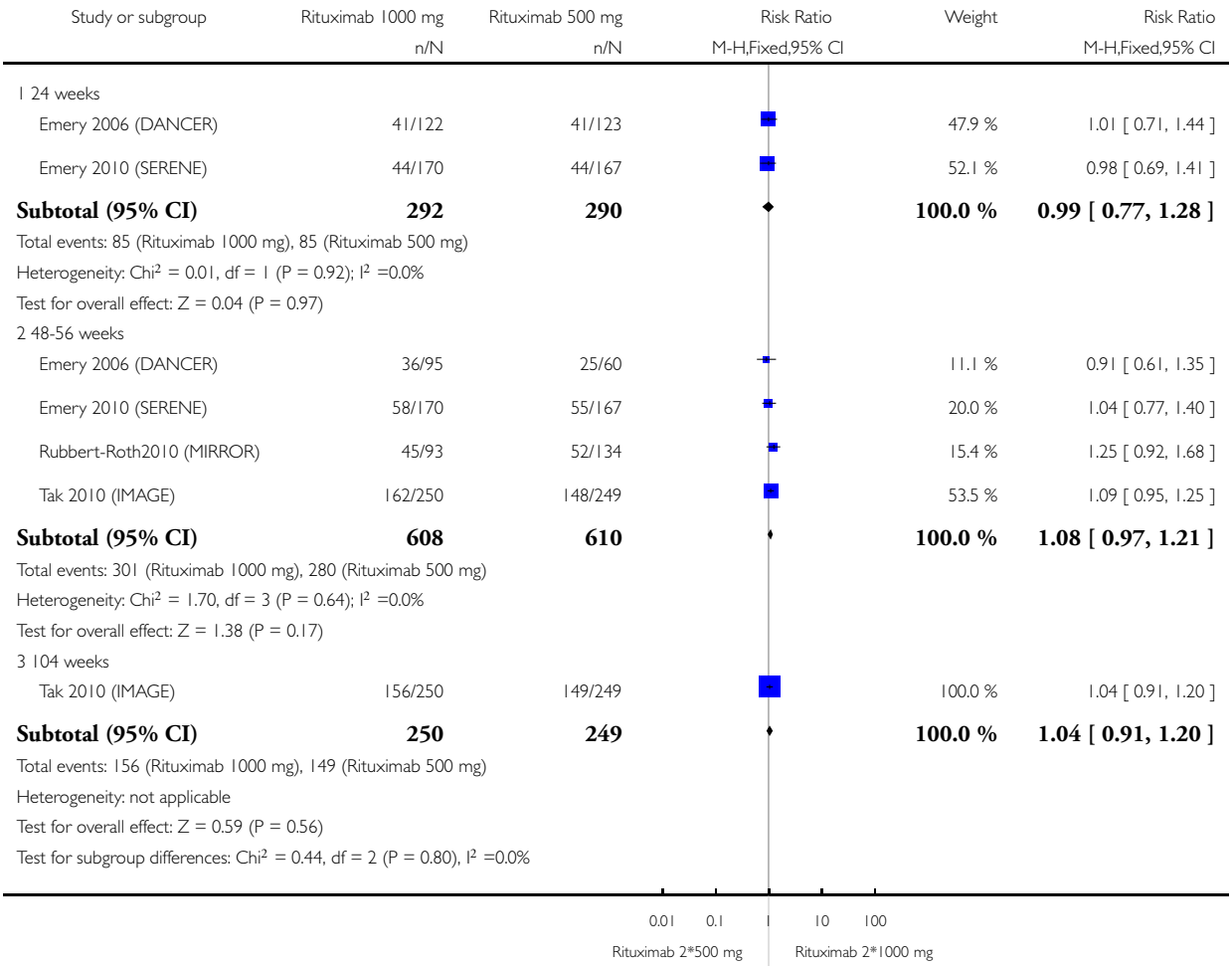
Analysis 19.2. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 2 ACR 50



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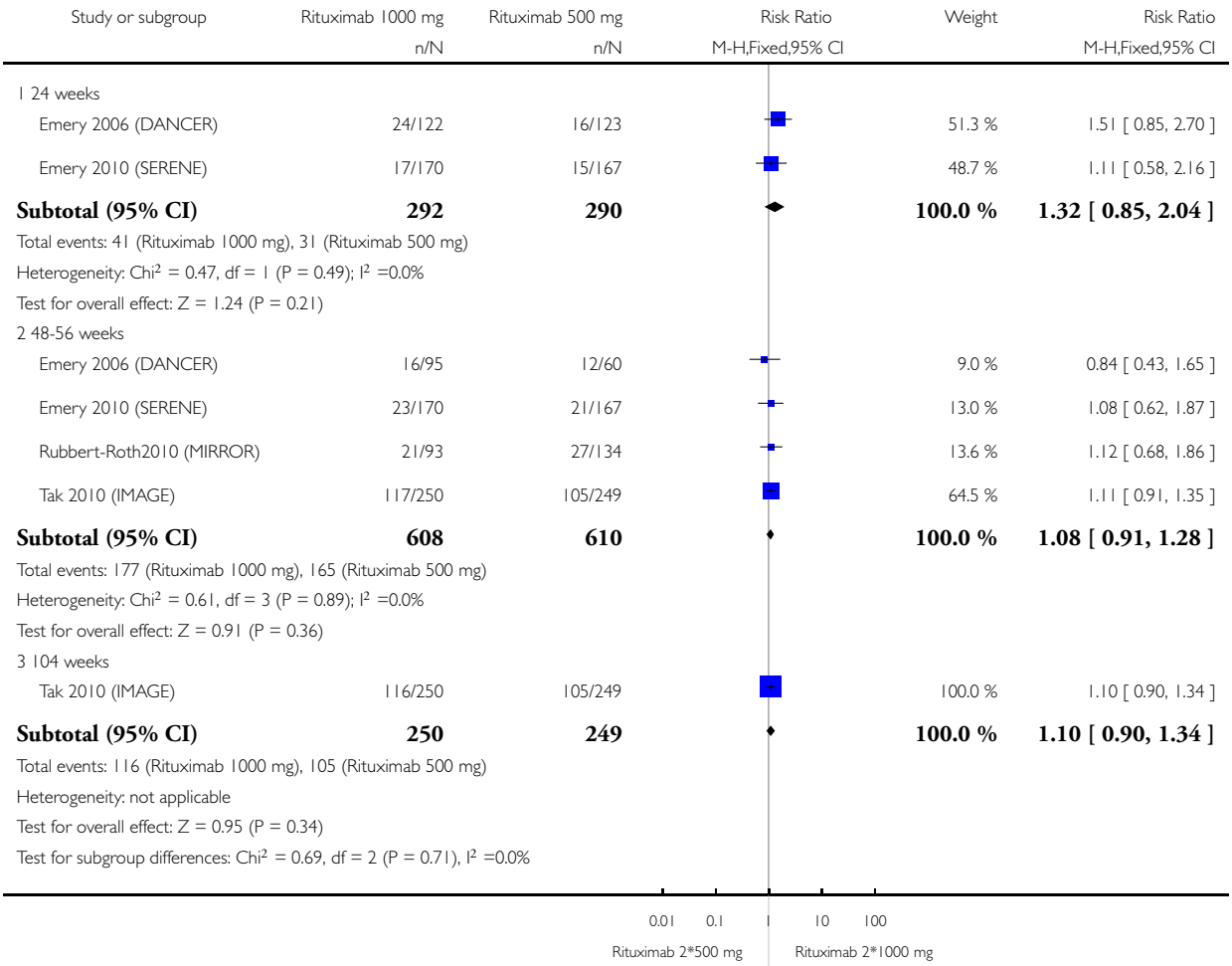
Analysis 19.3. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 3 ACR 70.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 3 ACR 70



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Analysis 19.4. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 4 ACR 90.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 4 ACR 90

Study or subgroup	Rituximab 1000 mg n/N	Rituximab 500 mg n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 52 weeks					
Tak 2010 (IMAGE)	41/250	43/250		100.0 %	0.95 [0.65, 1.41]
Subtotal (95% CI)	**250**	**250**		**100.0 %**	**0.95 [0.65, 1.41]**
Total events: 41 (Rituximab 1000 mg), 43 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.24 (P = 0.81)					
2 104 weeks					
Tak 2010 (IMAGE)	58/250	51/250		100.0 %	1.14 [0.82, 1.59]
Subtotal (95% CI)	**250**	**250**		**100.0 %**	**1.14 [0.82, 1.59]**
Total events: 58 (Rituximab 1000 mg), 51 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Chi^2 = 0.45, df = 1 (P = 0.50), I^2 =0.0%					

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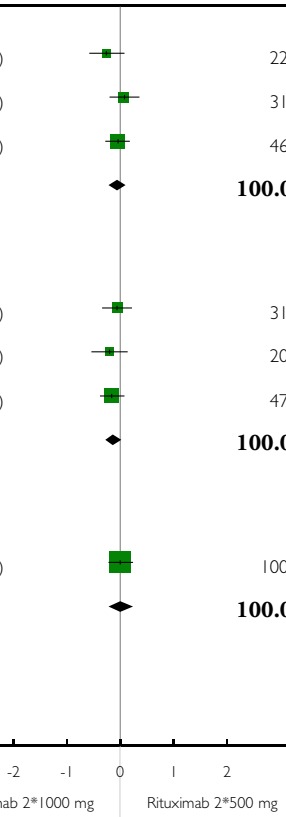
Analysis 19.5. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 5 DAS 28-ESR.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 5 DAS 28-ESR

Study or subgroup	Rituximab 1000 mg N	Mean(SD)	Rituximab 500 mg N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Emery 2006 (DANCER)	122	-2.05 (1.3)	123	-1.79 (1.3)		22.7 %	-0.26 [-0.59, 0.07]
Emery 2010 (SERENE)	170	-1.69 (1.3)	167	-1.76 (1.3)		31.2 %	0.07 [-0.21, 0.35]
Tak 2010 (IMAGE)	250	-2.9 (1.3)	249	-2.85 (1.3)		46.2 %	-0.05 [-0.28, 0.18]
Subtotal (95% CI)	**542**		**539**			**100.0 %**	**-0.06 [-0.22, 0.09]**
Heterogeneity: Chi^2 = 2.30, df = 2 (P = 0.32); I^2 =13%							
Test for overall effect: Z = 0.76 (P = 0.45)							
2 48-56 weeks							
Emery 2010 (SERENE)	170	-2.02 (1.3)	167	-1.96 (1.3)		31.9 %	-0.06 [-0.34, 0.22]
Rubbert-Roth2010 (MIRROR)	93	-2.5 (1.3)	134	-2.3 (1.3)		20.8 %	-0.20 [-0.54, 0.14]
Tak 2010 (IMAGE)	250	-3.21 (1.3)	249	-3.05 (1.3)		47.3 %	-0.16 [-0.39, 0.07]
Subtotal (95% CI)	**513**		**550**			**100.0 %**	**-0.14 [-0.29, 0.02]**
Heterogeneity: Chi^2 = 0.46, df = 2 (P = 0.79); I^2 =0.0%							
Test for overall effect: Z = 1.70 (P = 0.088)							
3 104 weeks							
Tak 2010 (IMAGE)	250	-3.79 (1.3)	249	-3.79 (1.3)		100.0 %	0.0 [-0.23, 0.23]
Subtotal (95% CI)	**250**		**249**			**100.0 %**	**0.0 [-0.23, 0.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Test for subgroup differences: Chi^2 = 1.03, df = 2 (P = 0.60), I^2 =0.0%							



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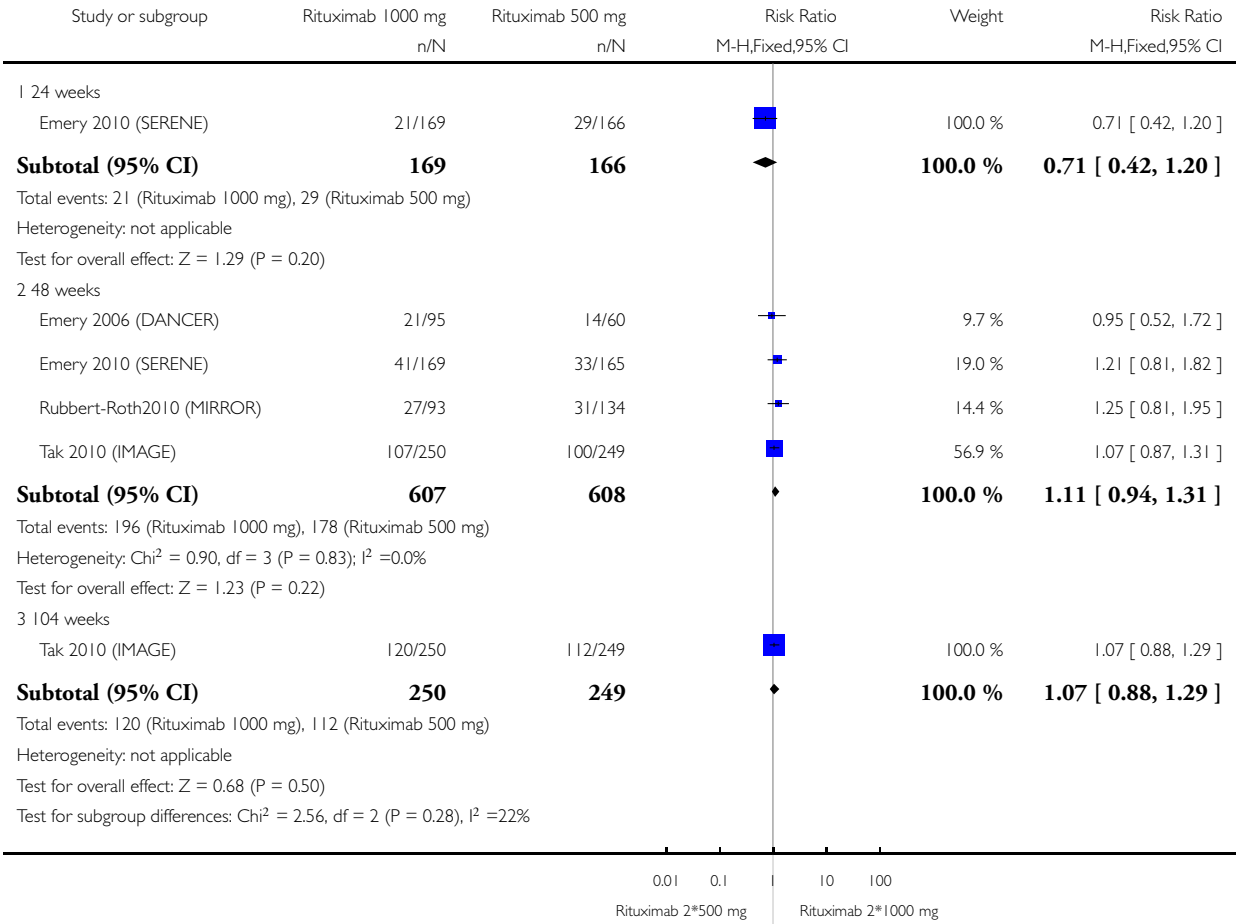
Analysis 19.6. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 6 LDA (DAS28 =or<3.2).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 6 LDA (DAS28 =or<3.2)



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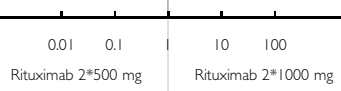
Analysis 19.7. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 7 Clinical Remission (DAS28<2.6).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 7 Clinical Remission (DAS28<2.6)

Study or subgroup	Rituximab 1000 mg n/N	Rituximab 500 mg n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Emery 2010 (SERENE)	16/169	16/166		10.2 %	0.98 [0.51, 1.90]
Subtotal (95% CI)	**169**	**166**		**10.2 %**	**0.98 [0.51, 1.90]**
Total events: 16 (Rituximab 1000 mg), 16 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
2 48-52 weeks					
Emery 2006 (DANCER)	10/95	10/60		7.2 %	0.63 [0.28, 1.43]
Emery 2010 (SERENE)	19/169	15/165		10.7 %	1.24 [0.65, 2.35]
Rubbert-Roth2010 (MIRROR)	18/93	12/134		9.7 %	2.16 [1.09, 4.27]
Tak 2010 (IMAGE)	76/250	63/249		29.5 %	1.20 [0.90, 1.60]
Subtotal (95% CI)	**607**	**608**		**57.1 %**	**1.23 [0.85, 1.78]**
Total events: 123 (Rituximab 1000 mg), 100 (Rituximab 500 mg)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 5.23, df = 3 (P = 0.16); I^2 =43%					
Test for overall effect: Z = 1.09 (P = 0.27)					
3 104 weeks					
Tak 2010 (IMAGE)	80/250	85/249		32.7 %	0.94 [0.73, 1.20]
Subtotal (95% CI)	**250**	**249**		**32.7 %**	**0.94 [0.73, 1.20]**
Total events: 80 (Rituximab 1000 mg), 85 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					
Total (95% CI)	**1026**	**1023**		**100.0 %**	**1.10 [0.87, 1.39]**
Total events: 219 (Rituximab 1000 mg), 201 (Rituximab 500 mg)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 7.69, df = 5 (P = 0.17); I^2 =35%					
Test for overall effect: Z = 0.80 (P = 0.43)					
Test for subgroup differences: Chi^2 = 1.43, df = 2 (P = 0.49), I^2 =0.0%					



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Analysis 19.8. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 8 Moderate or good EULAR response.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 8 Moderate or good EULAR response

Study or subgroup	Rituximab 1000 mg n/N	Rituximab 500 mg n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Emery 2006 (DANCER)	82/122	90/123		41.9 %	0.92 [0.78, 1.08]
Emery 2010 (SERENE)	107/170	111/167		45.1 %	0.95 [0.81, 1.11]
Tak 2010 (IMAGE)	66/250	65/250		13.0 %	1.02 [0.76, 1.36]
Subtotal (95% CI)	**542**	**540**		**100.0 %**	**0.94 [0.85, 1.05]**
Total events: 255 (Rituximab 1000 mg), 266 (Rituximab 500 mg)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.39, df = 2 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 1.08 (P = 0.28)					
2 48-52 weeks					
Emery 2010 (SERENE)	116/170	122/167		35.4 %	0.93 [0.81, 1.07]
Rubbert-Roth2010 (MIRROR)	83/93	98/134		36.8 %	1.22 [1.08, 1.38]
Tak 2010 (IMAGE)	107/250	99/249		27.8 %	1.08 [0.87, 1.33]
Subtotal (95% CI)	**513**	**550**		**100.0 %**	**1.07 [0.90, 1.28]**
Total events: 306 (Rituximab 1000 mg), 319 (Rituximab 500 mg)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 8.24, df = 2 (P = 0.02); I^2 =76%					
Test for overall effect: Z = 0.76 (P = 0.45)					
3 104 weeks					
Tak 2010 (IMAGE)	120/250	110/249		100.0 %	1.09 [0.90, 1.31]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**1.09 [0.90, 1.31]**
Total events: 120 (Rituximab 1000 mg), 110 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					
Test for subgroup differences: Chi^2 = 2.45, df = 2 (P = 0.29), I^2 =19%					

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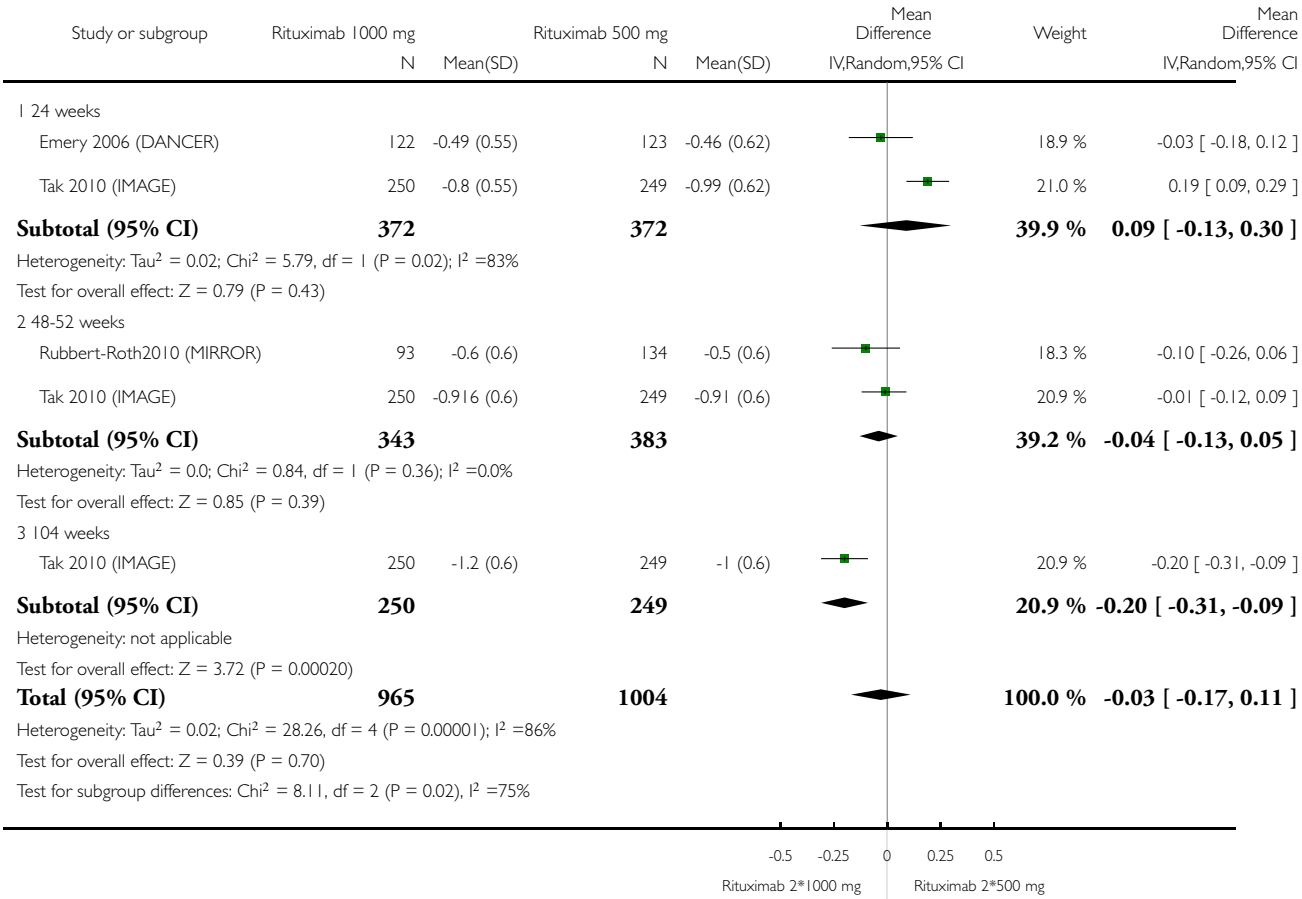
Analysis 19.9. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 9 HAQ-DI.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 9 HAQ-DI



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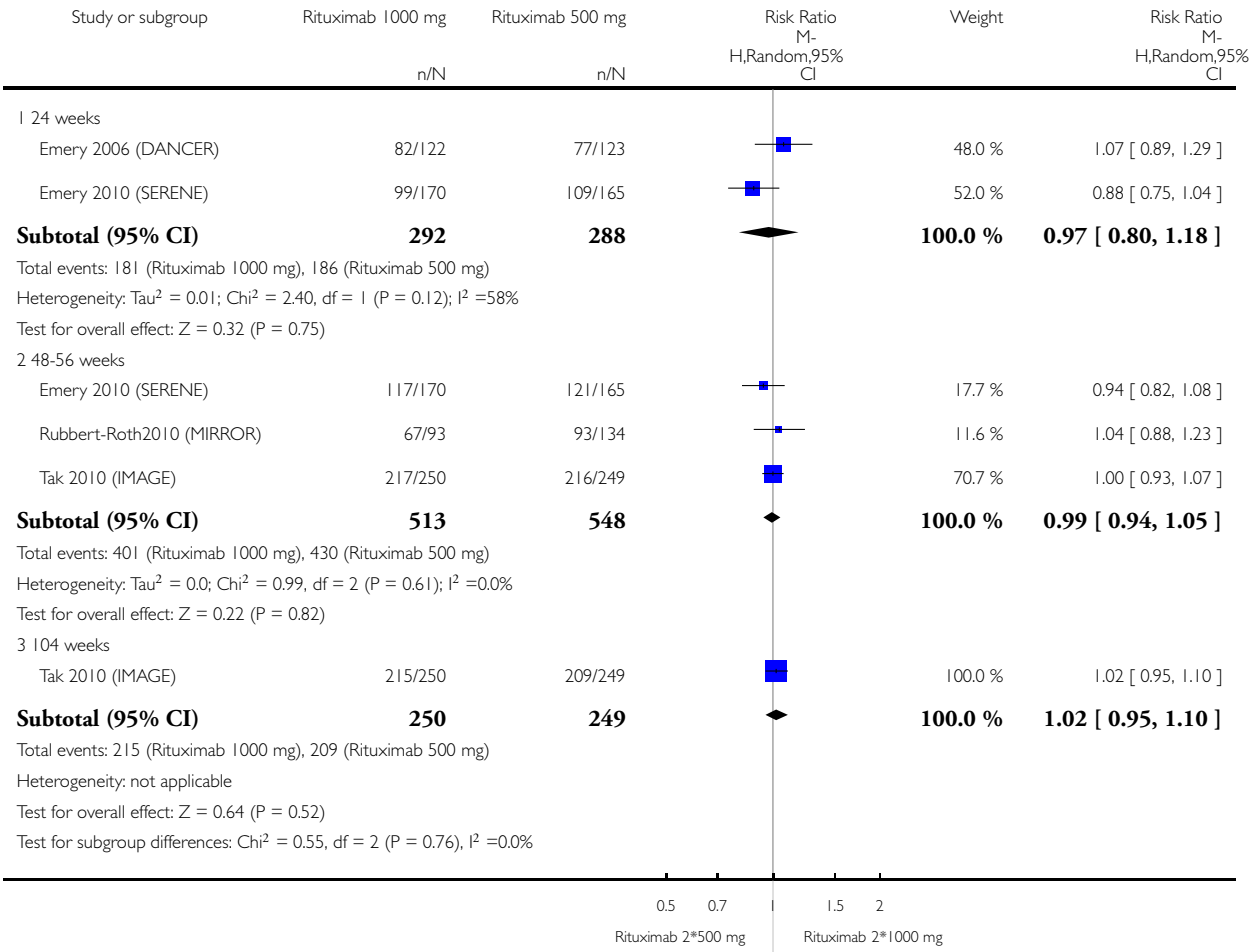
Analysis 19.10. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 10 HAQ-DI MCID=-0.22.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 10 HAQ-DI MCID=-0.22



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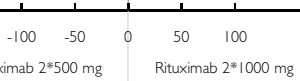
Analysis 19.11. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 11 SF-36 PCS.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 11 SF-36 PCS

Study or subgroup	Rituximab 1000 mg N	Mean(SD)	Rituximab 500 mg N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Emery 2006 (DANCER)	115	7.4 (8.36)	123	7.08 (8.5)		22.3 %	0.32 [-1.82, 2.46]
Emery 2010 (SERENE)	155	5.7 (8.36)	152	5.91 (8.5)		28.7 %	-0.21 [-2.10, 1.68]
Subtotal (95% CI)	**270**		**275**			**51.0 %**	**0.02 [-1.39, 1.44]**
Heterogeneity: Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%							
Test for overall effect: Z = 0.03 (P = 0.98)							
2 48-52 weeks							
Rubbert-Roth2010 (MIRROR)	87	9 (9.7)	121	7.2 (8.5)		15.8 %	1.80 [-0.74, 4.34]
Tak 2010 (IMAGE)	211	10.763 (9.7)	203	10.07 (8.5)		33.2 %	0.69 [-1.07, 2.45]
Subtotal (95% CI)	**298**		**324**			**49.0 %**	**1.05 [-0.39, 2.49]**
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%							
Test for overall effect: Z = 1.42 (P = 0.15)							
Total (95% CI)	**568**		**599**			**100.0 %**	**0.53 [-0.49, 1.54]**
Heterogeneity: Chi^2 = 1.62, df = 3 (P = 0.65); I^2 =0.0%							
Test for overall effect: Z = 1.02 (P = 0.31)							
Test for subgroup differences: Chi^2 = 0.99, df = 1 (P = 0.32), I^2 =0.0%							



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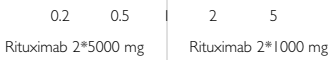
Analysis 19.12. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 12 SF-36 PCS (=or>MCID of 5 or 5.42).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 12 SF-36 PCS (=or>MCID of 5 or 5.42)

Study or subgroup	Rituximab 1000 mg n/N	Rituximab 500 mg n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	64/122	68/123		18.7 %	0.95 [0.75, 1.20]
Emery 2010 (SERENE)	75/170	70/167		19.5 %	1.05 [0.82, 1.35]
Subtotal (95% CI)	**292**	**290**		**38.2 %**	**1.00 [0.85, 1.19]**
Total events: 139 (Rituximab 1000 mg), 138 (Rituximab 500 mg)					
Heterogeneity: Chi^2 = 0.37, df = 1 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.02 (P = 0.98)					
2 48-52 weeks					
Rubbert-Roth2010 (MIRROR)	53/93	69/134		15.6 %	1.11 [0.87, 1.41]
Tak 2010 (IMAGE)	185/242	165/236		46.2 %	1.09 [0.98, 1.22]
Subtotal (95% CI)	**335**	**370**		**61.8 %**	**1.10 [0.99, 1.21]**
Total events: 238 (Rituximab 1000 mg), 234 (Rituximab 500 mg)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 1.78 (P = 0.075)					
Total (95% CI)	**627**	**660**		**100.0 %**	**1.06 [0.97, 1.16]**
Total events: 377 (Rituximab 1000 mg), 372 (Rituximab 500 mg)					
Heterogeneity: Chi^2 = 1.31, df = 3 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 1.28 (P = 0.20)					
Test for subgroup differences: Chi^2 = 0.81, df = 1 (P = 0.37), I^2 =0.0%					



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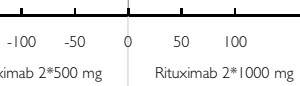
Analysis 19.13. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 13 SF-36 MCS.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 13 SF-36 MCS

Study or subgroup	Rituximab 1000 mg N	Mean(SD)	Rituximab 500 mg N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Emery 2006 (DANCER)	115	-3.03 (11.9)	123	-4.49 (13.5)		18.8 %	1.46 [-1.77, 4.69]
Emery 2010 (SERENE)	155	-4.58 (11.9)	152	-3.31 (13.5)		24.2 %	-1.27 [-4.12, 1.58]
Subtotal (95% CI)	**270**		**275**			**43.0 %**	**-0.07 [-2.21, 2.06]**
Heterogeneity: Chi^2 = 1.54, df = 1 (P = 0.21); I^2 =35%							
Test for overall effect: Z = 0.07 (P = 0.95)							
2 48-52 weeks							
Rubbert-Roth2010 (MIRROR)	87	4.7 (11.1)	121	5.6 (12.4)		19.0 %	-0.90 [-4.11, 2.31]
Tak 2010 (IMAGE)	211	6.662 (11.1)	203	6.18 (12.4)		38.0 %	0.48 [-1.79, 2.75]
Subtotal (95% CI)	**298**		**324**			**57.0 %**	**0.02 [-1.83, 1.88]**
Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%							
Test for overall effect: Z = 0.02 (P = 0.98)							
Total (95% CI)	**568**		**599**			**100.0 %**	**-0.02 [-1.42, 1.38]**
Heterogeneity: Chi^2 = 2.02, df = 3 (P = 0.57); I^2 =0.0%							
Test for overall effect: Z = 0.03 (P = 0.98)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%							



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Analysis 19.14. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 14 SF-36 MCS (=or>MCID of 6.33).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 14 SF-36 MCS (=or>MCID of 6.33)

Study or subgroup	Rituximab 1000 mg n/N	Rituximab 500 mg n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 48-52 weeks					
Rubbert-Roth2010 (MIRROR)	37/93	58/134		28.1 %	0.92 [0.67, 1.26]
Tak 2010 (IMAGE)	138/242	120/236		71.9 %	1.12 [0.95, 1.32]
Subtotal (95% CI)	**335**	**370**		**100.0 %**	**1.06 [0.92, 1.23]**
Total events: 175 (Rituximab 1000 mg), 178 (Rituximab 500 mg)					
Heterogeneity: Chi^2 = 1.20, df = 1 (P = 0.27); I^2 =17%					
Test for overall effect: Z = 0.83 (P = 0.41)					
Test for subgroup differences: Not applicable					

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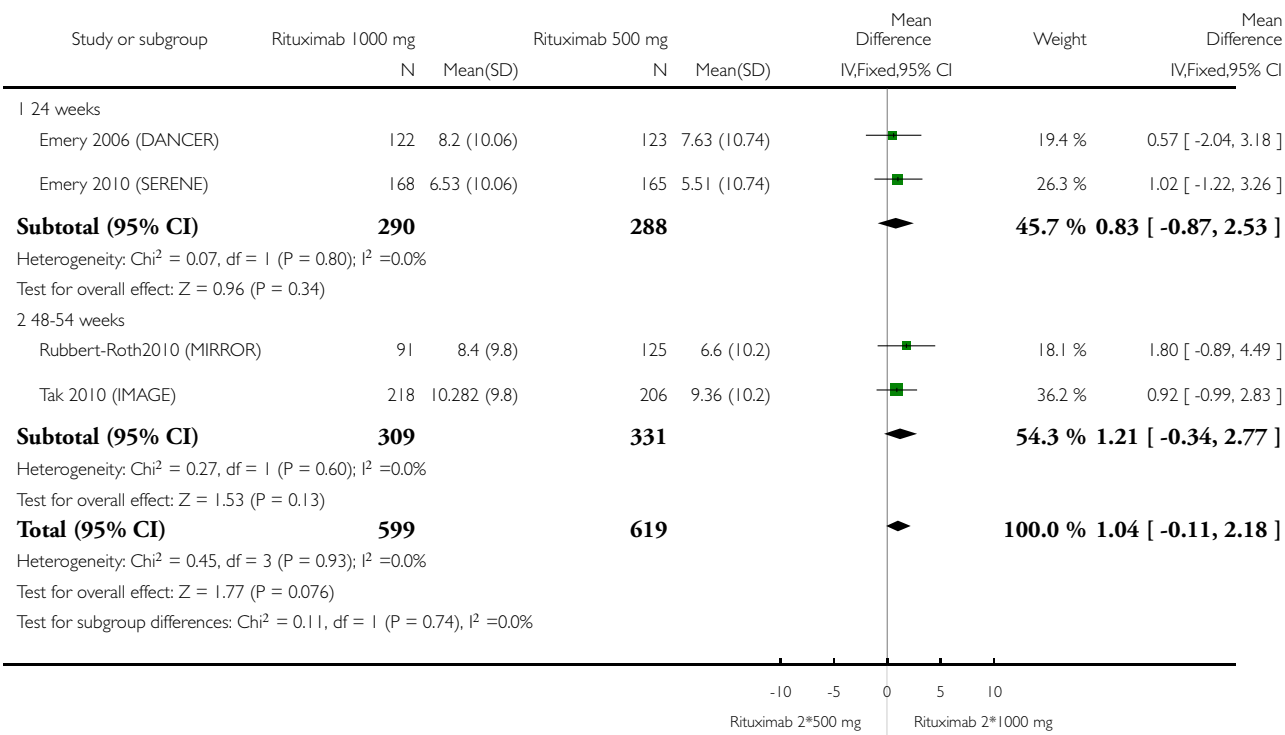
Analysis 19.15. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 15 FACIT-F.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 15 FACIT-F



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Analysis 19.16. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 16 FACIT-F (=or>MCID of 3.5).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 16 FACIT-F (=or>MCID of 3.5)

Study or subgroup	Rituximab 1000 mg n/N	Rituximab 500 mg n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	80/122	68/123		52.7 %	1.19 [0.97, 1.46]
Subtotal (95% CI)	**122**	**123**		**52.7 %**	**1.19 [0.97, 1.46]**
Total events: 80 (Rituximab 1000 mg), 68 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					
2 48 weeks					
Rubbert-Roth2010 (MIRROR)	63/91	72/125		47.3 %	1.20 [0.98, 1.47]
Subtotal (95% CI)	**91**	**125**		**47.3 %**	**1.20 [0.98, 1.47]**
Total events: 63 (Rituximab 1000 mg), 72 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.076)					
Total (95% CI)	**213**	**248**		**100.0 %**	**1.19 [1.03, 1.38]**
Total events: 143 (Rituximab 1000 mg), 140 (Rituximab 500 mg)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 2.40 (P = 0.016)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.93), I^2 =0.0%					

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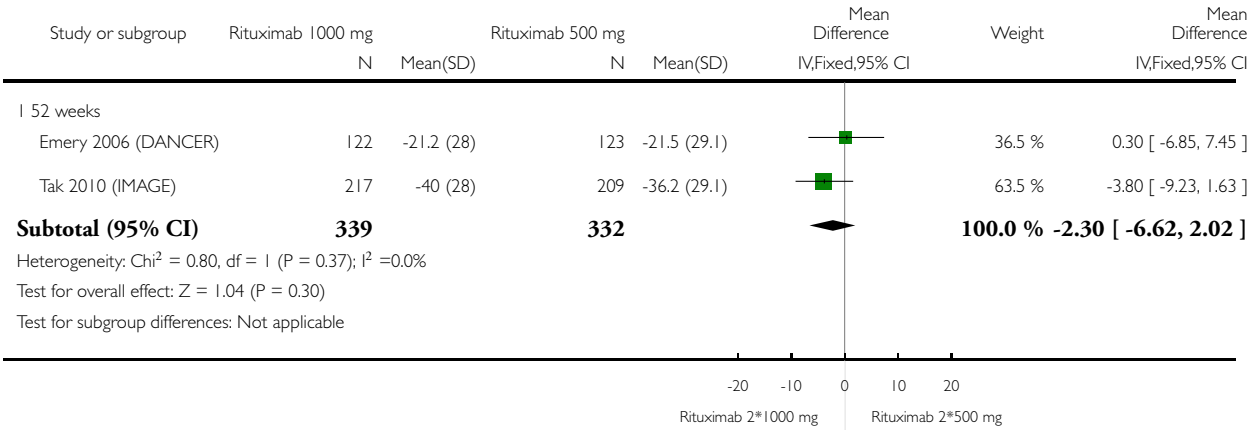
Analysis 19.17. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 17 VAS Pain.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 17 VAS Pain



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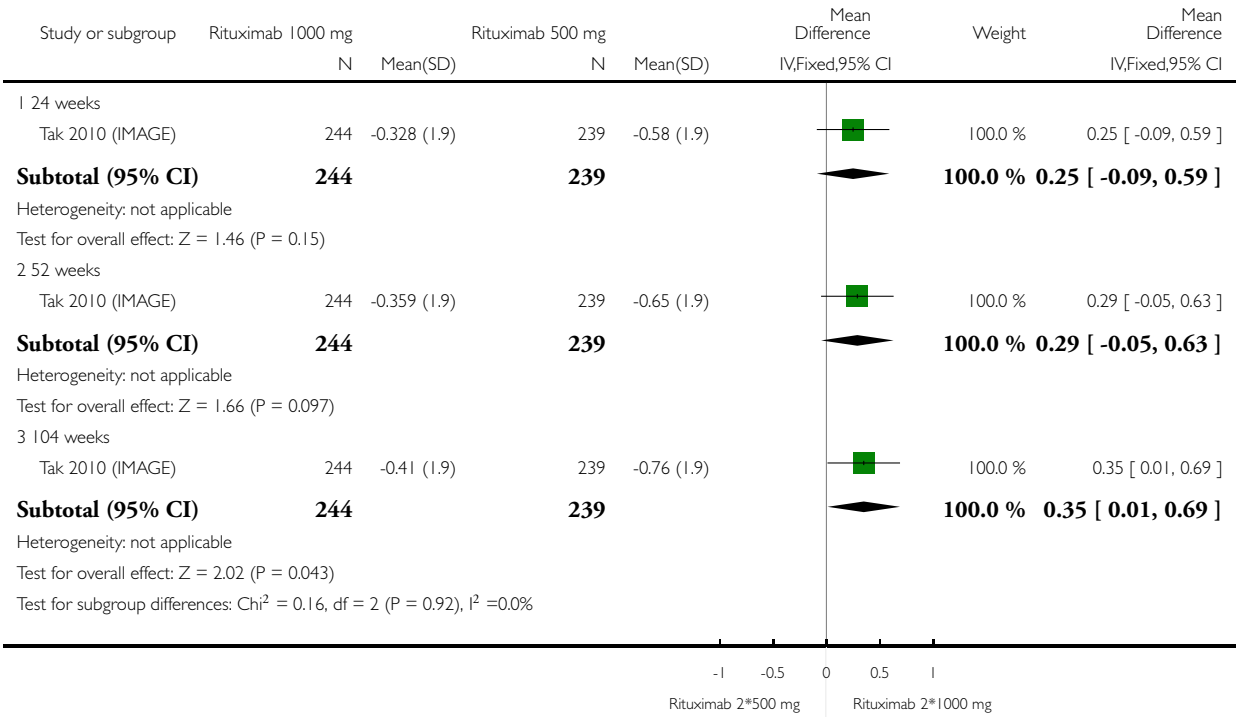
Analysis 19.18. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 18 Total radiographic score.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 18 Total radiographic score

Study or subgroup	Rituximab 1000 mg N	Mean(SD)	Rituximab 500 mg N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Tak 2010 (IMAGE)	244	-0.328 (1.9)	239	-0.58 (1.9)		100.0 %	0.25 [-0.09, 0.59]
Subtotal (95% CI)	**244**		**239**			**100.0 %**	**0.25 [-0.09, 0.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.46 (P = 0.15)							
2 52 weeks							
Tak 2010 (IMAGE)	244	-0.359 (1.9)	239	-0.65 (1.9)		100.0 %	0.29 [-0.05, 0.63]
Subtotal (95% CI)	**244**		**239**			**100.0 %**	**0.29 [-0.05, 0.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.66 (P = 0.097)							
3 104 weeks							
Tak 2010 (IMAGE)	244	-0.41 (1.9)	239	-0.76 (1.9)		100.0 %	0.35 [0.01, 0.69]
Subtotal (95% CI)	**244**		**239**			**100.0 %**	**0.35 [0.01, 0.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.02 (P = 0.043)							
Test for subgroup differences: Chi^2 = 0.16, df = 2 (P = 0.92), I^2 =0.0%							



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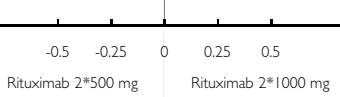
Analysis 19.19. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 19 Joint space narrowing.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 19 Joint space narrowing

Study or subgroup	Rituximab 1000 mg N	Mean(SD)	Rituximab 500 mg N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Tak 2010 (IMAGE)	242	-0.11 (0.8)	238	-0.18 (0.8)		100.0 %	0.07 [-0.07, 0.21]
Subtotal (95% CI)	**242**		**238**			**100.0 %**	**0.07 [-0.07, 0.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
2 104 weeks							
Tak 2010 (IMAGE)	244	-0.18 (0.8)	239	-0.26 (0.8)		100.0 %	0.08 [-0.06, 0.22]
Subtotal (95% CI)	**244**		**239**			**100.0 %**	**0.08 [-0.06, 0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.10 (P = 0.27)							
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 =0.0%							



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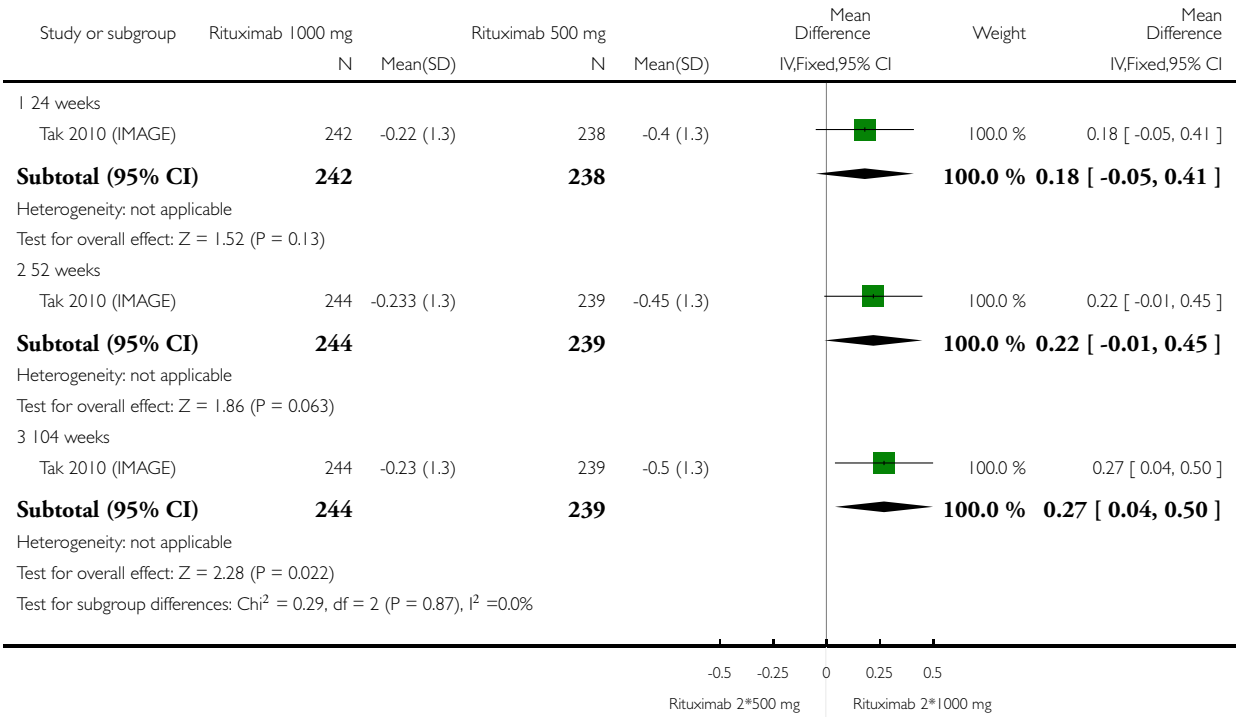
Analysis 19.20. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 20 Radiographic erosions.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 20 Radiographic erosions

Study or subgroup	Rituximab 1000 mg N	Mean(SD)	Rituximab 500 mg N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Tak 2010 (IMAGE)	242	-0.22 (1.3)	238	-0.4 (1.3)		100.0 %	0.18 [-0.05, 0.41]
Subtotal (95% CI)	**242**		**238**			**100.0 %**	**0.18 [-0.05, 0.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.52 (P = 0.13)							
2 52 weeks							
Tak 2010 (IMAGE)	244	-0.233 (1.3)	239	-0.45 (1.3)		100.0 %	0.22 [-0.01, 0.45]
Subtotal (95% CI)	**244**		**239**			**100.0 %**	**0.22 [-0.01, 0.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.86 (P = 0.063)							
3 104 weeks							
Tak 2010 (IMAGE)	244	-0.23 (1.3)	239	-0.5 (1.3)		100.0 %	0.27 [0.04, 0.50]
Subtotal (95% CI)	**244**		**239**			**100.0 %**	**0.27 [0.04, 0.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.28 (P = 0.022)							
Test for subgroup differences: Chi^2 = 0.29, df = 2 (P = 0.87), I^2 =0.0%							



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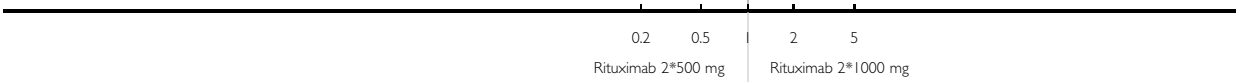
Analysis 19.21. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 21 No radiographic progression.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 21 No radiographic progression

Study or subgroup	Rituximab 1000 mg n/N	Rituximab 500 mg n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Tak 2010 (IMAGE)	170/244	151/239		100.0 %	1.10 [0.97, 1.25]
Subtotal (95% CI)	**244**	**239**		**100.0 %**	**1.10 [0.97, 1.25]**
Total events: 170 (Rituximab 1000 mg), 151 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.51 (P = 0.13)					
2 52 weeks					
Tak 2010 (IMAGE)	156/244	139/239		100.0 %	1.10 [0.95, 1.27]
Subtotal (95% CI)	**244**	**239**		**100.0 %**	**1.10 [0.95, 1.27]**
Total events: 156 (Rituximab 1000 mg), 139 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
3 104 weeks					
Tak 2010 (IMAGE)	139/244	117/239		100.0 %	1.16 [0.98, 1.38]
Subtotal (95% CI)	**244**	**239**		**100.0 %**	**1.16 [0.98, 1.38]**
Total events: 139 (Rituximab 1000 mg), 117 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.76 (P = 0.079)					
Test for subgroup differences: Chi^2 = 0.31, df = 2 (P = 0.86), I^2 =0.0%					



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Analysis 19.22. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 22 No worsening of erosions.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 22 No worsening of erosions

Study or subgroup	Rituximab 1000 mg n/N	Rituximab 500 mg n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 104 weeks					
Tak 2010 (IMAGE)	144/244	127/239		100.0 %	1.11 [0.95, 1.30]
Subtotal (95% CI)	**244**	**239**		**100.0 %**	**1.11 [0.95, 1.30]**
Total events: 144 (Rituximab 1000 mg), 127 (Rituximab 500 mg)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
Test for subgroup differences: Not applicable					

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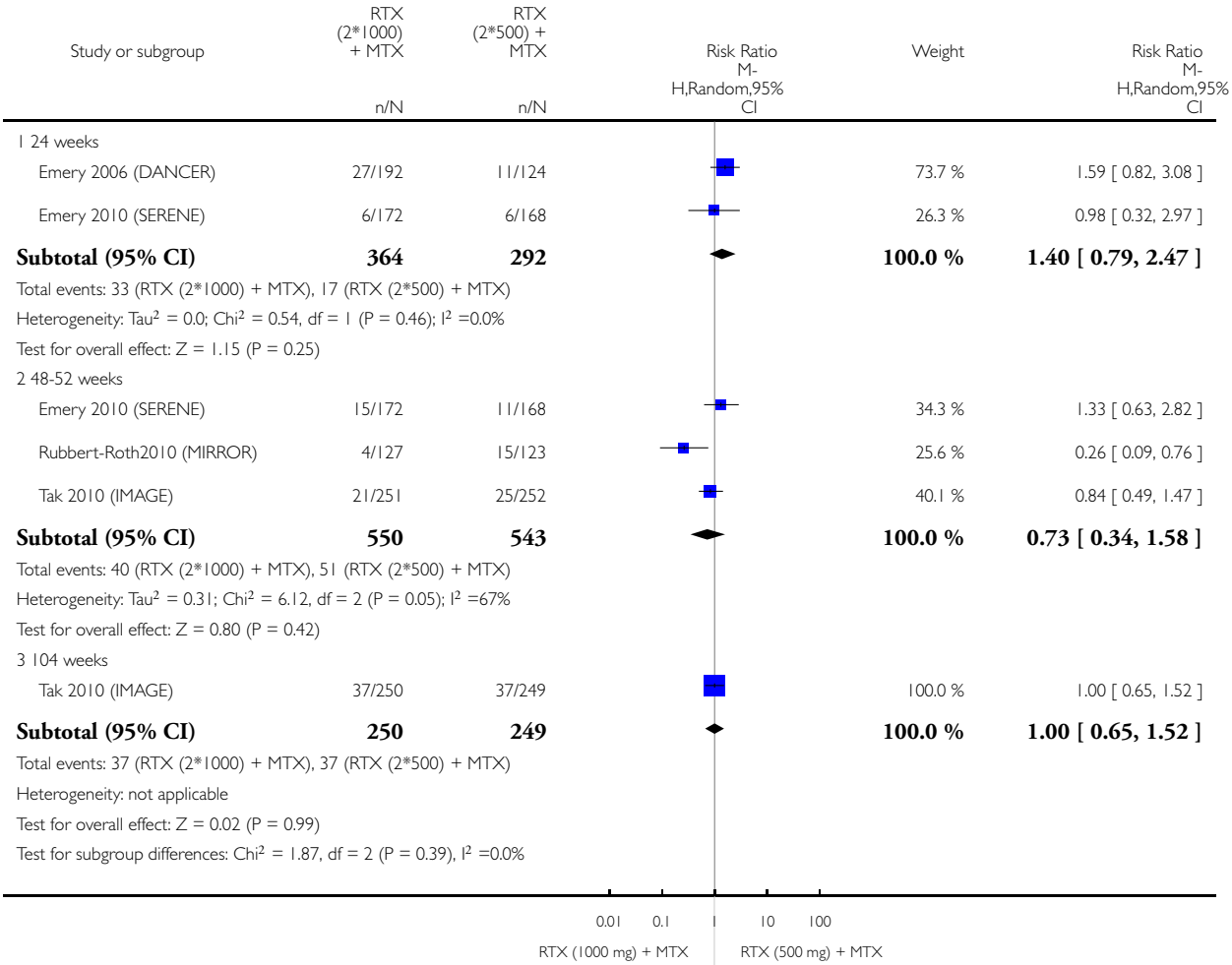
Analysis 19.23. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 23 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 23 Total discontinuations



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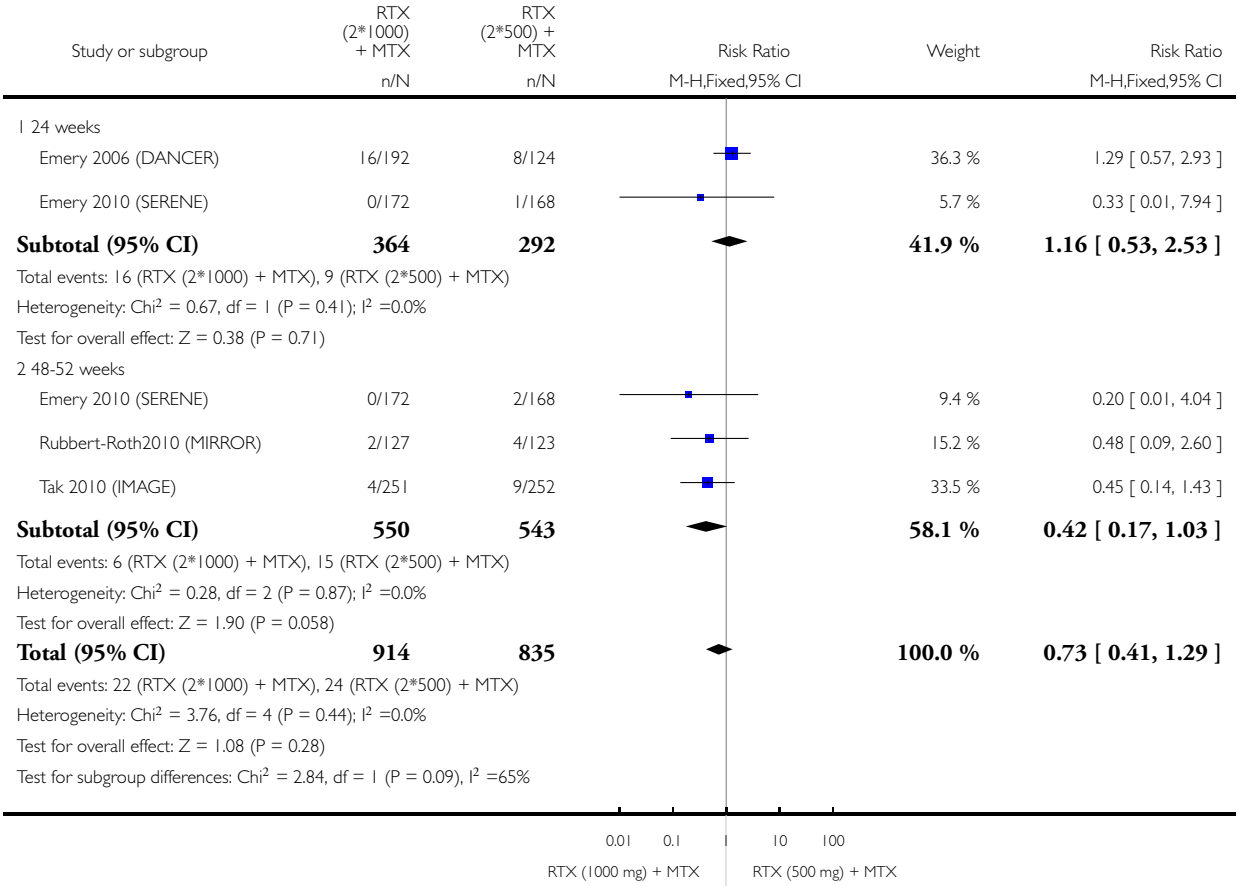
Analysis 19.24. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 24 Discontinuation due to lack of efficacy.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 24 Discontinuation due to lack of efficacy



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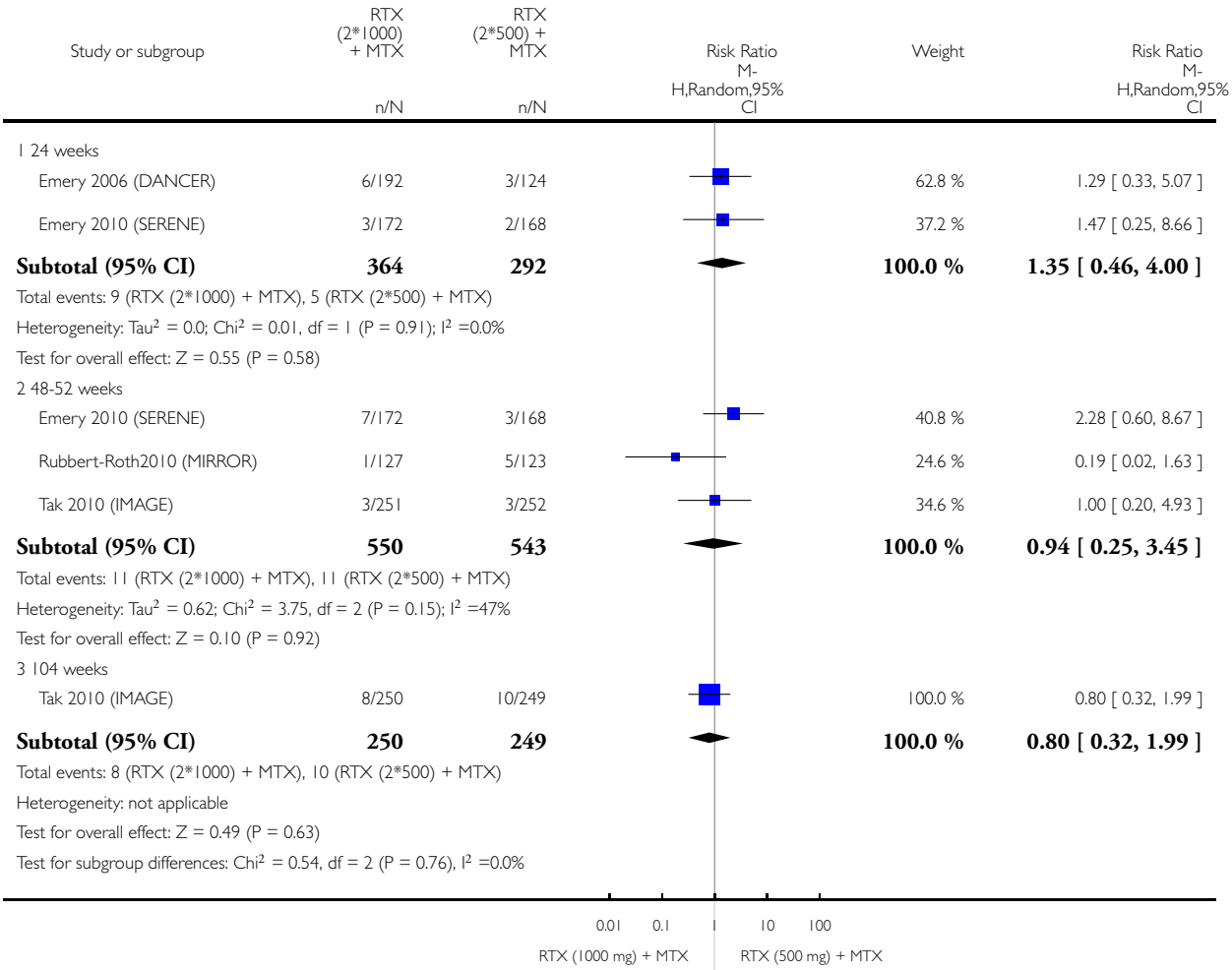
Analysis 19.25. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 25 Discontinuations due to adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 25 Discontinuations due to adverse Events



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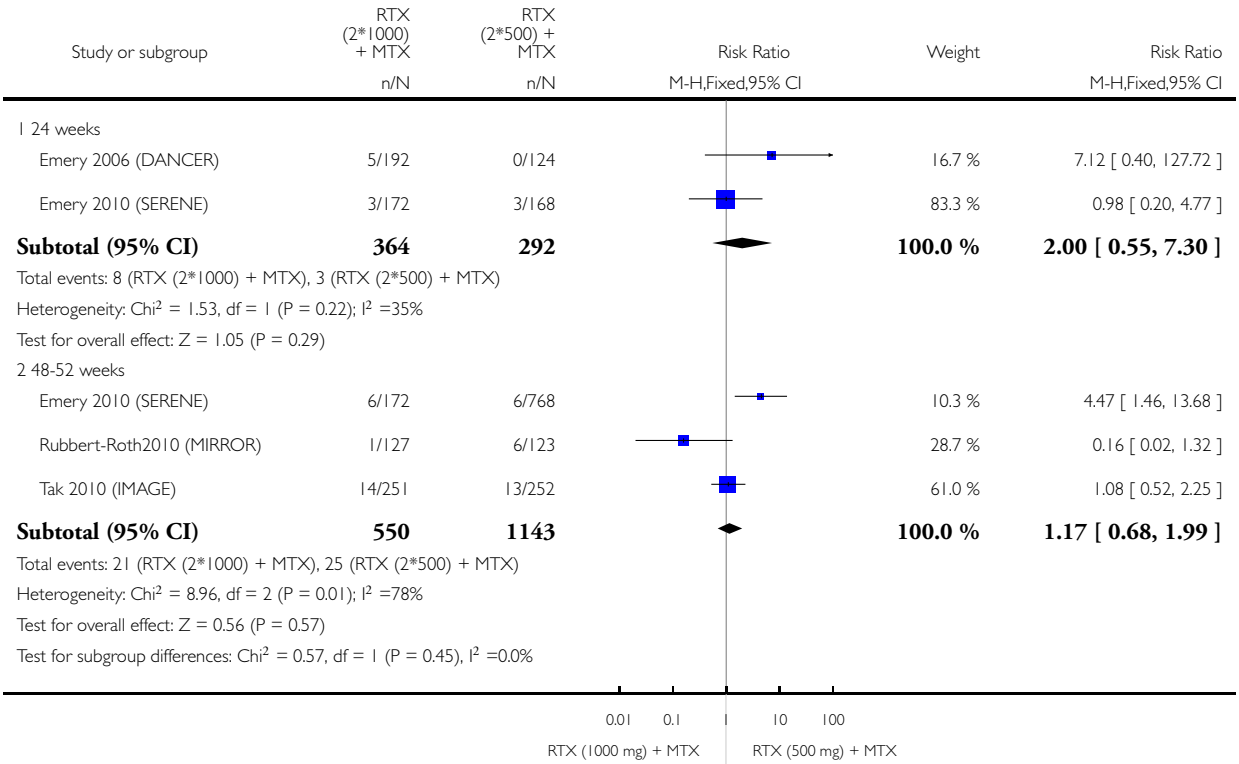
Analysis 19.26. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 26 Discontinuations due to other reasons.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 26 Discontinuations due to other reasons



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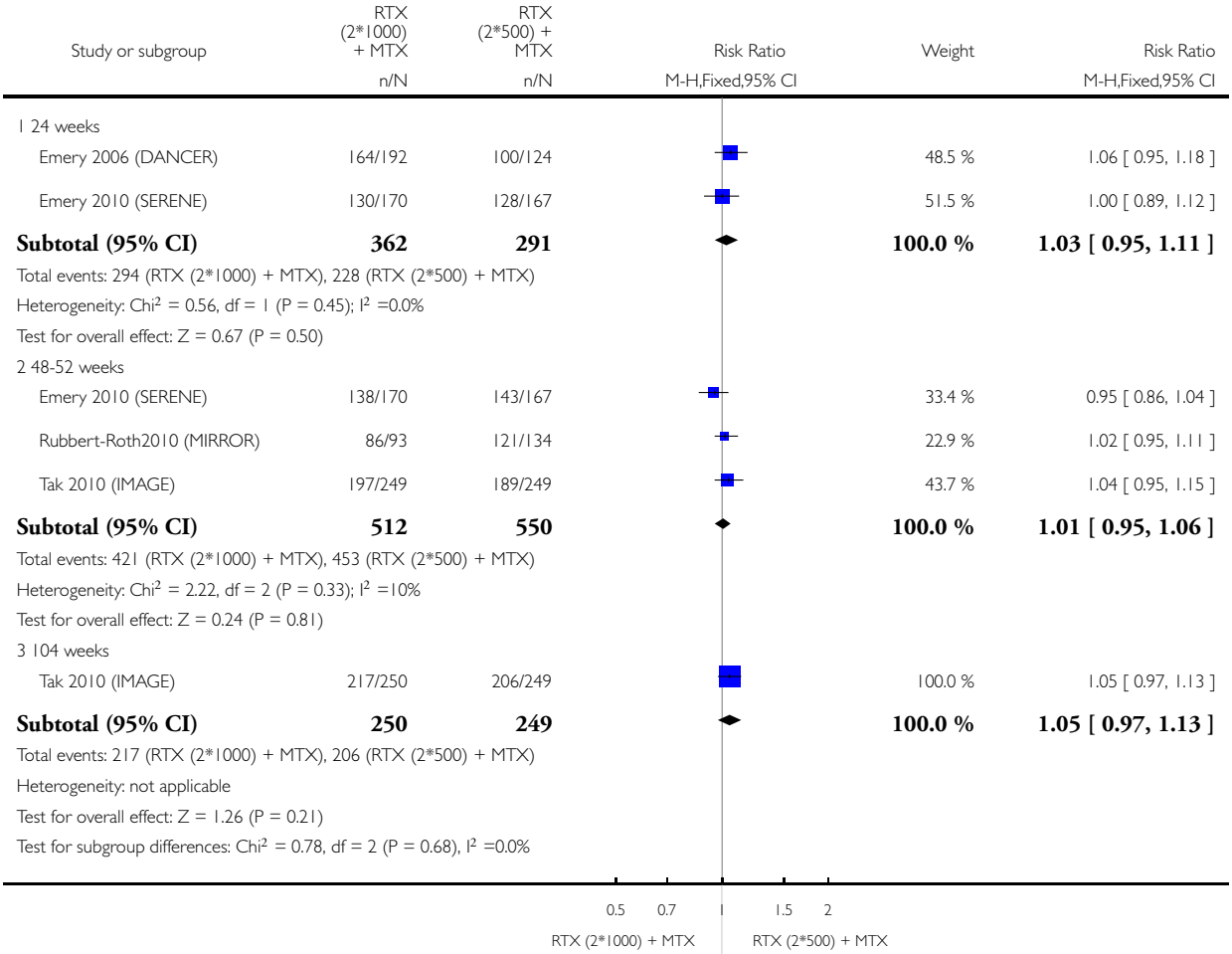
Analysis 19.27. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 27 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 27 Any Adverse Event



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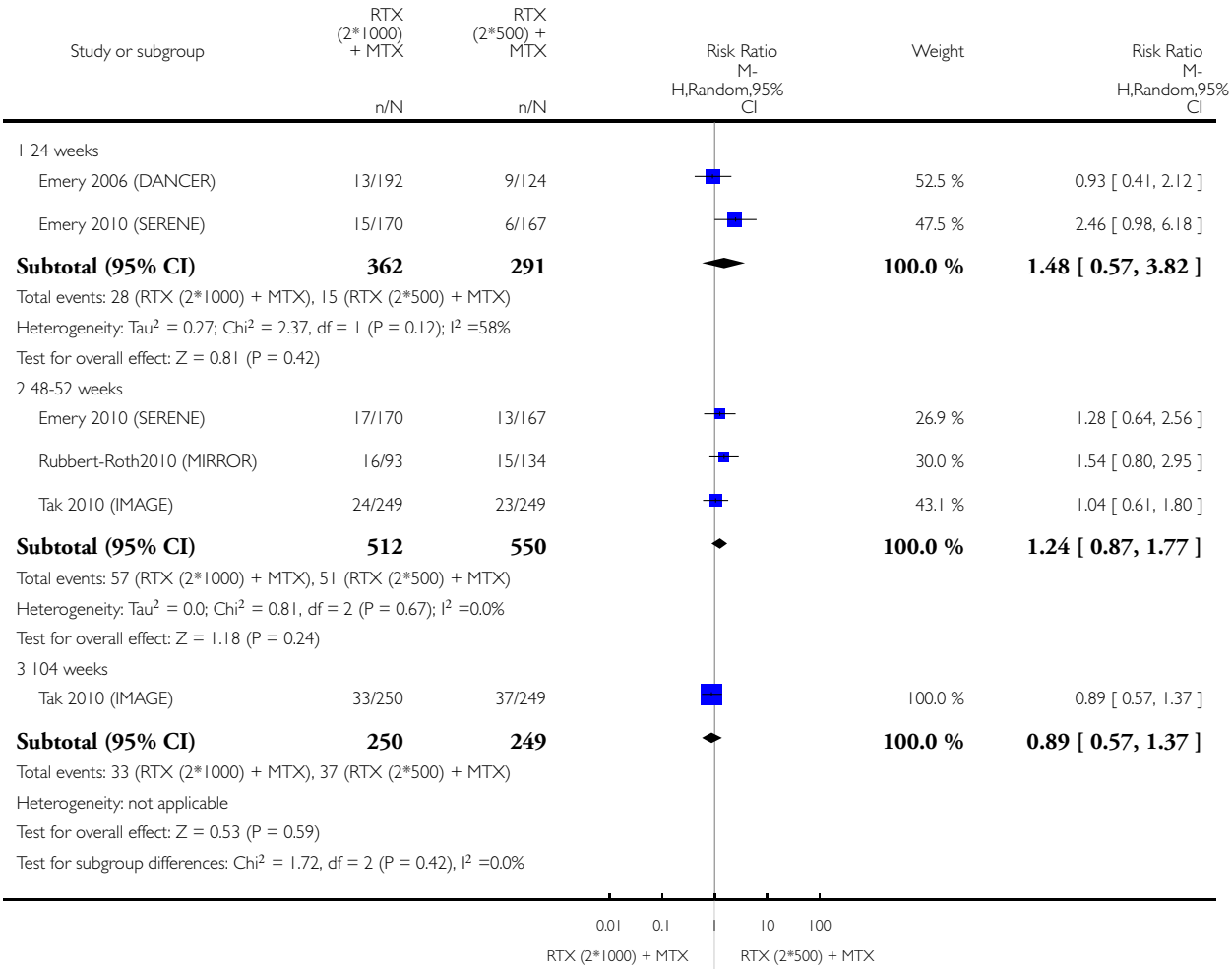
Analysis 19.28. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 28 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 28 Serious Adverse Events



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Analysis 19.29. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 29 Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 29 Infections

Study or subgroup	RTX (2*1000) + MTX n/N	RTX (2*500) + MTX n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Emery 2006 (DANCER)	67/192	43/124		43.3 %	1.01 [0.74, 1.37]
Emery 2010 (SERENE)	61/170	69/167		56.7 %	0.87 [0.66, 1.14]
Subtotal (95% CI)	**362**	**291**		**100.0 %**	**0.93 [0.76, 1.13]**
Total events: 128 (RTX (2*1000) + MTX), 112 (RTX (2*500) + MTX)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.49, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 48-52 weeks					
Emery 2010 (SERENE)	85/170	96/167		32.3 %	0.87 [0.71, 1.06]
Rubbert-Roth2010 (MIRROR)	60/93	75/134		29.9 %	1.15 [0.93, 1.43]
Tak 2010 (IMAGE)	129/249	127/249		37.9 %	1.02 [0.86, 1.20]
Subtotal (95% CI)	**512**	**550**		**100.0 %**	**1.00 [0.86, 1.17]**
Total events: 274 (RTX (2*1000) + MTX), 298 (RTX (2*500) + MTX)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 3.64, df = 2 (P = 0.16); I^2 =45%					
Test for overall effect: Z = 0.04 (P = 0.97)					
3 104 weeks					
Tak 2010 (IMAGE)	160/250	162/249		100.0 %	0.98 [0.86, 1.12]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**0.98 [0.86, 1.12]**
Total events: 160 (RTX (2*1000) + MTX), 162 (RTX (2*500) + MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
Test for subgroup differences: Chi^2 = 0.40, df = 2 (P = 0.82), I^2 =0.0%					

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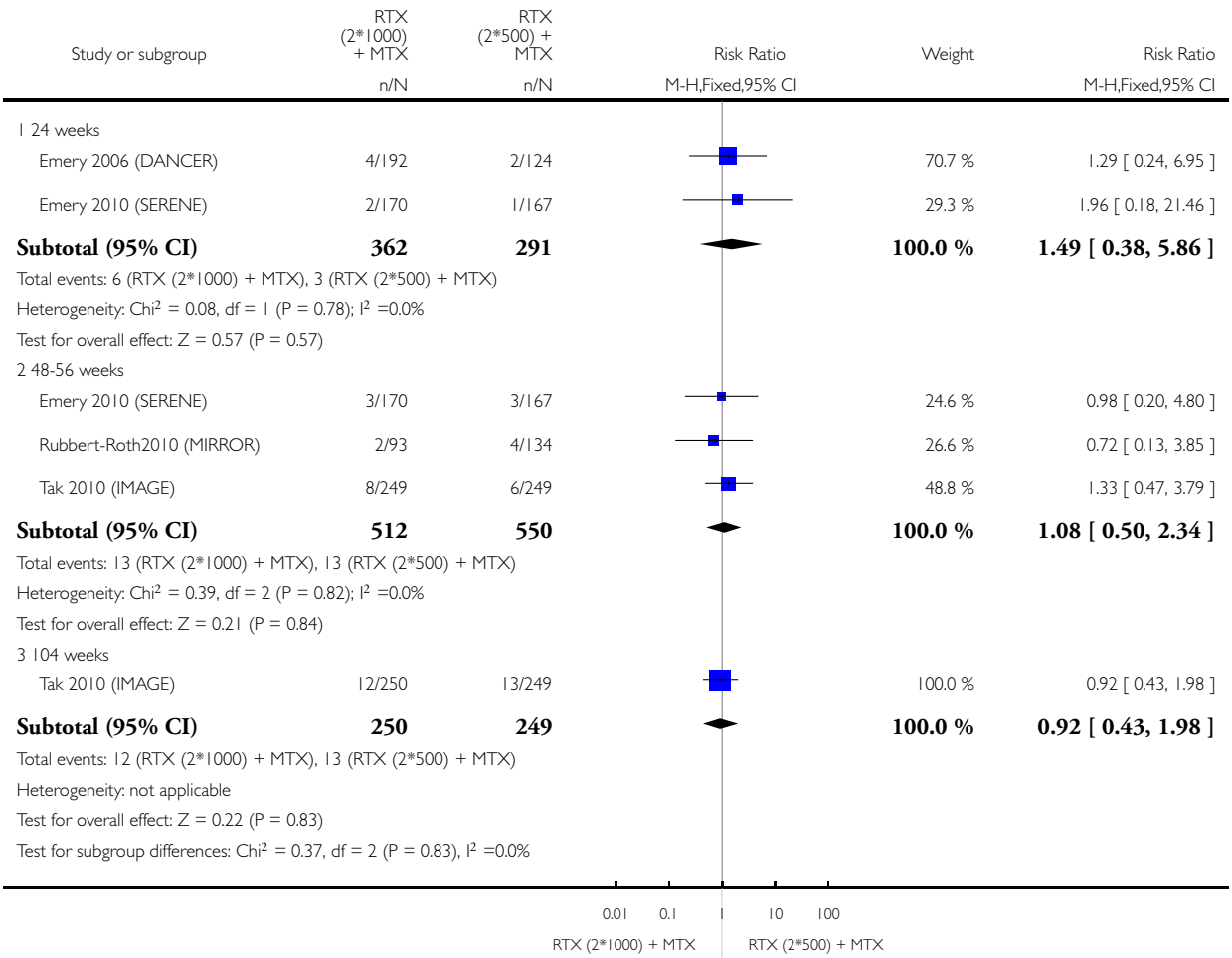
Analysis 19.30. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 30 Serious Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 30 Serious Infections



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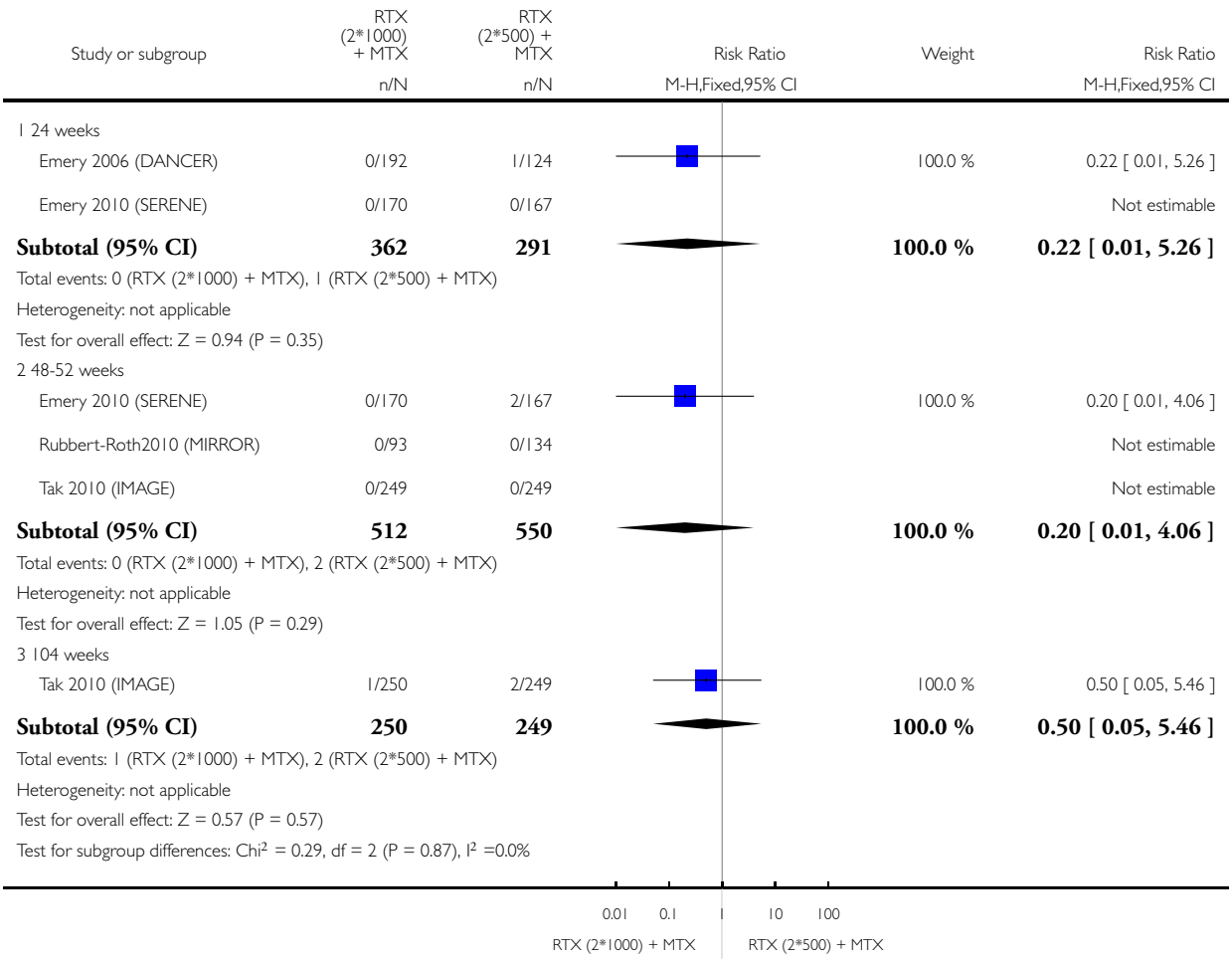
Analysis 19.31. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 31 Death.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 31 Death



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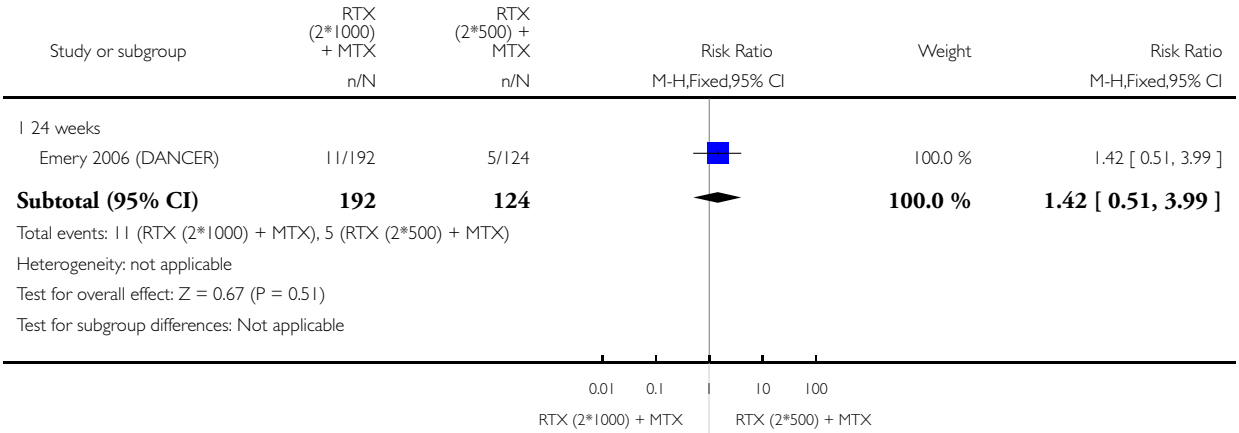
Analysis 19.32. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 32 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 32 Arthralgia



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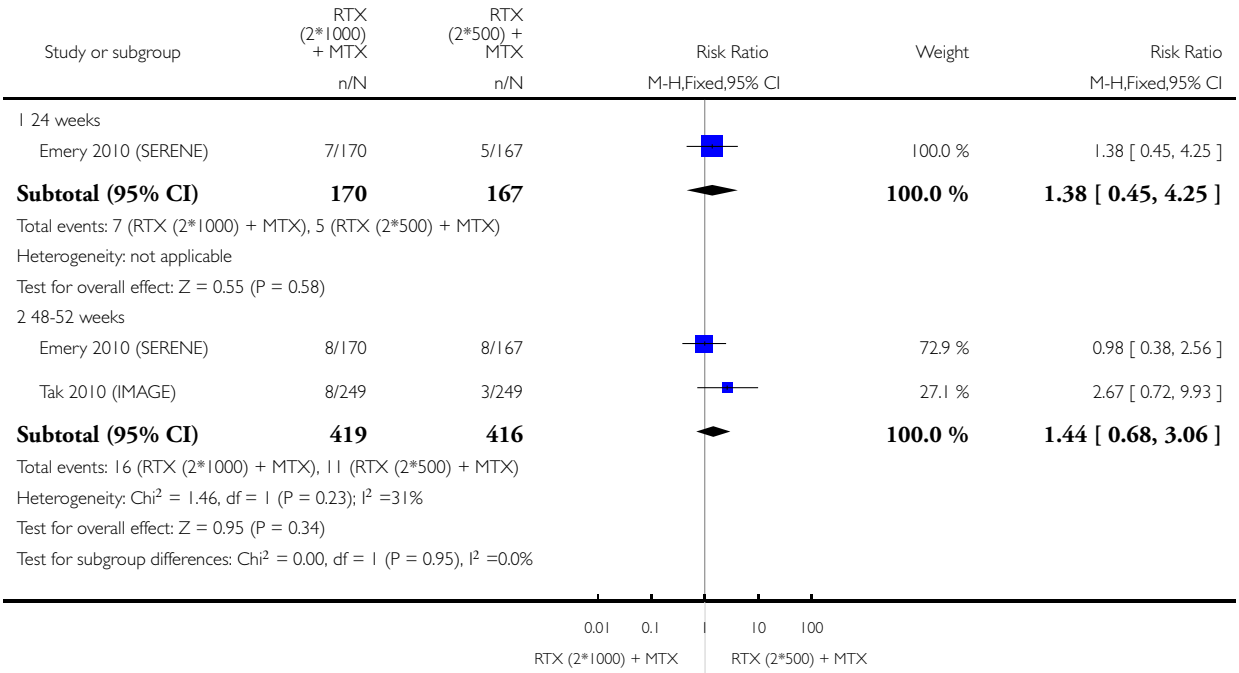
Analysis 19.33. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 33 Cardiac event (any).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 33 Cardiac event (any)



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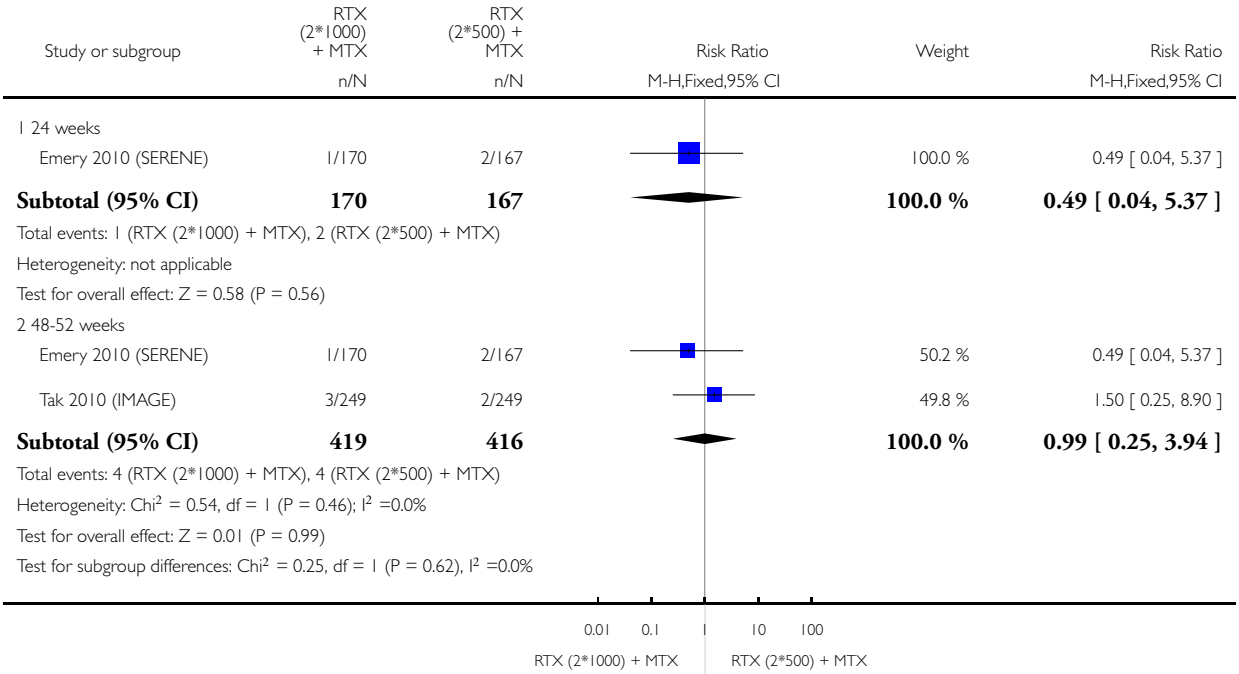
Analysis 19.34. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 34 Cardiac event (Serious).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 34 Cardiac event (Serious)



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Analysis 19.35. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 35 Diarrhea.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 35 Diarrhea

Study or subgroup	RTX (2*1000) + MTX n/N	RTX (2*500) + MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	6/192	7/124		100.0 %	0.55 [0.19, 1.61]
Subtotal (95% CI)	**192**	**124**		**100.0 %**	**0.55 [0.19, 1.61]**
Total events: 6 (RTX (2*1000) + MTX), 7 (RTX (2*500) + MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.28)					
Test for subgroup differences: Not applicable					

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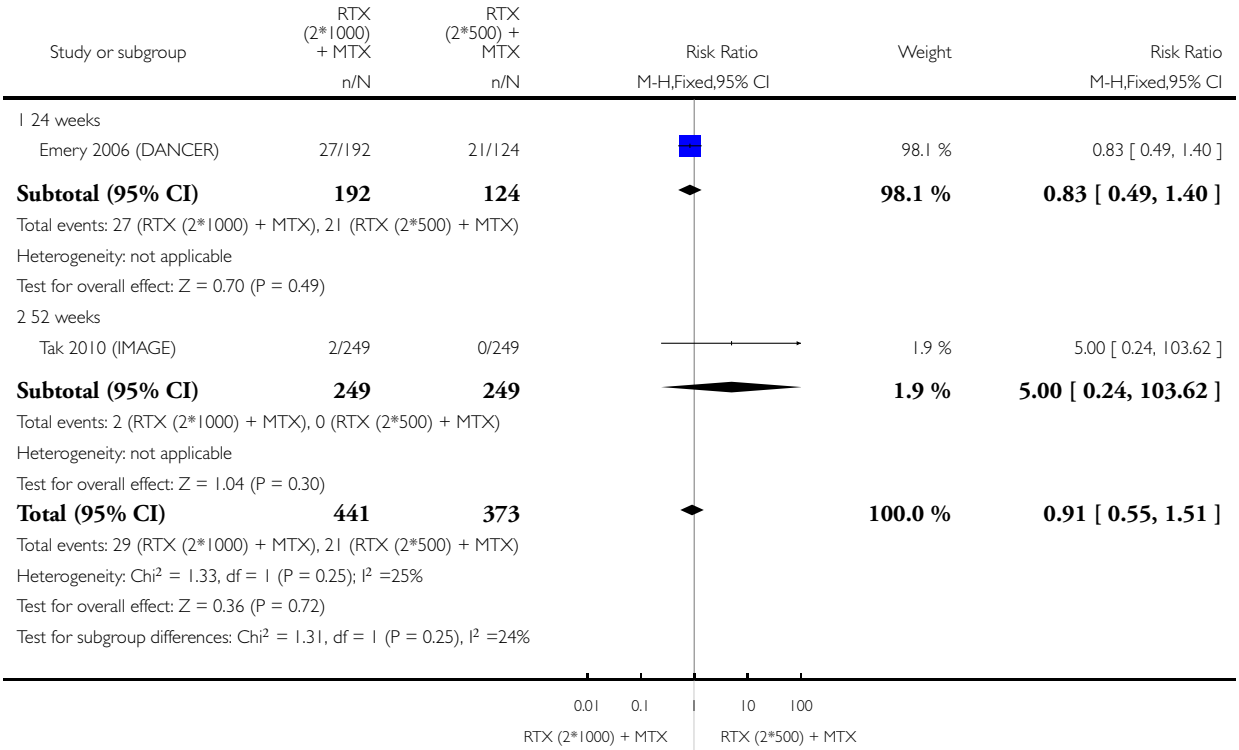
Analysis 19.36. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 36 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 36 Exacerbation of RA



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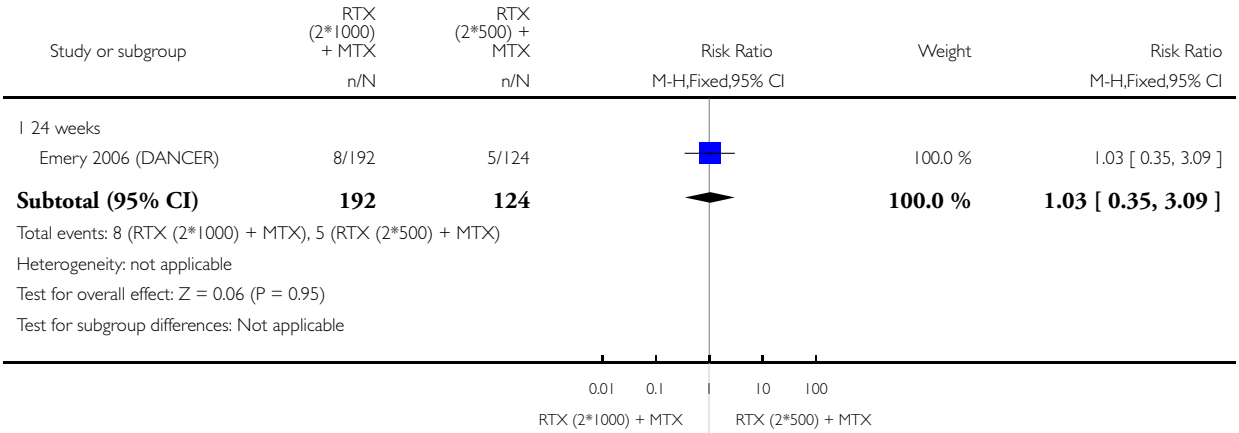
Analysis 19.37. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 37 Fatigue.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 37 Fatigue



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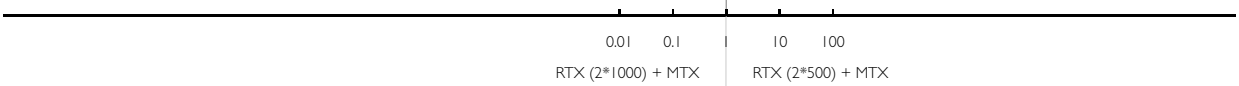
Analysis 19.38. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 38 HACA.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 38 HACA

Study or subgroup	RTX (2*1000) + MTX n/N	RTX (2*500) + MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Emery 2006 (DANCER)	5/192	5/124		51.4 %	0.65 [0.19, 2.19]
Rubbert-Roth2010 (MIRROR)	2/93	7/134		48.6 %	0.41 [0.09, 1.94]
Subtotal (95% CI)	**285**	**258**		**100.0 %**	**0.53 [0.20, 1.38]**
Total events: 7 (RTX (2*1000) + MTX), 12 (RTX (2*500) + MTX)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 1.29 (P = 0.20)					
Test for subgroup differences: Not applicable					



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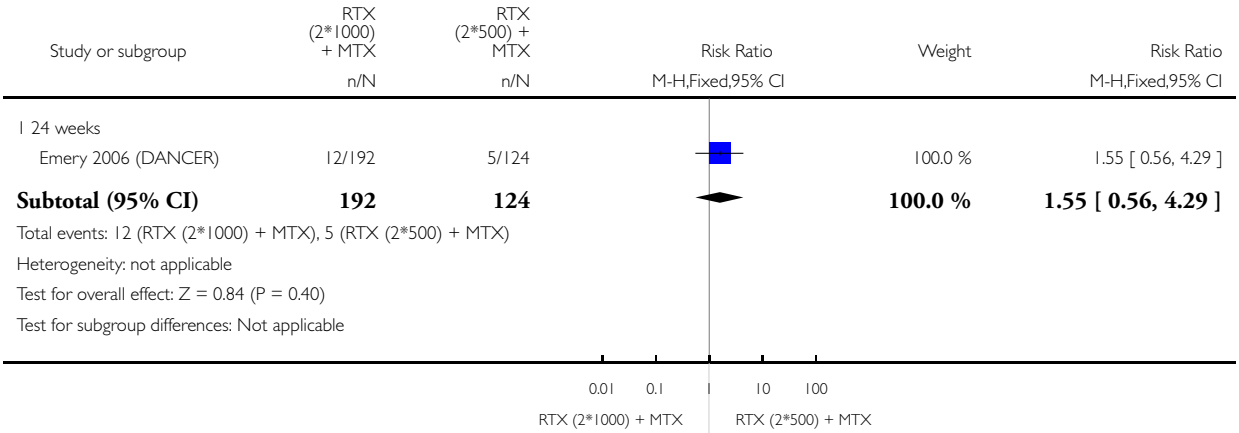
Analysis 19.39. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 39 Hypertension.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 39 Hypertension



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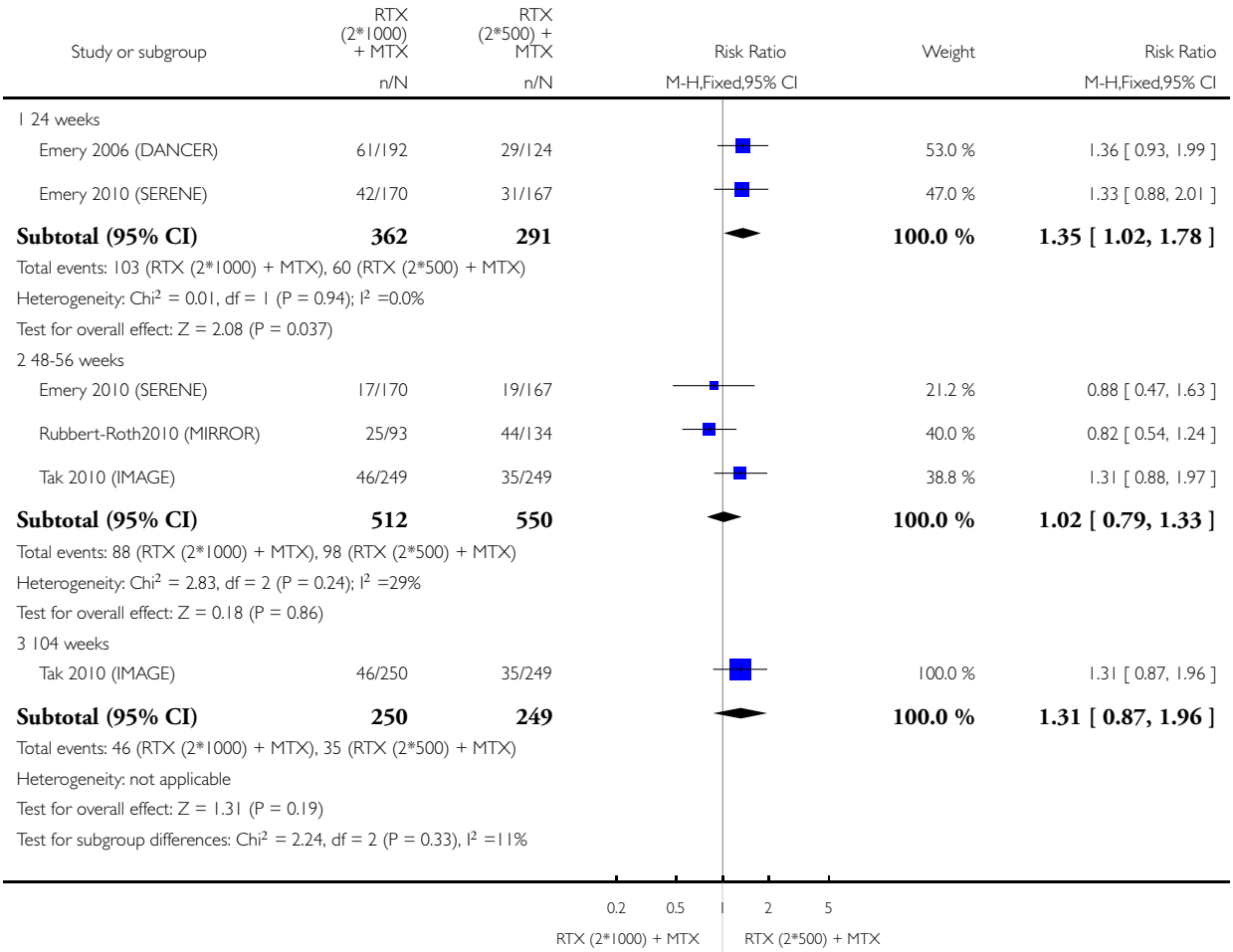
Analysis 19.40. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 40 Infusion-related reactions (1st course -1st infusion).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 40 Infusion-related reactions (1st course -1st infusion)



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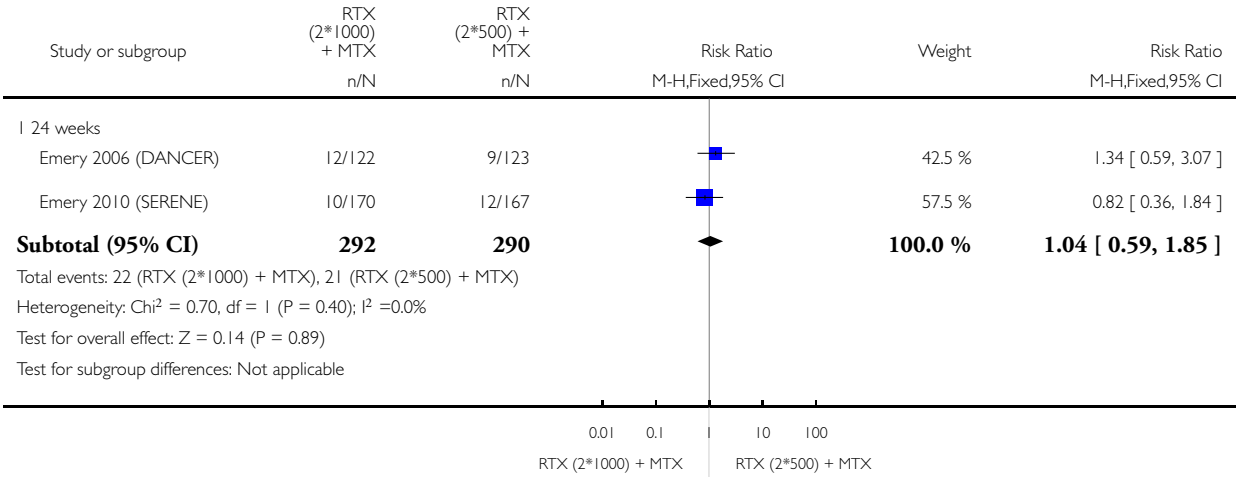
Analysis 19.41. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 41 Infusion-related reaction (1st course -2nd infusion).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 41 Infusion-related reaction (1st course -2nd infusion)



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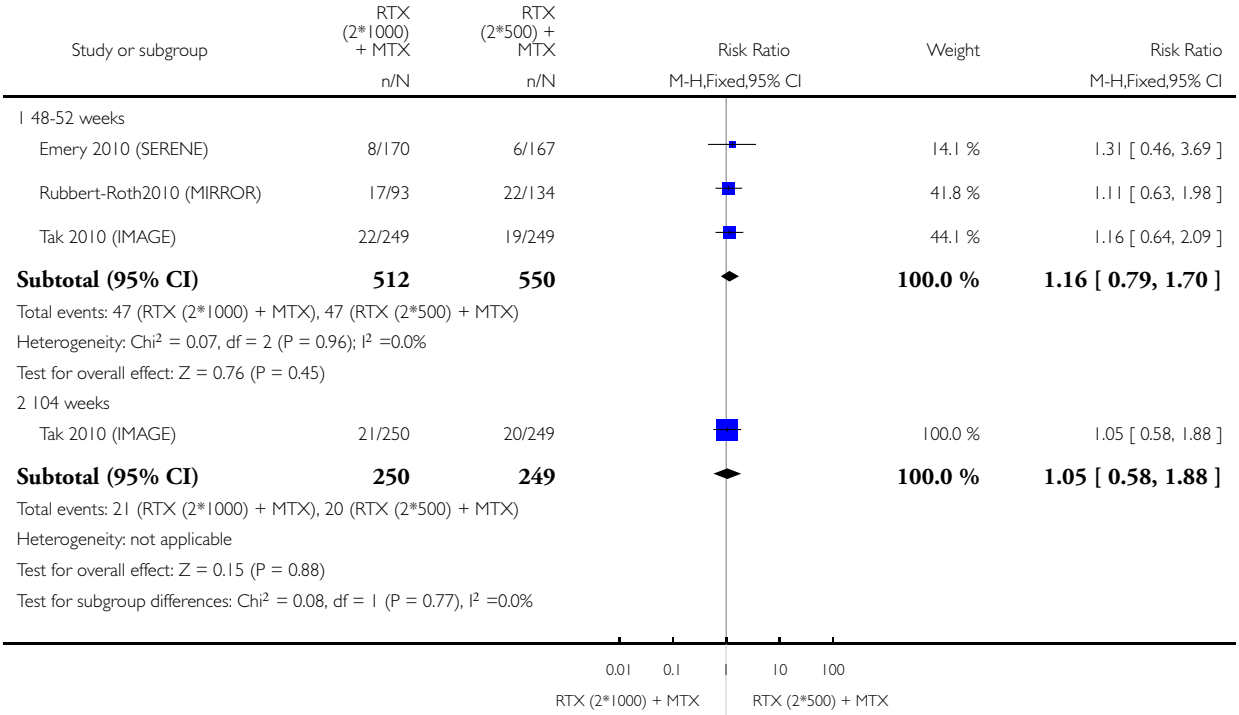
Analysis 19.42. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 42 Infusion-related reaction (2nd course).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 42 Infusion-related reaction (2nd course)



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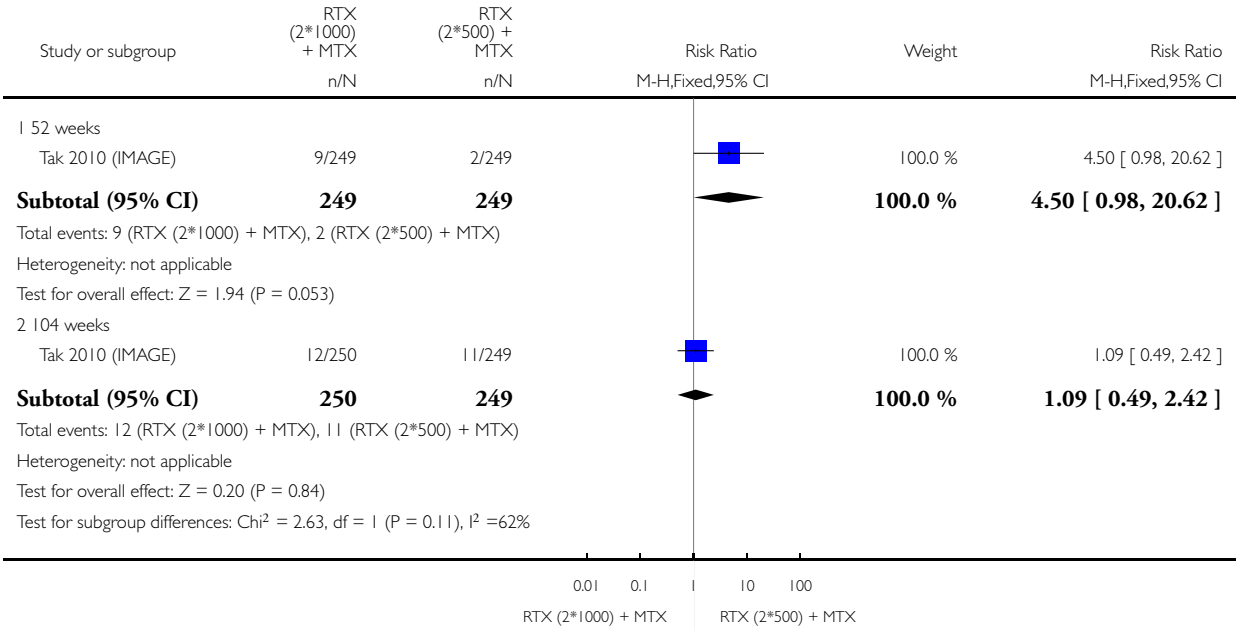
Analysis 19.43. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 43 Infusion-related reaction (3rd course).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 43 Infusion-related reaction (3rd course)



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Analysis 19.44. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 44 Infusion-related reaction (4th course).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 44 Infusion-related reaction (4th course)

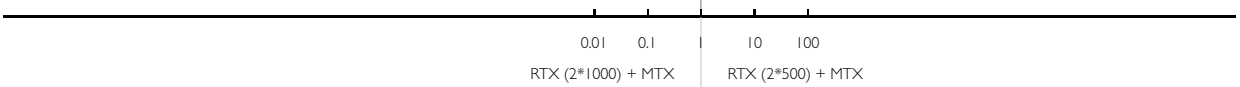
Study or subgroup	RTX (2*1000) + MTX n/N	RTX (2*500) + MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 104 weeks					
Tak 2010 (IMAGE)	8/250	10/249		100.0 %	0.80 [0.32, 1.99]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**0.80 [0.32, 1.99]**

Total events: 8 (RTX (2*1000) + MTX), 10 (RTX (2*500) + MTX)

Heterogeneity: not applicable

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

Test for subgroup differences: Not applicable



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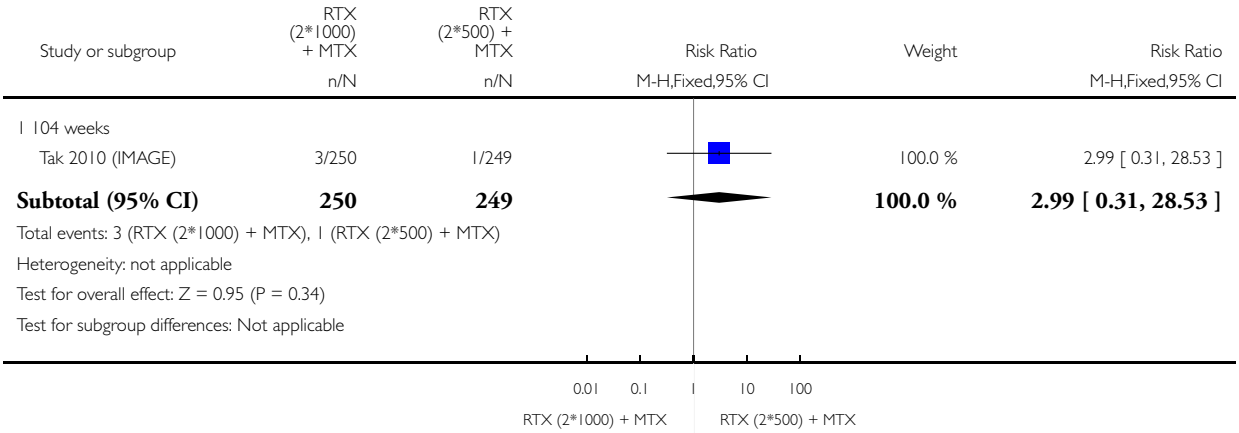
Analysis 19.45. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 45 Infusion-related reaction (5th course).

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 45 Infusion-related reaction (5th course)



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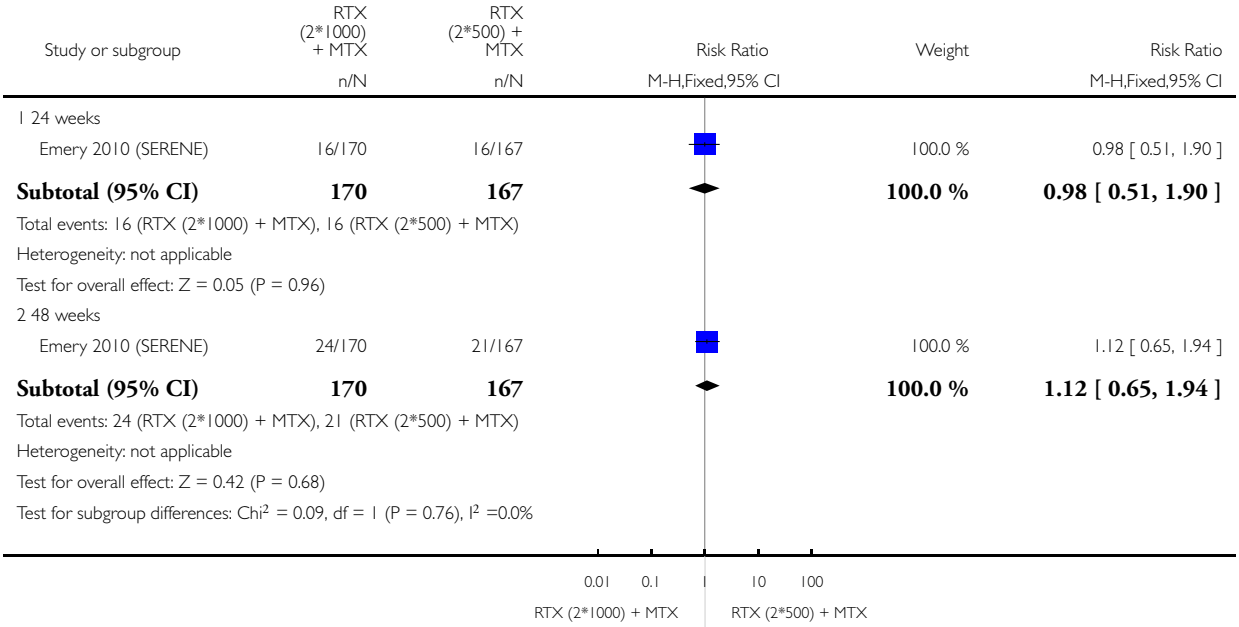
Analysis 19.46. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 46 Lower gastrointestinal events.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 46 Lower gastrointestinal events



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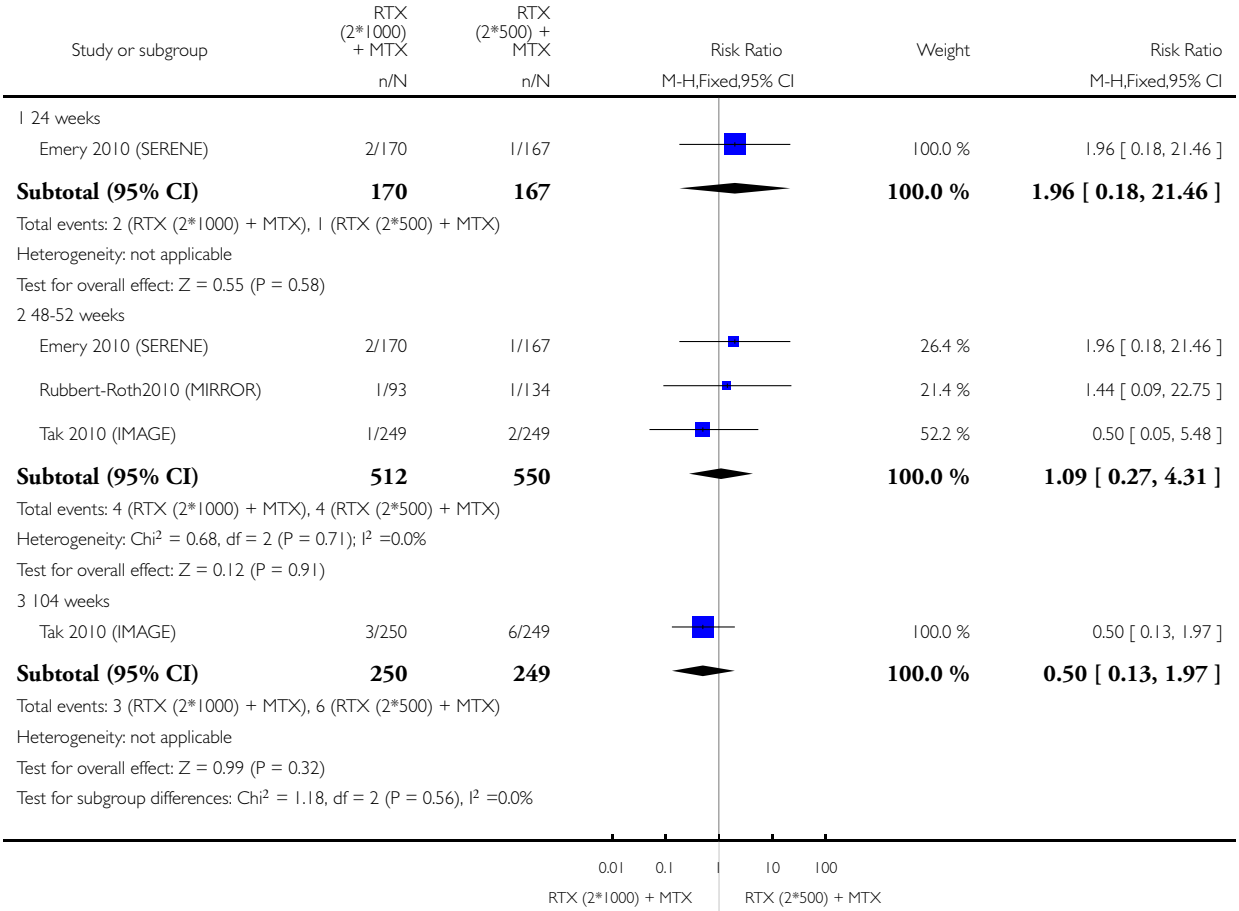
Analysis 19.47. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 47 Malignancy.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 47 Malignancy



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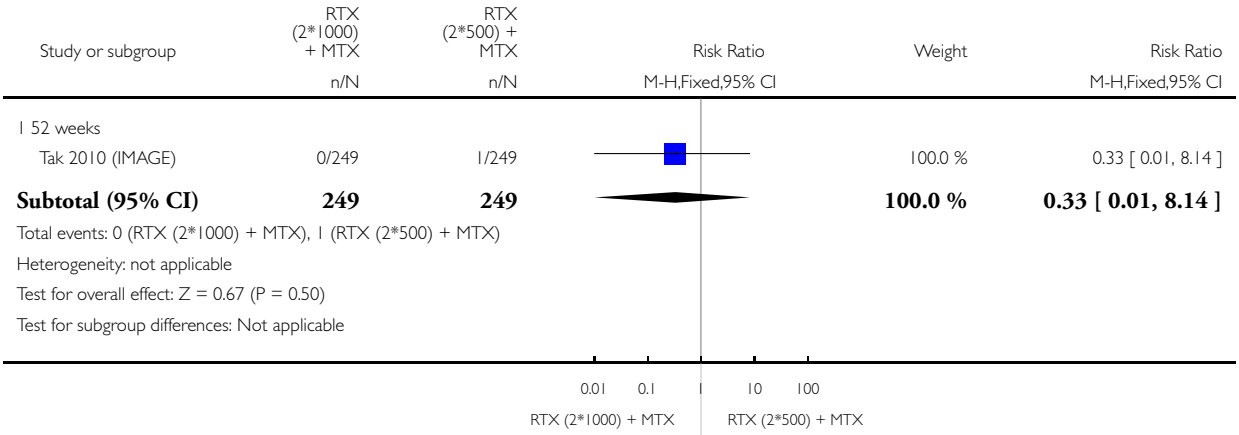
Analysis 19.48. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 48 Pneumonia.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 48 Pneumonia

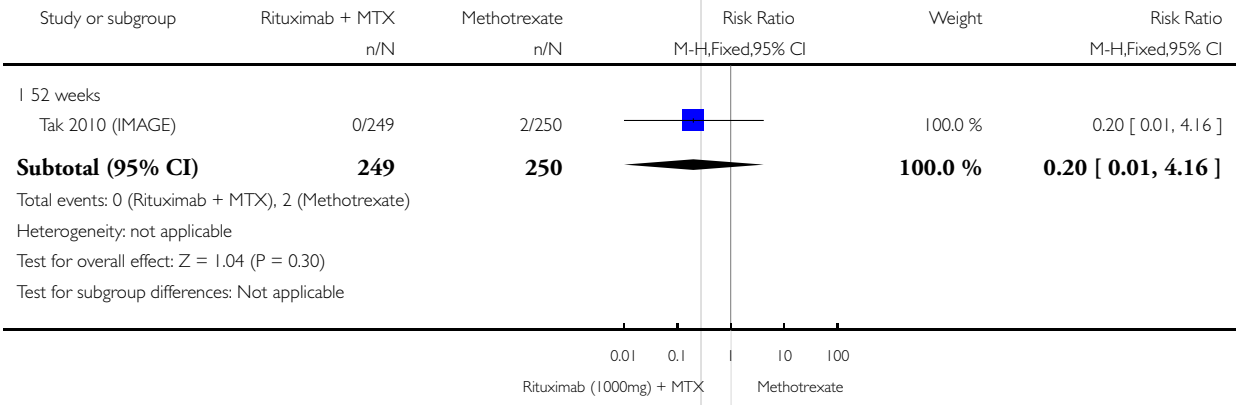


Analysis 19.49. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 49 Urinary tract infection.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 49 Urinary tract infection



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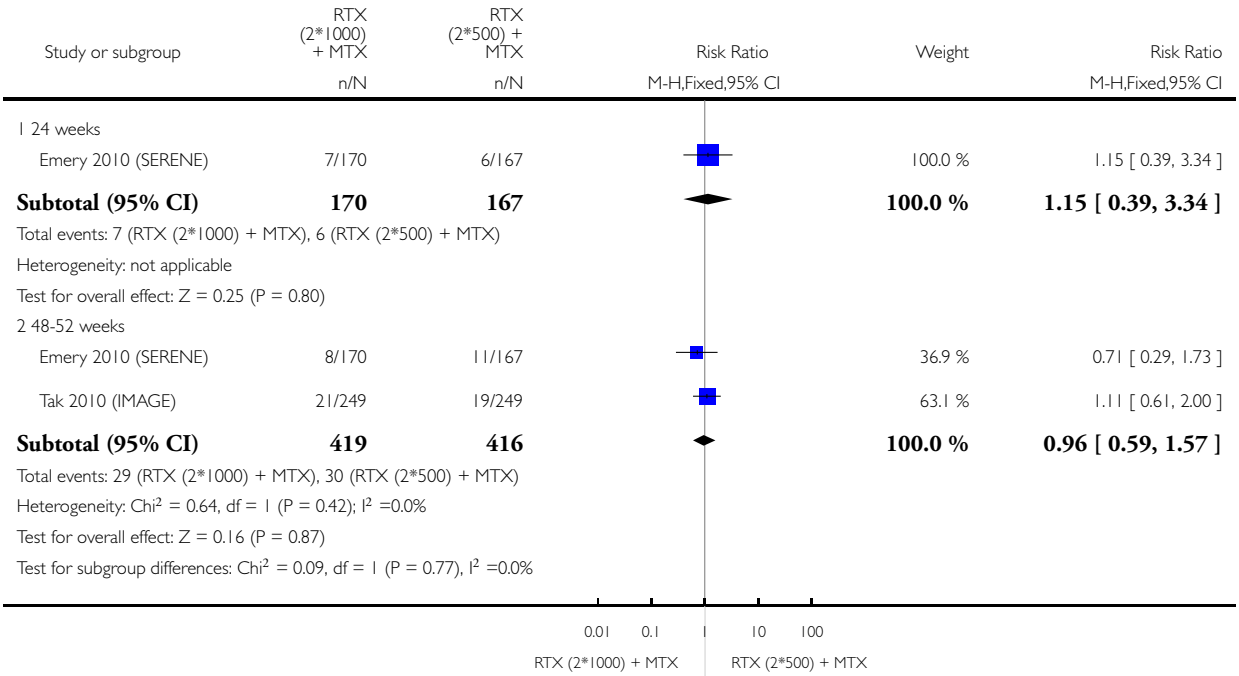
Analysis 19.50. Comparison 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis), Outcome 50 Vascular disorders.

Review: Rituximab for rheumatoid arthritis

Comparison: 19 Dosage 2 x 1000 mg versus 2 x 500 mg (sensitivity analysis)

Outcome: 50 Vascular disorders



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Analysis 20.1. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 1 ACR 20.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 1 ACR 20

Study or subgroup	Rituximab+CTX n/N	Rituximab+MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	31/41	29/40		100.0 %	1.04 [0.81, 1.35]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**1.04 [0.81, 1.35]**
Total events: 31 (Rituximab+CTX), 29 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
2 48 weeks					
Edwards 2004 (WA16291)	20/41	27/40		100.0 %	0.72 [0.49, 1.06]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.72 [0.49, 1.06]**
Total events: 20 (Rituximab+CTX), 27 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.094)					
3 104 weeks					
Edwards 2004 (WA16291)	5/41	13/40		100.0 %	0.38 [0.15, 0.96]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.38 [0.15, 0.96]**
Total events: 5 (Rituximab+CTX), 13 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.040)					
Test for subgroup differences: Chi^2 = 5.88, df = 2 (P = 0.05), I^2 =66%					

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Analysis 20.2. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 2 ACR 50

Study or subgroup	Rituximab+CTX n/N	Rituximab+MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	17/41	17/40		100.0 %	0.98 [0.58, 1.63]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.98 [0.58, 1.63]**
Total events: 17 (Rituximab+CTX), 17 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.92)					
2 48 weeks					
Edwards 2004 (WA16291)	11/41	14/40		100.0 %	0.77 [0.40, 1.48]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.77 [0.40, 1.48]**
Total events: 11 (Rituximab+CTX), 14 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
3 104 weeks					
Edwards 2004 (WA16291)	4/41	8/40		100.0 %	0.49 [0.16, 1.49]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.49 [0.16, 1.49]**
Total events: 4 (Rituximab+CTX), 8 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.26 (P = 0.21)					
Test for subgroup differences: Chi^2 = 1.31, df = 2 (P = 0.52), I^2 =0.0%					

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Analysis 20.3. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 3 ACR 70.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 3 ACR 70

Study or subgroup	Rituximab+CTX n/N	Rituximab+MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	6/41	9/40		100.0 %	0.65 [0.25, 1.66]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.65 [0.25, 1.66]**
Total events: 6 (Rituximab+CTX), 9 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.90 (P = 0.37)					
2 48 weeks					
Edwards 2004 (WA16291)	4/41	6/40		100.0 %	0.65 [0.20, 2.13]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.65 [0.20, 2.13]**
Total events: 4 (Rituximab+CTX), 6 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
3 104 weeks					
Edwards 2004 (WA16291)	3/41	4/40		100.0 %	0.73 [0.17, 3.06]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.73 [0.17, 3.06]**
Total events: 3 (Rituximab+CTX), 4 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Chi^2 = 0.02, df = 2 (P = 0.99), I^2 =0.0%					

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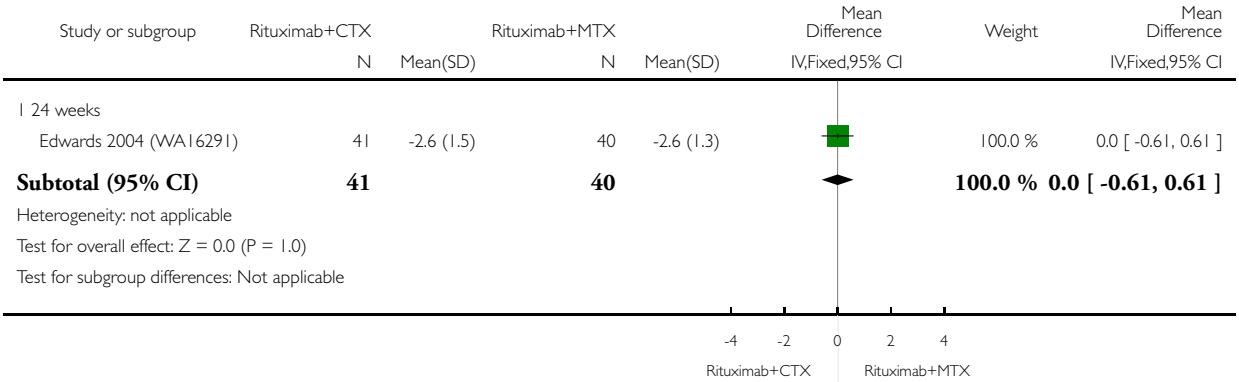
Analysis 20.4. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 4 DAS 28.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 4 DAS 28

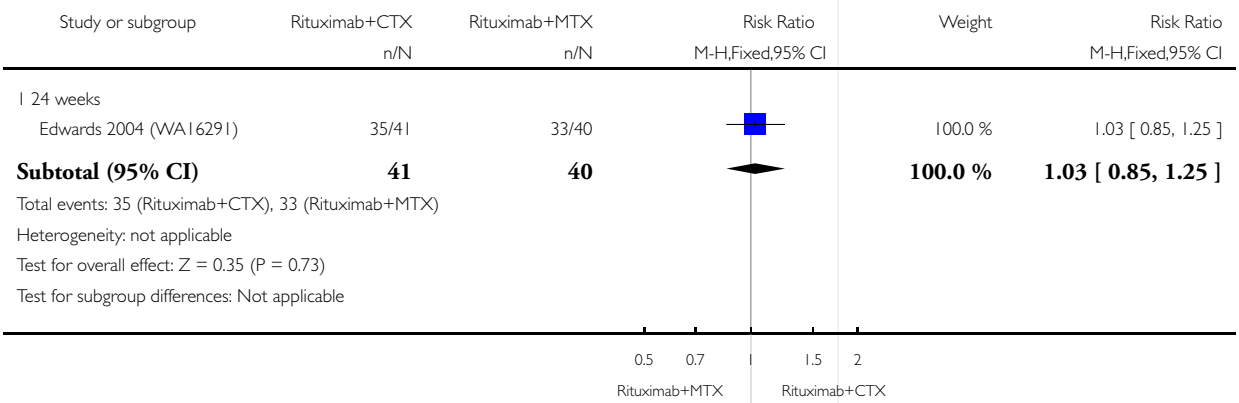


Analysis 20.5. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 5 Moderate or good EULAR response.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 5 Moderate or good EULAR response



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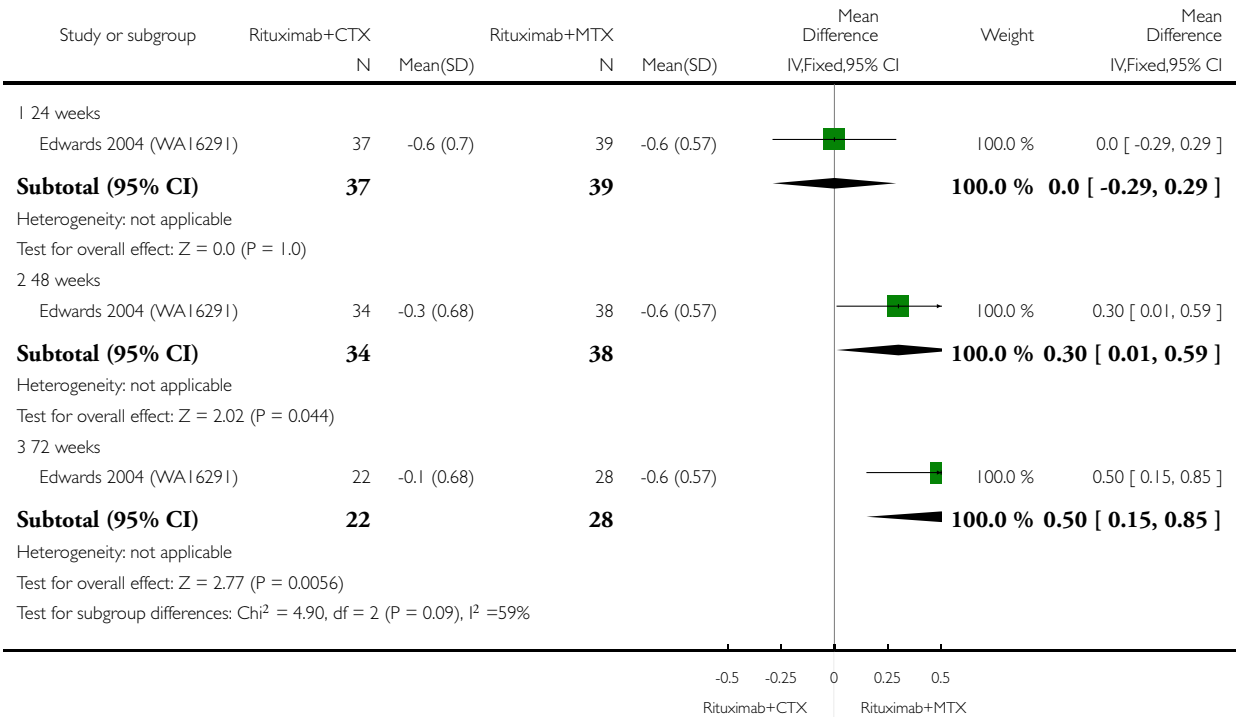
Analysis 20.6. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 6 HAQ-DI.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 6 HAQ-DI



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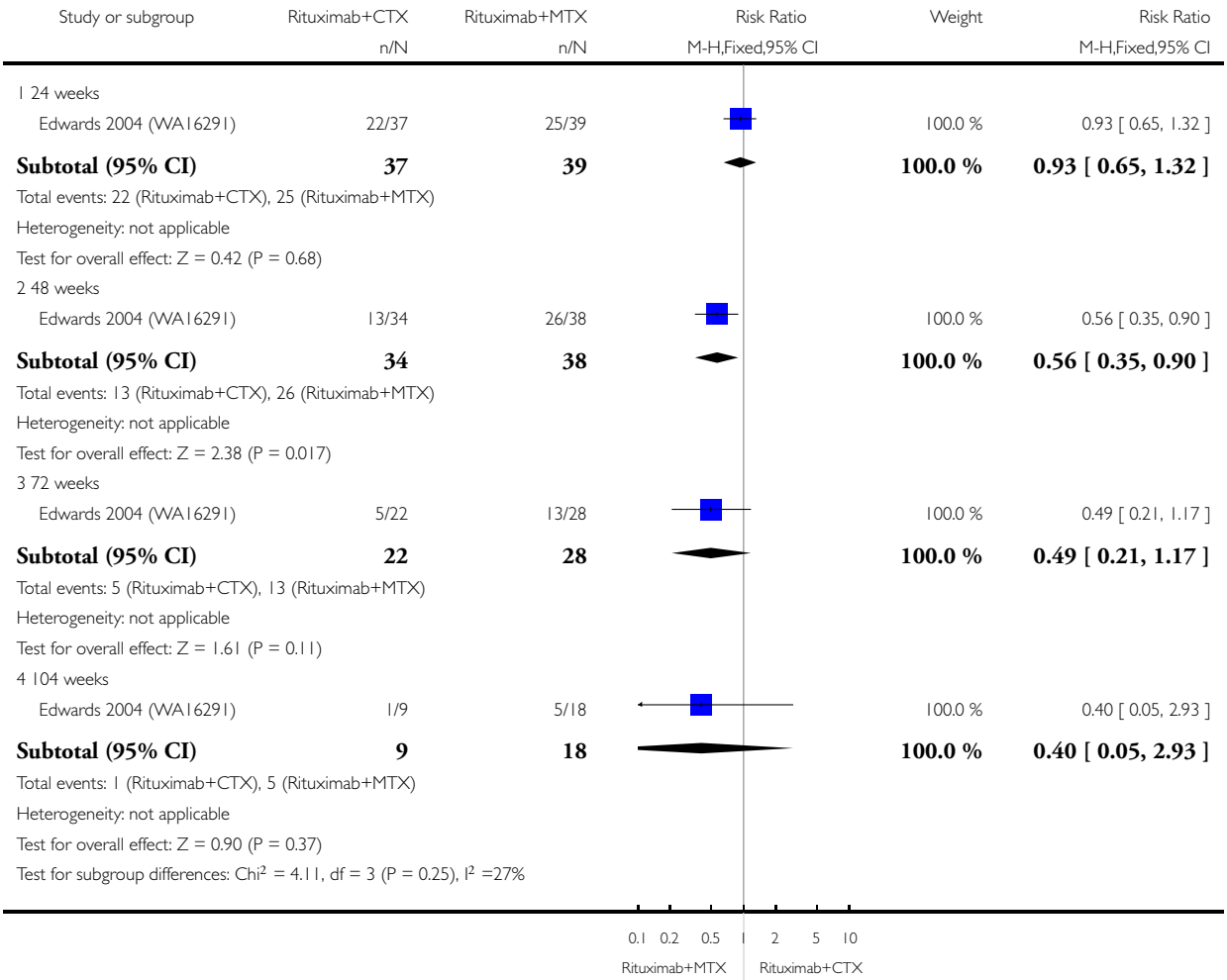
Analysis 20.7. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 7 HAQ-DI MCID=-0.22.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 7 HAQ-DI MCID=-0.22



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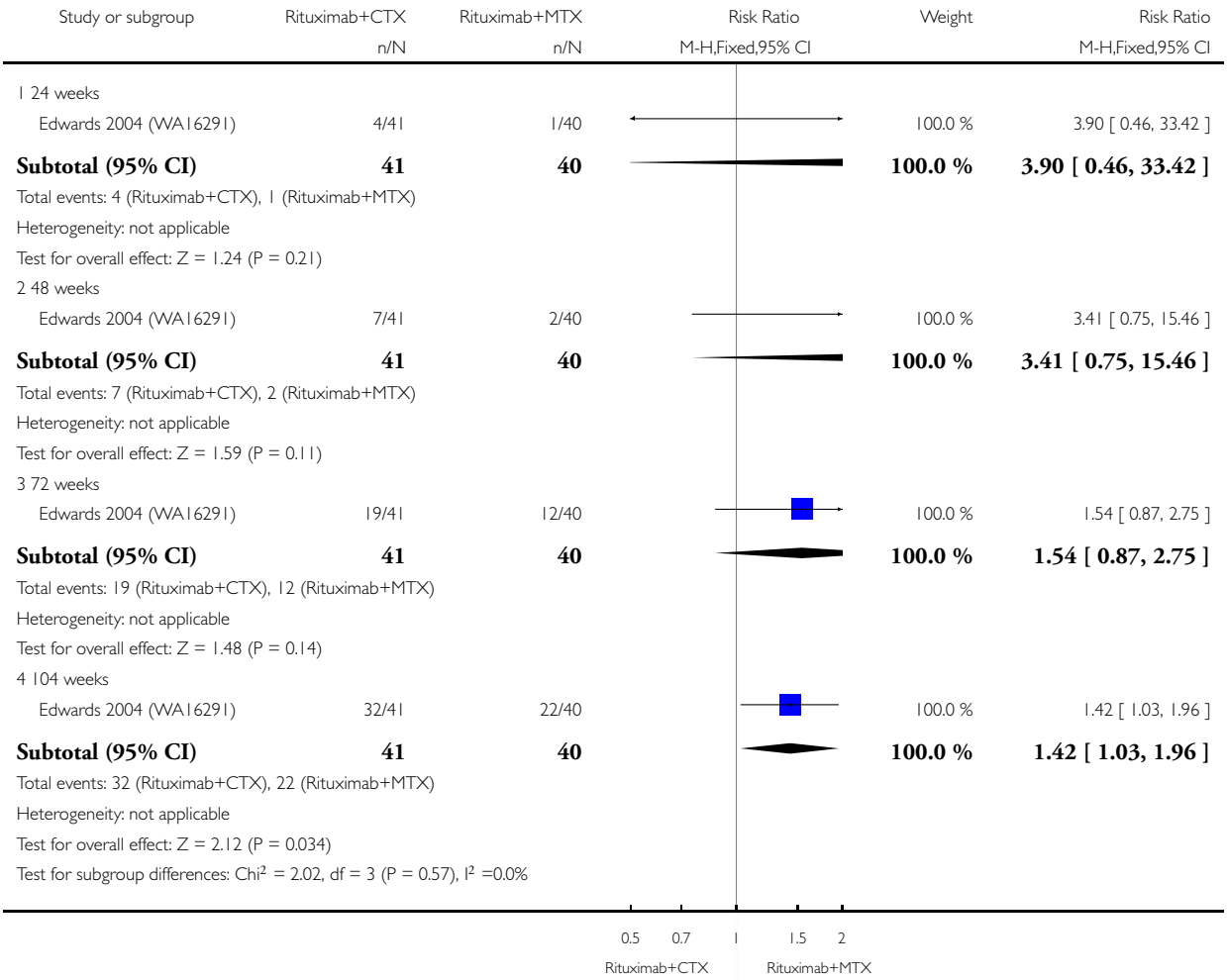
Analysis 20.8. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 8 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 8 Total discontinuations



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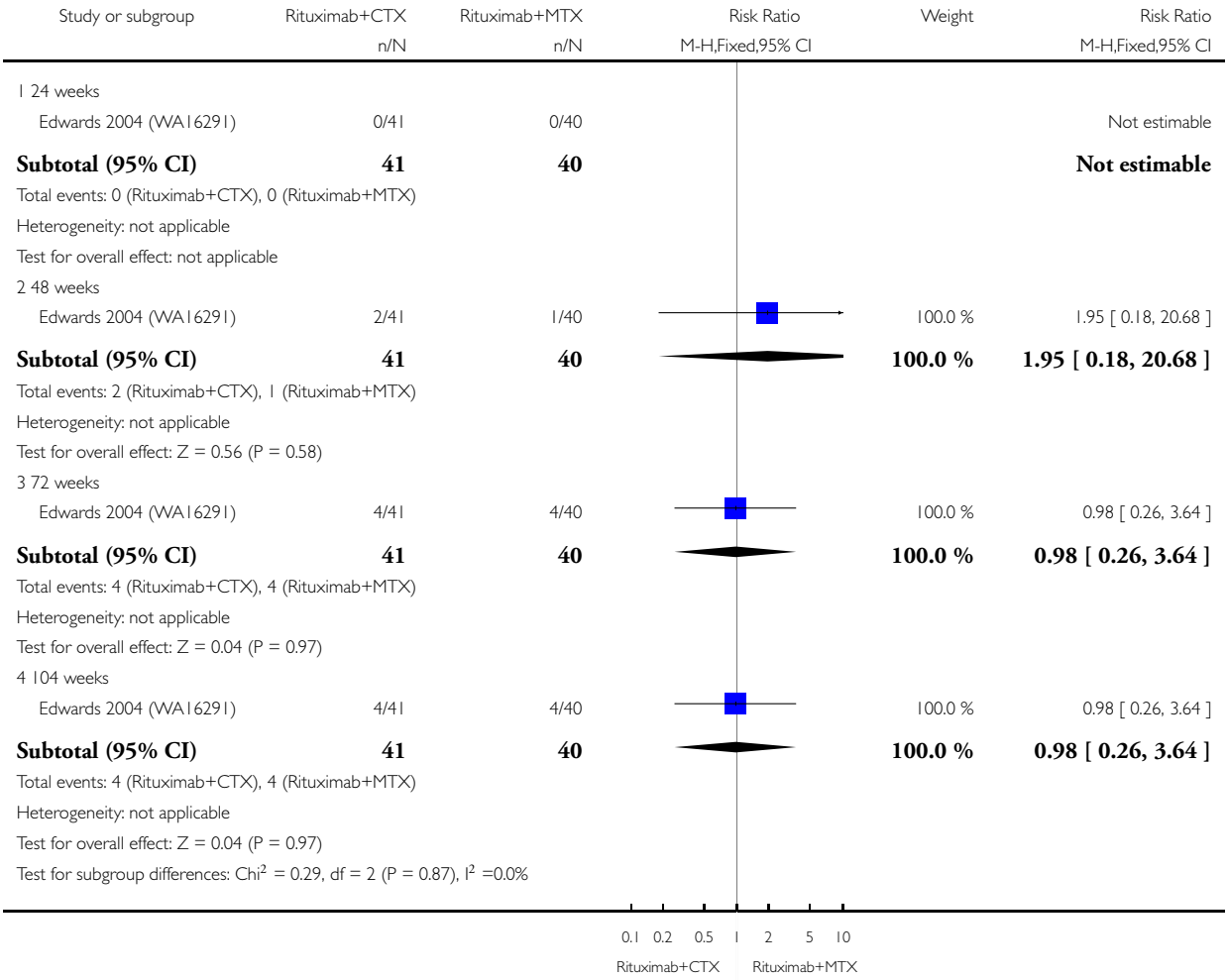
Analysis 20.9. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 9 Withdrawals due to lack of efficacy.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 9 Withdrawals due to lack of efficacy



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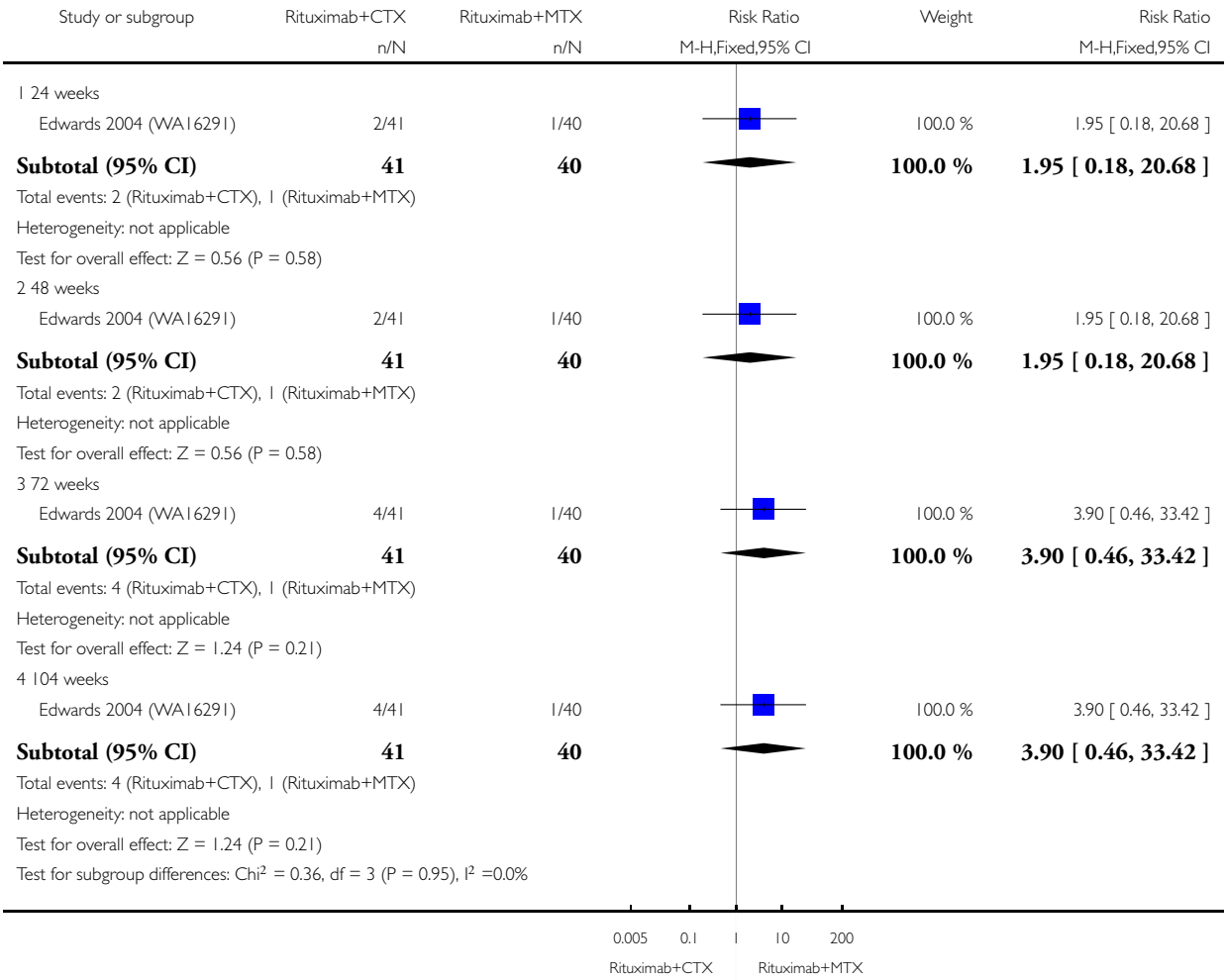
Analysis 20.10. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 10 Withdrawals due to adverse events.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 10 Withdrawals due to adverse events



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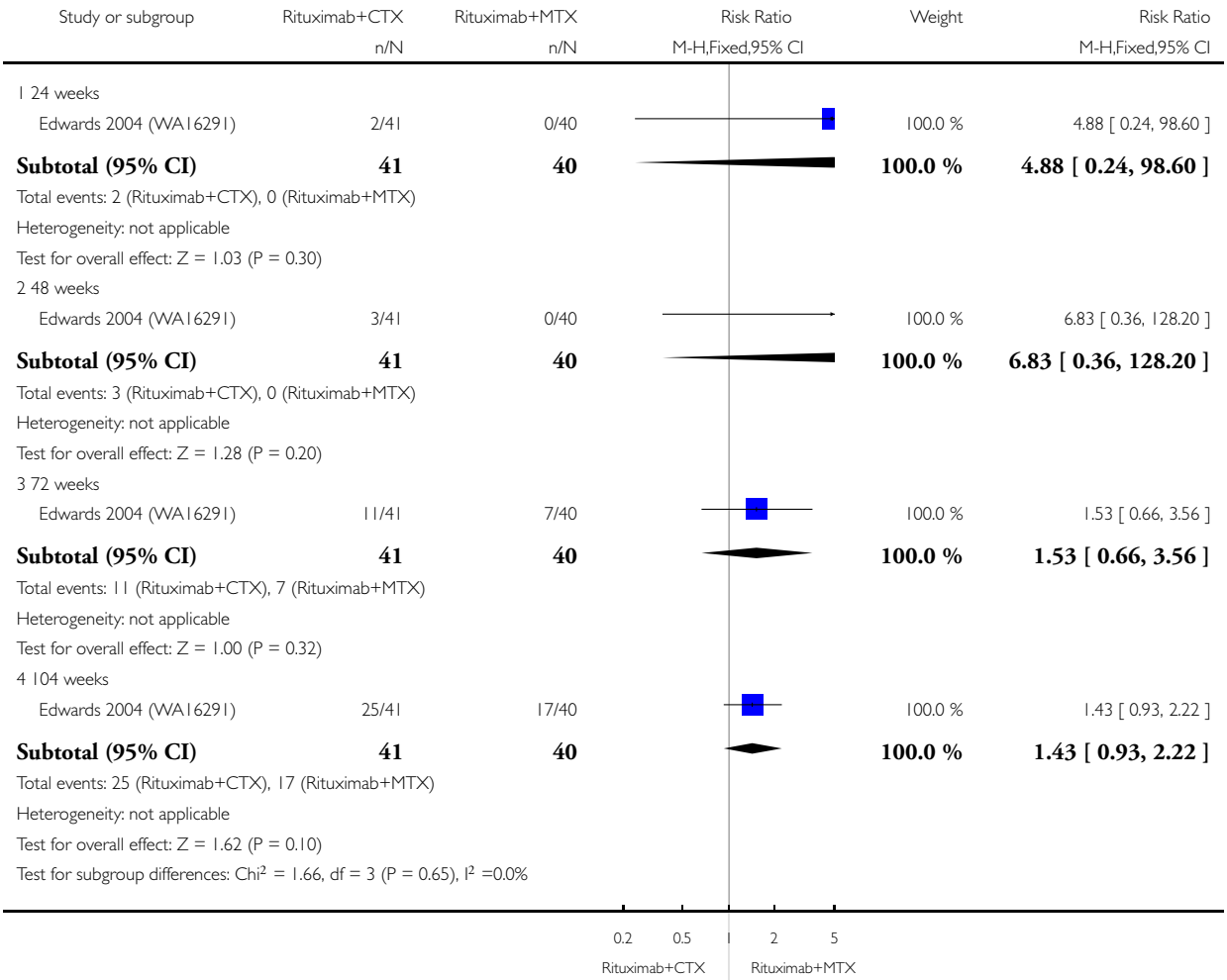
Analysis 20.11. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 11 Withdrawals due to other reasons.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 11 Withdrawals due to other reasons



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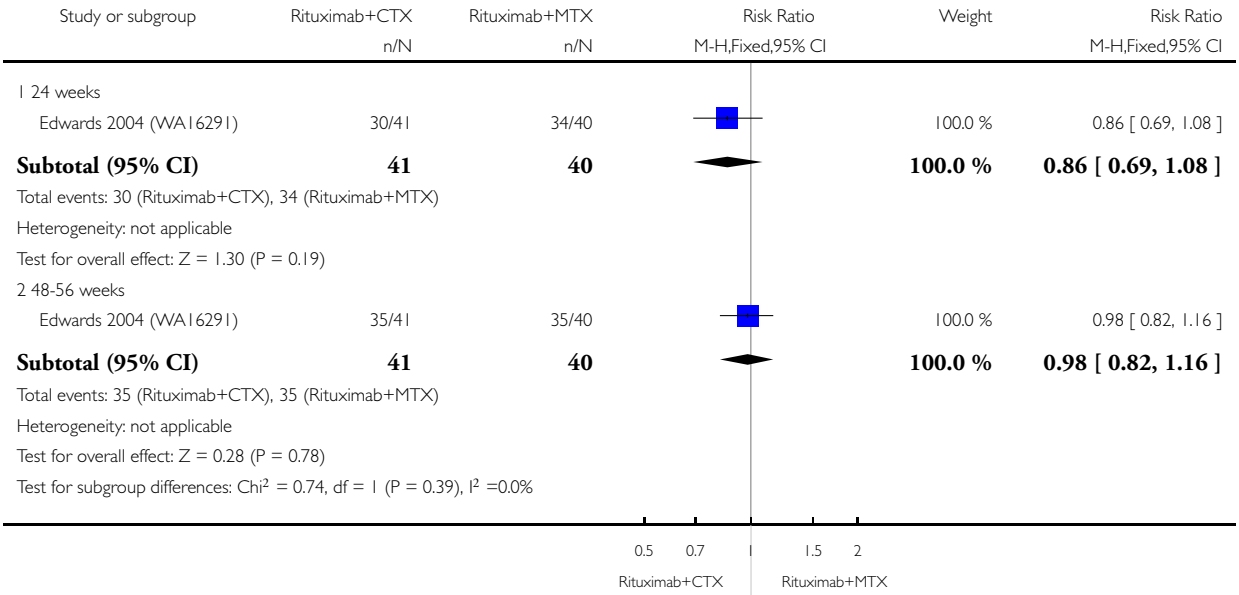
Analysis 20.12. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 12 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 12 Any Adverse Event



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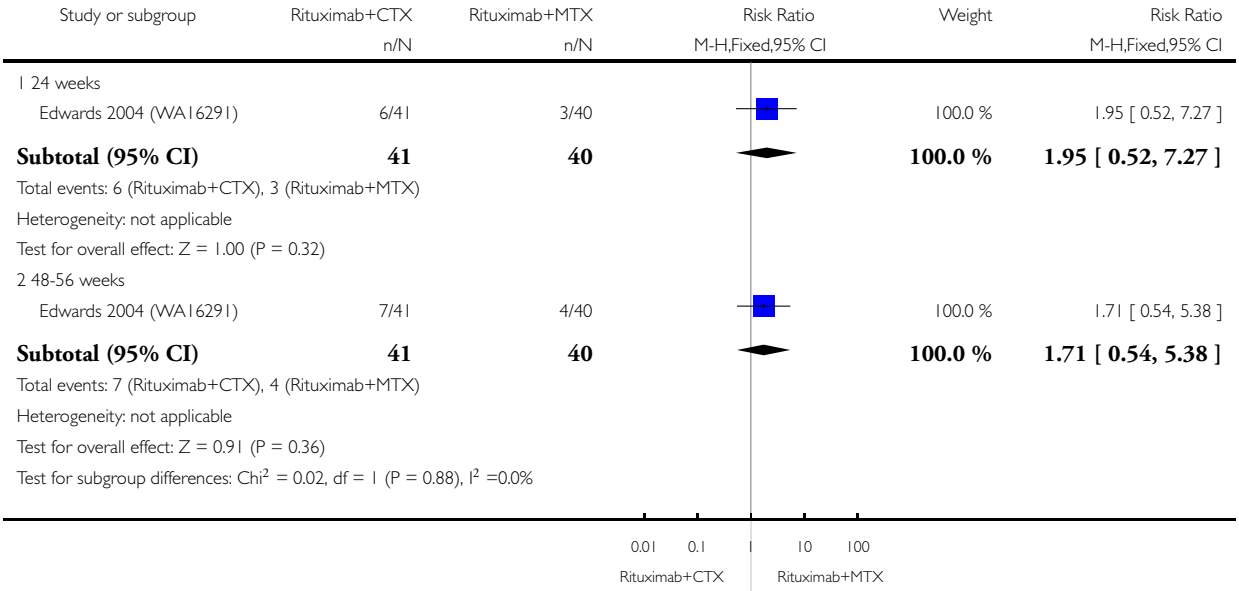
Analysis 20.13. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 13 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 13 Serious Adverse Events



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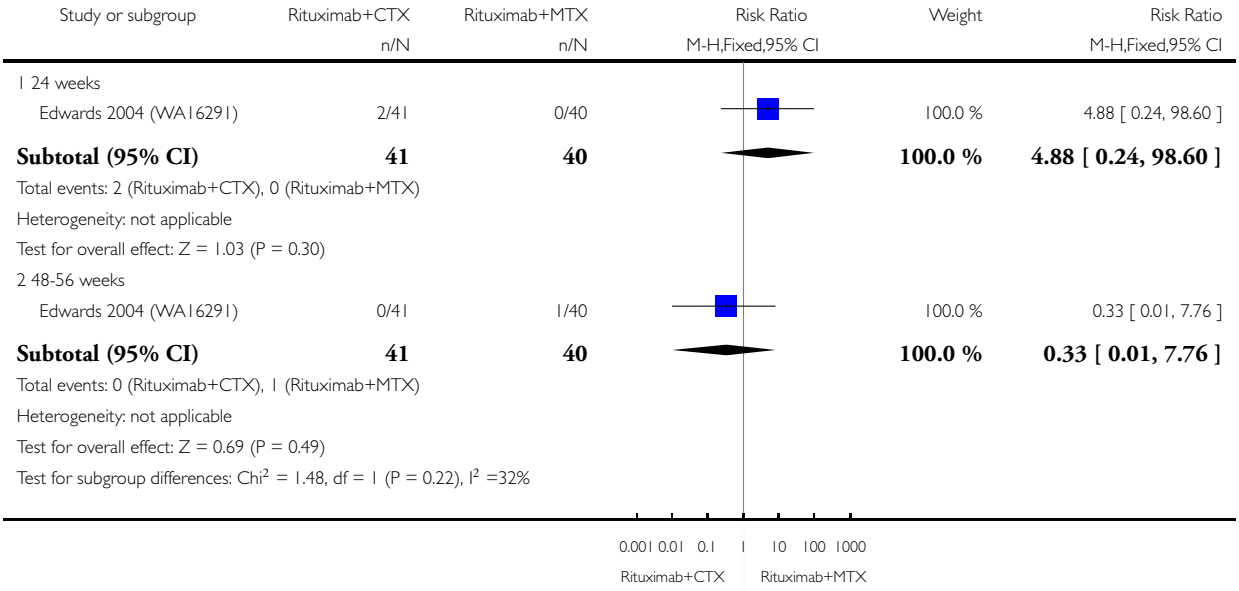
Analysis 20.14. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 14 Serious Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 14 Serious Infections



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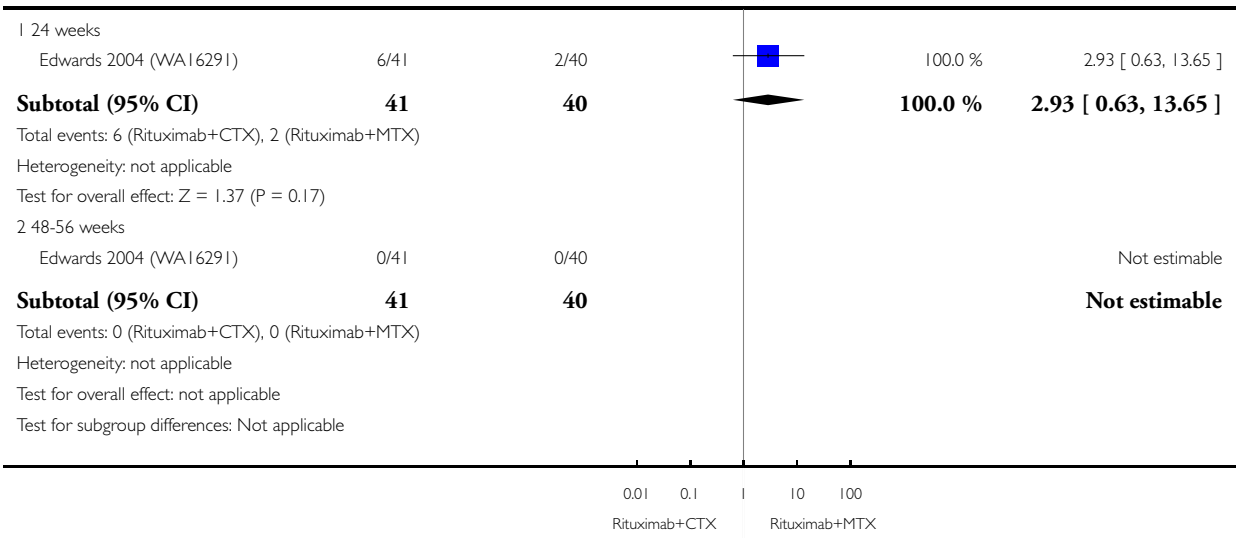
Analysis 20.15. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 15 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 15 Exacerbation of RA

Study or subgroup	Rituximab+CTX n/N	Rituximab+MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	6/41	2/40		100.0 %	2.93 [0.63, 13.65]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**2.93 [0.63, 13.65]**
Total events: 6 (Rituximab+CTX), 2 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 48-56 weeks					
Edwards 2004 (WA16291)	0/41	0/40			Not estimable
Subtotal (95% CI)	**41**	**40**			**Not estimable**
Total events: 0 (Rituximab+CTX), 0 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



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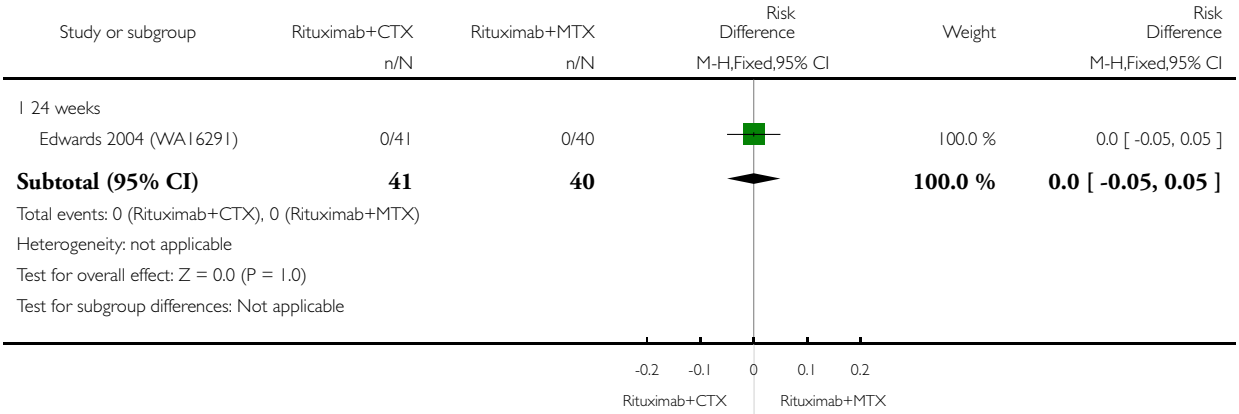
Analysis 20.16. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 16 Death.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 16 Death

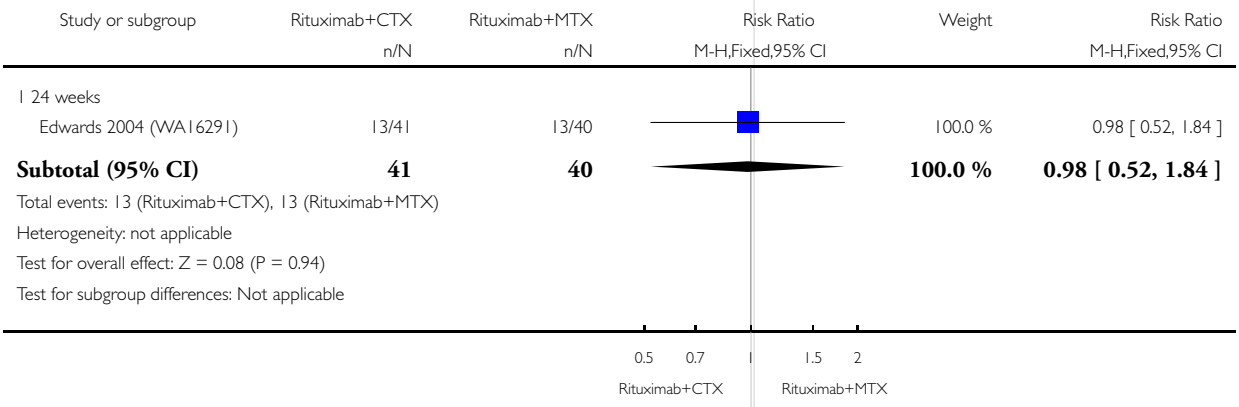


Analysis 20.17. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 17 Any Event Associated with 1st Infusion.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 17 Any Event Associated with 1st Infusion



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Analysis 20.18. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 18 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 18 Arthralgia

Study or subgroup	Rituximab+CTX n/N	Rituximab+MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	1/41	4/40		100.0 %	0.24 [0.03, 2.09]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.24 [0.03, 2.09]**
Total events: 1 (Rituximab+CTX), 4 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					
Test for subgroup differences: Not applicable					

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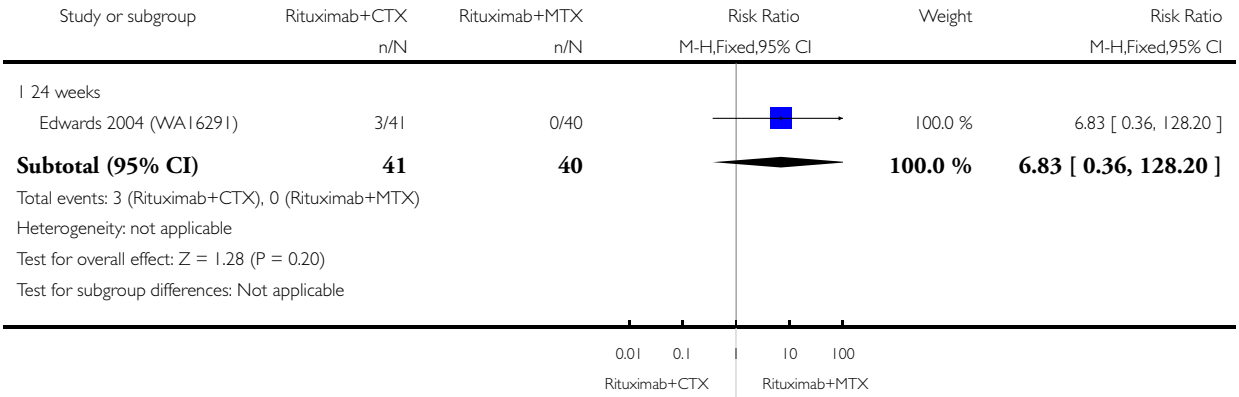
Analysis 20.19. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 19 Back pain.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 19 Back pain

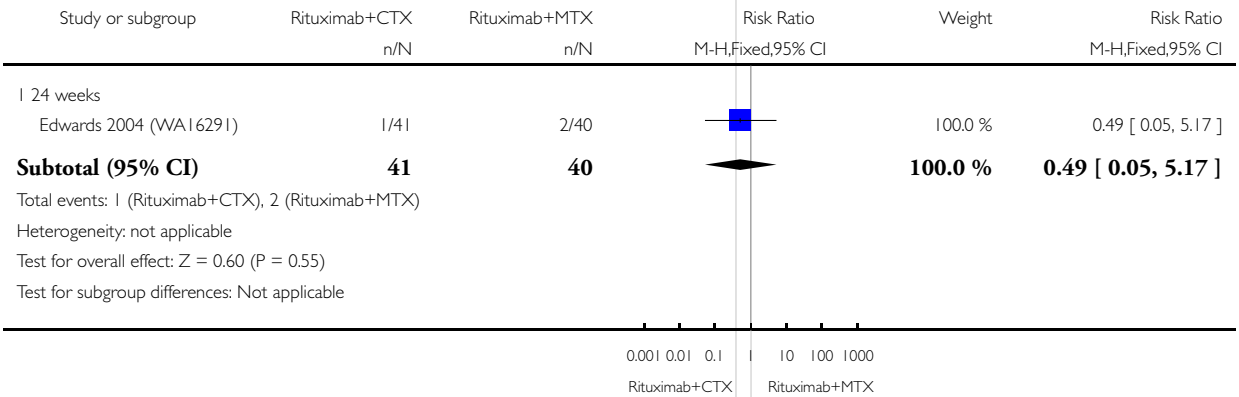


Analysis 20.20. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 20 Cough.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 20 Cough



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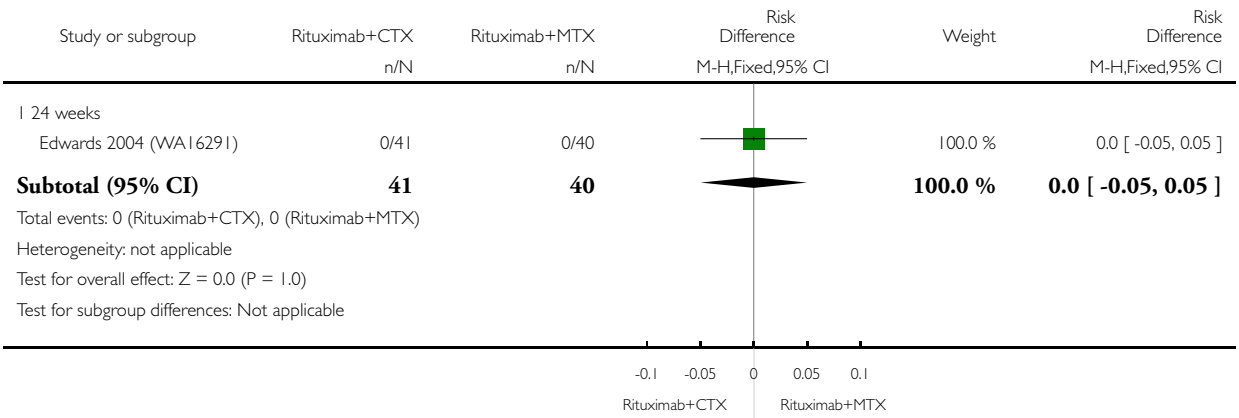
Analysis 20.21. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 21 Dyspnea.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 21 Dyspnea



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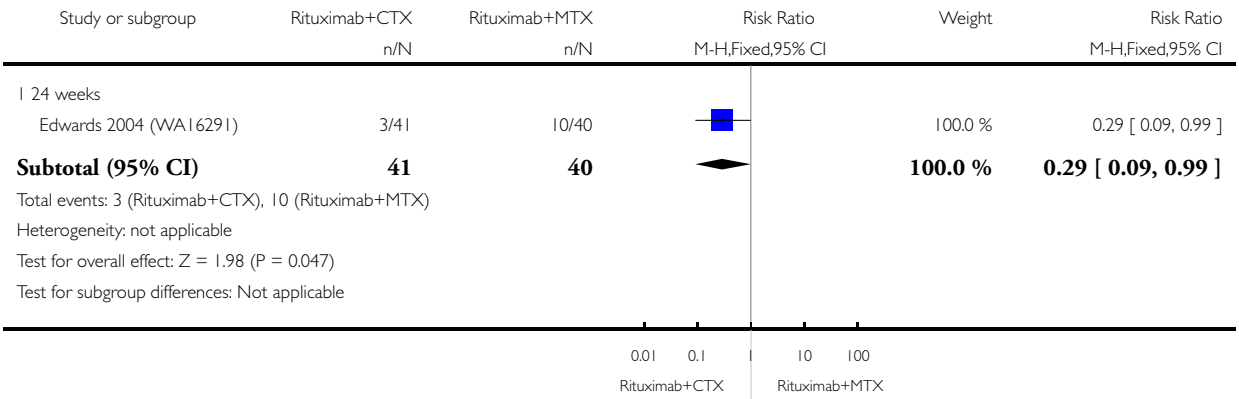
Analysis 20.22. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 22 Hypertension.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 22 Hypertension

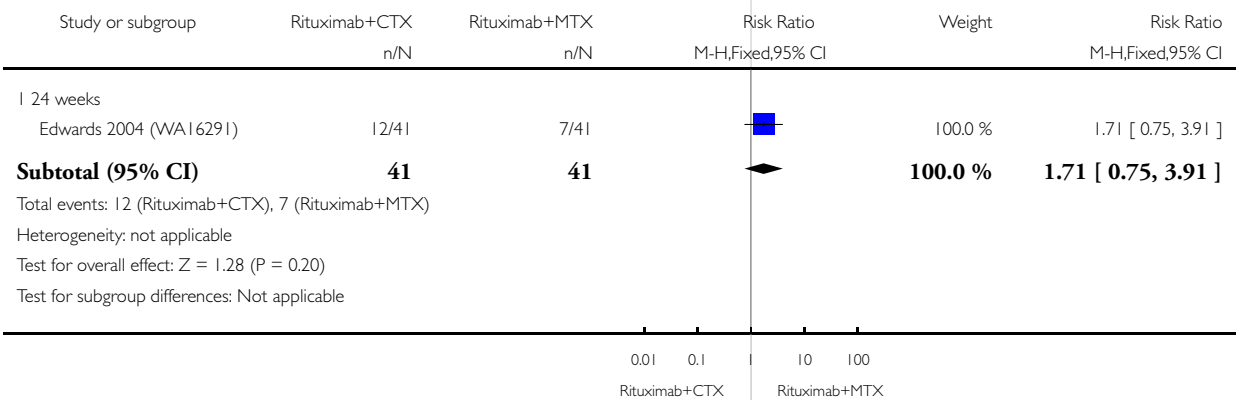


Analysis 20.23. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 23 Hypotension.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 23 Hypotension



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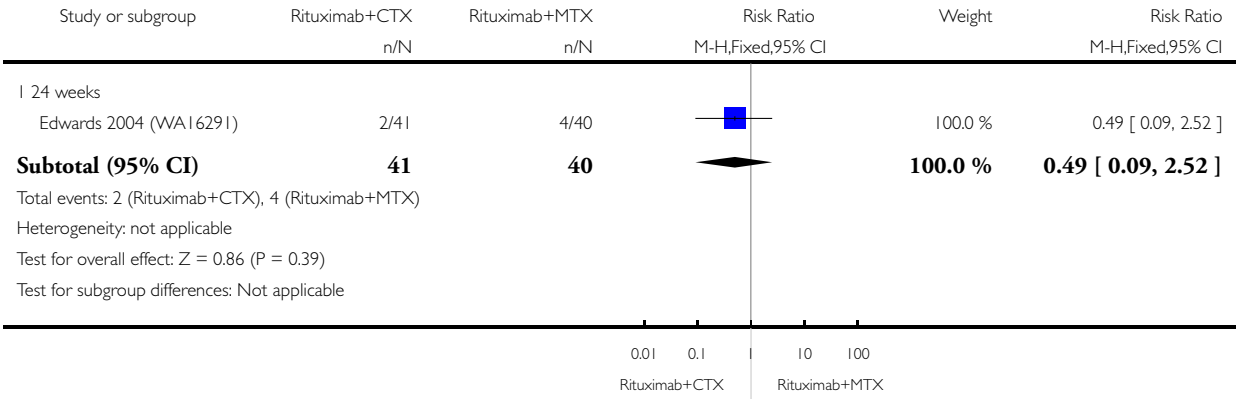
Analysis 20.24. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 24 Nasopharyngitis.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 24 Nasopharyngitis



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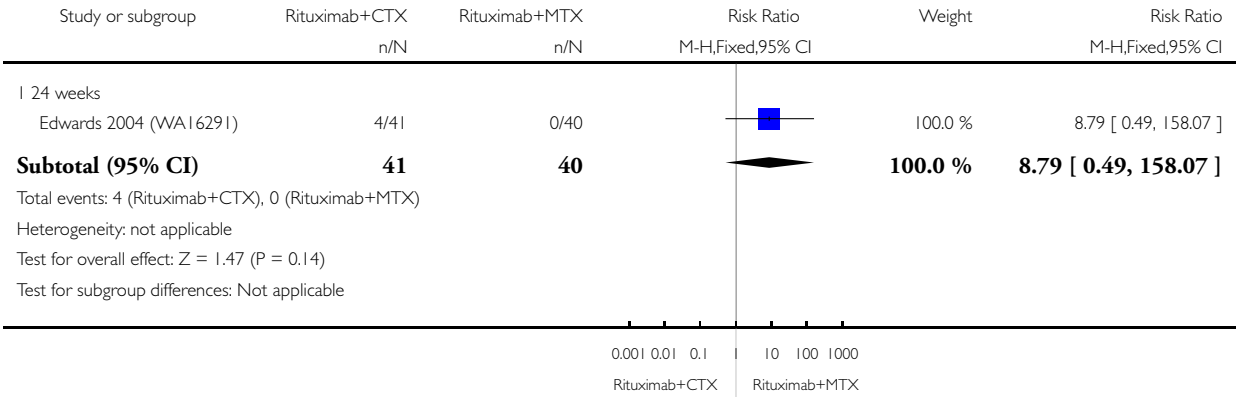
Analysis 20.25. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 25 Nausea.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 25 Nausea

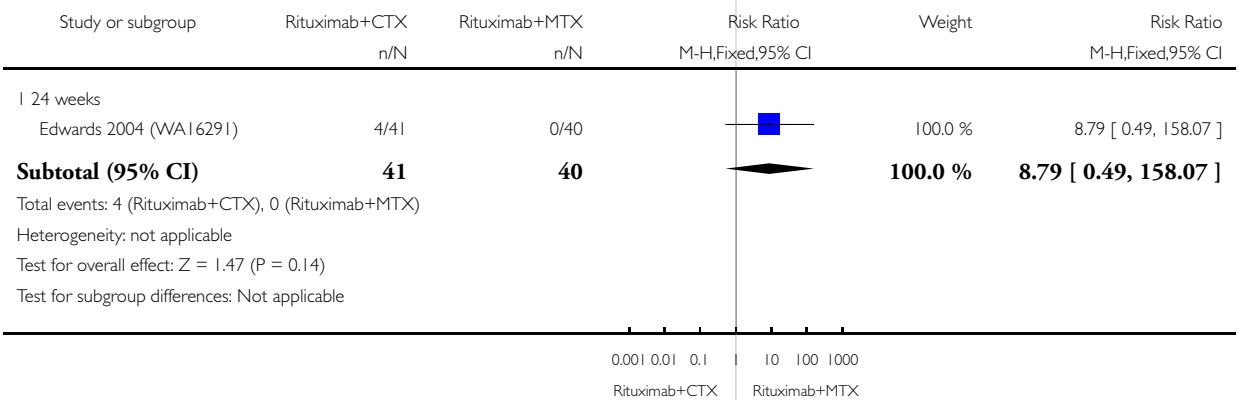


Analysis 20.26. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 26 Pruritus.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 26 Pruritus



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Analysis 20.27. Comparison 20 Concomitant treatment CTX versus MTX (sensitivity analysis), Outcome 27 Rash.

Review: Rituximab for rheumatoid arthritis

Comparison: 20 Concomitant treatment CTX versus MTX (sensitivity analysis)

Outcome: 27 Rash

Study or subgroup	Rituximab+CTX n/N	Rituximab+MTX n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	4/41	1/40		100.0 %	3.90 [0.46, 33.42]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**3.90 [0.46, 33.42]**
Total events: 4 (Rituximab+CTX), 1 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.21)					
2 48 weeks					
Edwards 2004 (WA16291)	0/41	0/40			Not estimable
Subtotal (95% CI)	**41**	**40**			**Not estimable**
Total events: 0 (Rituximab+CTX), 0 (Rituximab+MTX)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

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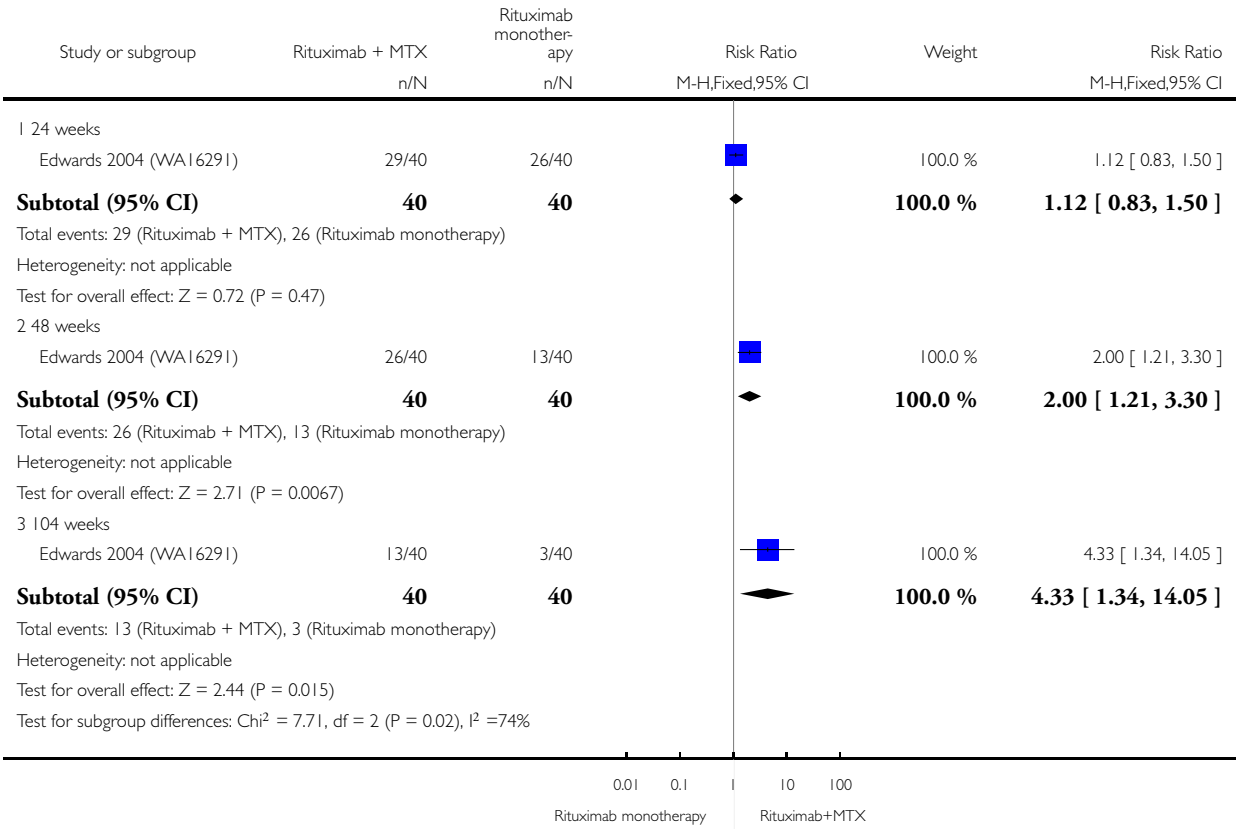
Analysis 21.1. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 1 ACR 20.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 1 ACR 20



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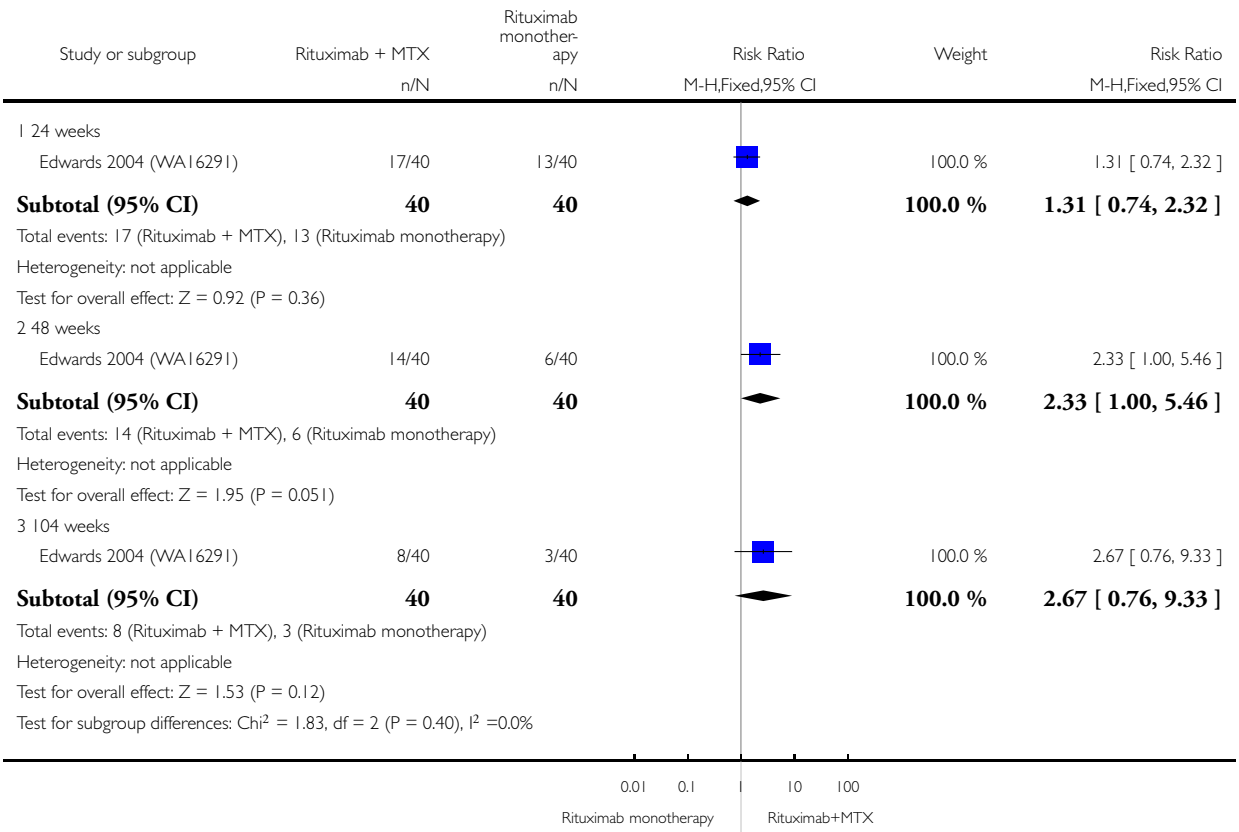
Analysis 21.2. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 2 ACR 50



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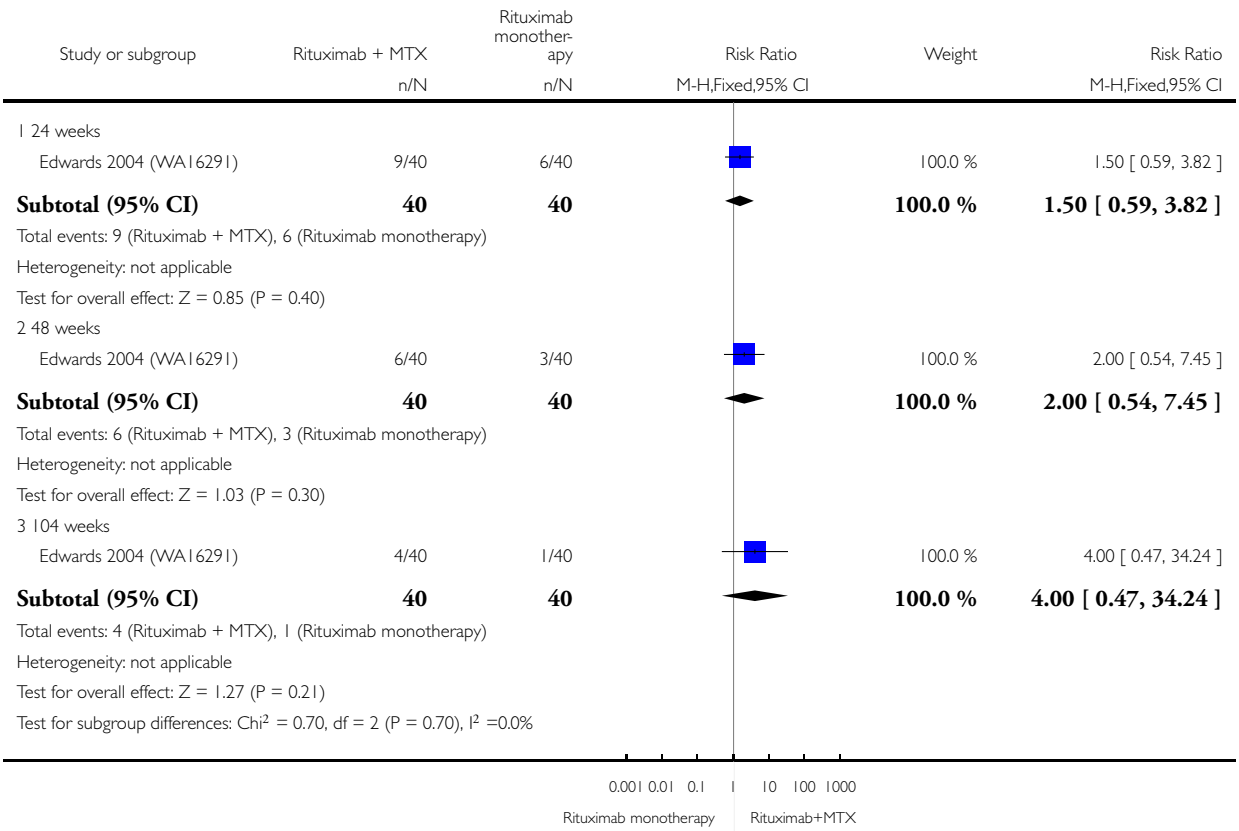
Analysis 21.3. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 3 ACR 70.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 3 ACR 70



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Analysis 21.4. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 4 DAS 28.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

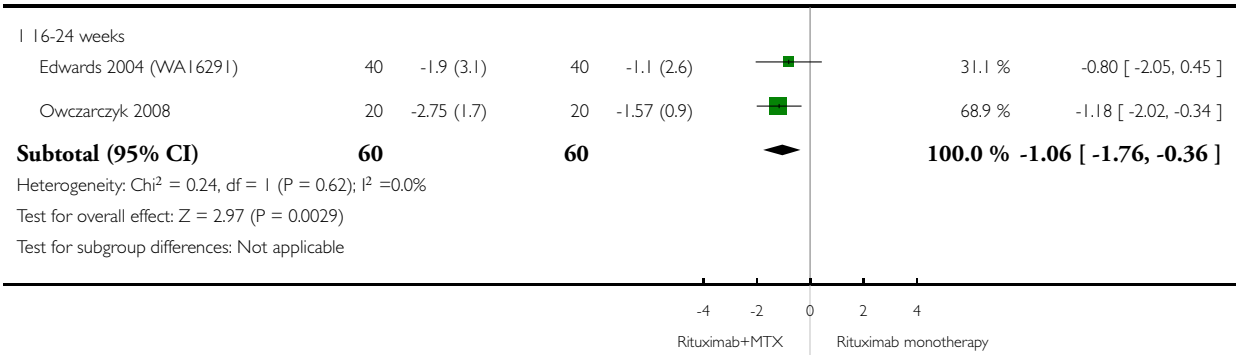
Outcome: 4 DAS 28

Study or subgroup	Rituximab + MTX		Rituximab monotherapy		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 16-24 weeks							
Edwards 2004 (WA16291)	40	-1.9 (3.1)	40	-1.1 (2.6)		31.1 %	-0.80 [-2.05, 0.45]
Owczarczyk 2008	20	-2.75 (1.7)	20	-1.57 (0.9)		68.9 %	-1.18 [-2.02, -0.34]
Subtotal (95% CI)	**60**		**60**			**100.0 %**	**-1.06 [-1.76, -0.36]**

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² =0.0%

Test for overall effect: Z = 2.97 (P = 0.0029)

Test for subgroup differences: Not applicable



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Analysis 21.5. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 5 Moderate or good EULAR response.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 5 Moderate or good EULAR response

Study or subgroup	Rituximab + MTX n/N	Rituximab monotherapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 16-24 weeks					
Edwards 2004 (WA16291)	33/40	34/40		70.8 %	0.97 [0.80, 1.18]
Owczarczyk 2008	17/20	14/20		29.2 %	1.21 [0.86, 1.71]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**1.04 [0.88, 1.23]**
Total events: 50 (Rituximab + MTX), 48 (Rituximab monotherapy)					
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² =23%					
Test for overall effect: Z = 0.47 (P = 0.64)					
2 104 weeks					
Edwards 2004 (WA16291)	13/40	4/40		100.0 %	3.25 [1.16, 9.12]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**3.25 [1.16, 9.12]**
Total events: 13 (Rituximab + MTX), 4 (Rituximab monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.24 (P = 0.025)					
Test for subgroup differences: Chi² = 4.55, df = 1 (P = 0.03), I² =78%					

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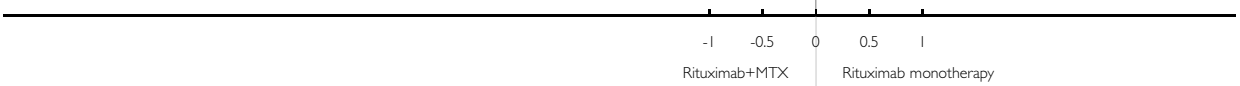
Analysis 21.6. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 6 HAQ-DI.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 6 HAQ-DI

Study or subgroup	Rituximab + MTX N	Mean(SD)	Rituximab monotherapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 24 weeks							
Edwards 2004 (WA16291)	40	-0.6 (0.6)	40	-0.8 (0.6)		100.0 %	0.20 [-0.06, 0.46]
Subtotal (95% CI)	**40**		**40**			**100.0 %**	**0.20 [-0.06, 0.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							
2 48 weeks							
Edwards 2004 (WA16291)	40	-0.6 (0.6)	40	-0.5 (0.6)		100.0 %	-0.10 [-0.36, 0.16]
Subtotal (95% CI)	**40**		**40**			**100.0 %**	**-0.10 [-0.36, 0.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.75 (P = 0.46)							
3 72 weeks							
Edwards 2004 (WA16291)	40	-0.6 (0.6)	40	-0.6 (0.6)		100.0 %	0.0 [-0.26, 0.26]
Subtotal (95% CI)	**40**		**40**			**100.0 %**	**0.0 [-0.26, 0.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Test for subgroup differences: Chi^2 = 2.59, df = 2 (P = 0.27), I^2 =23%							



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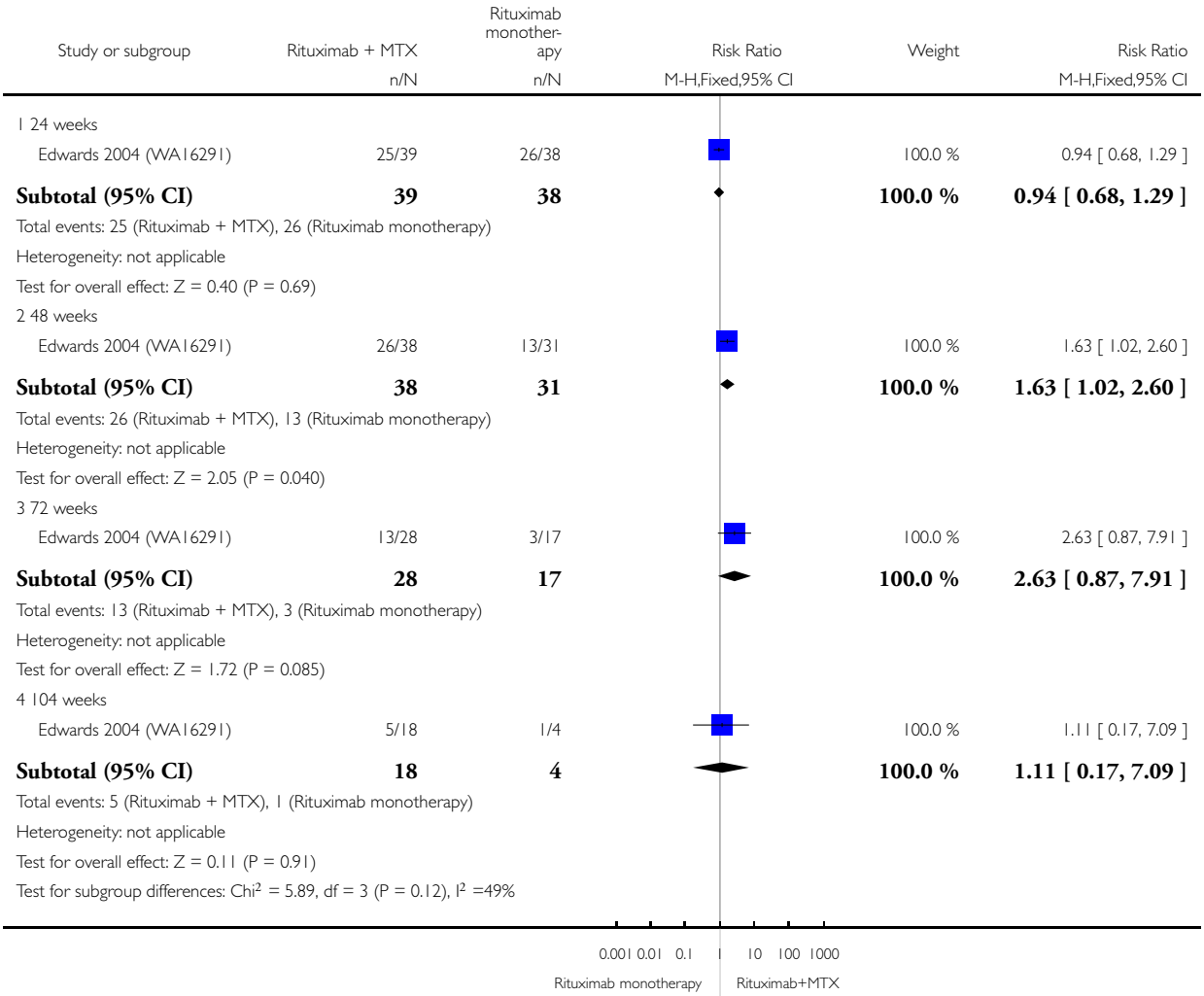
Analysis 21.7. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 7 HAQ-DI MCID=-0.22.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 7 HAQ-DI MCID=-0.22



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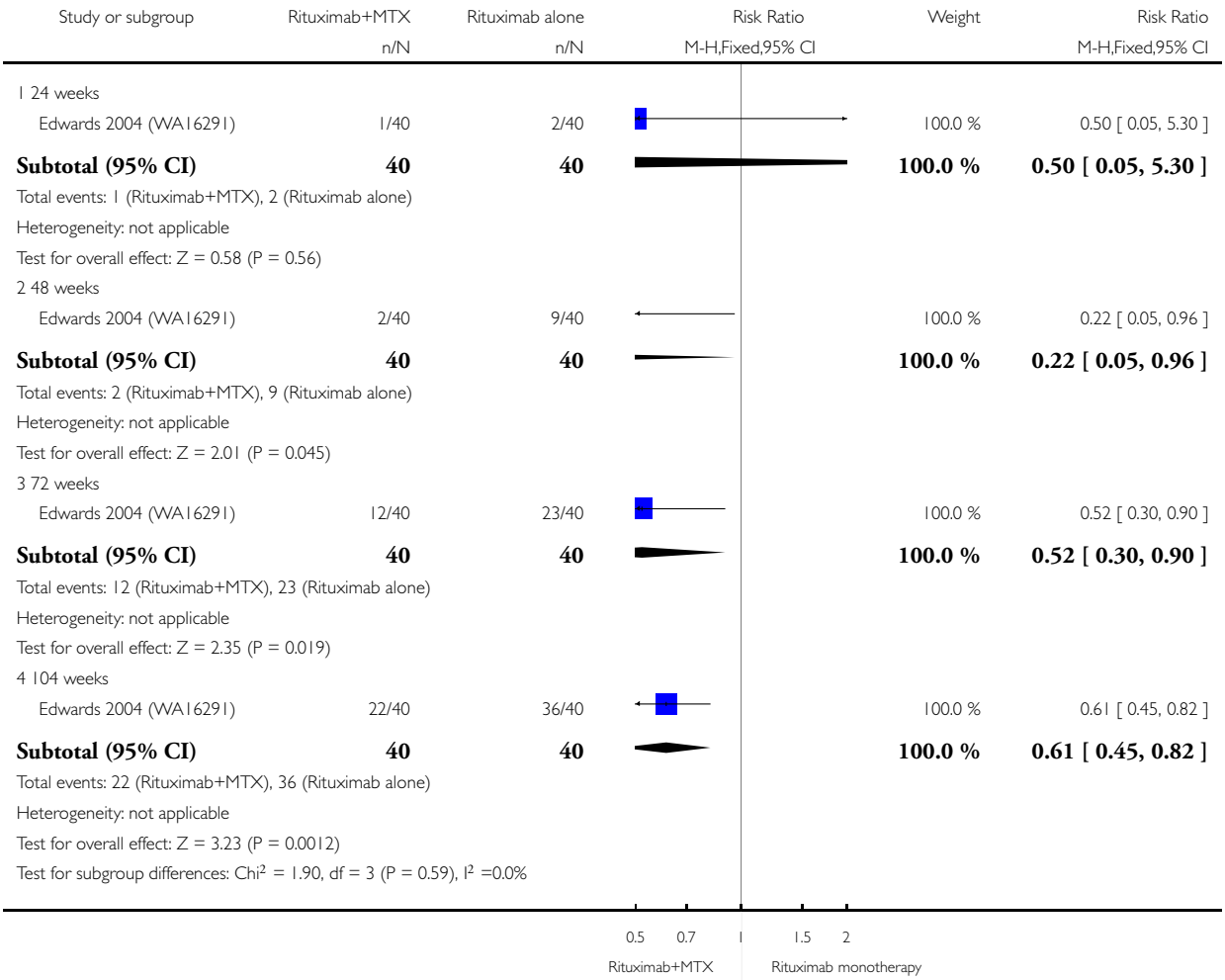
Analysis 21.8. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 8 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 8 Total discontinuations



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Analysis 21.9. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 9 Withdrawals due to lack of efficacy.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 9 Withdrawals due to lack of efficacy

Study or subgroup	Rituximab+MTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/40	0/40			Not estimable
Subtotal (95% CI)	**40**	**40**			**Not estimable**
Total events: 0 (Rituximab+MTX), 0 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 48 weeks					
Edwards 2004 (WA16291)	1/40	2/40		100.0 %	0.50 [0.05, 5.30]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.50 [0.05, 5.30]**
Total events: 1 (Rituximab+MTX), 2 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
3 72 weeks					
Edwards 2004 (WA16291)	4/40	3/40		100.0 %	1.33 [0.32, 5.58]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**1.33 [0.32, 5.58]**
Total events: 4 (Rituximab+MTX), 3 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.69)					
4 104 weeks					
Edwards 2004 (WA16291)	4/40	5/40		100.0 %	0.80 [0.23, 2.76]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.80 [0.23, 2.76]**
Total events: 4 (Rituximab+MTX), 5 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.72)					
Test for subgroup differences: Chi^2 = 0.56, df = 2 (P = 0.75), I^2 =0.0%					

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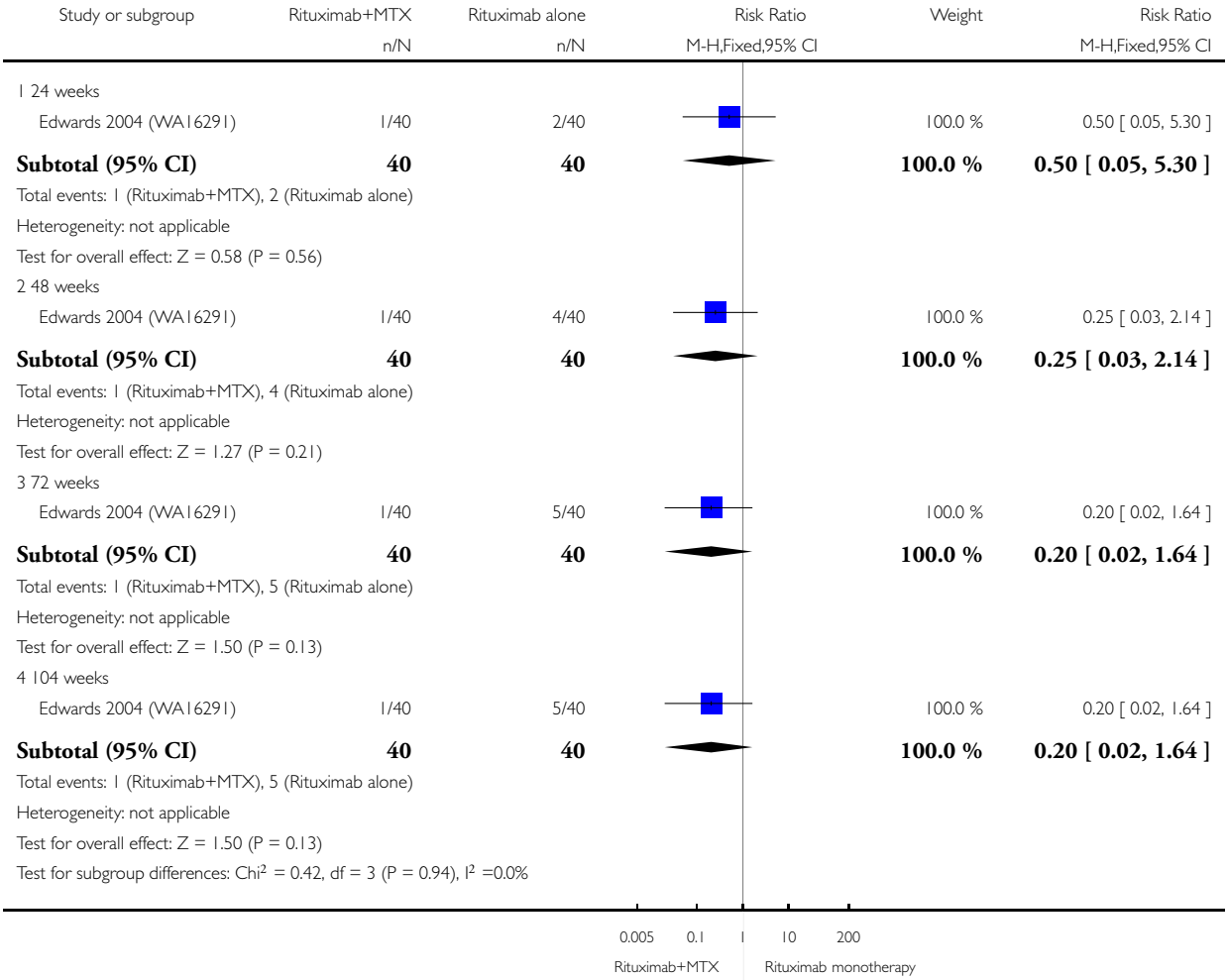
Analysis 21.10. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 10 Withdrawals due to adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 10 Withdrawals due to adverse Events



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Analysis 21.11. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 11 Withdrawals due to other reasons.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 11 Withdrawals due to other reasons

Study or subgroup	Rituximab+MTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/40	0/40			Not estimable
Subtotal (95% CI)	**40**	**40**			**Not estimable**
Total events: 0 (Rituximab+MTX), 0 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 48 weeks					
Edwards 2004 (WA16291)	0/40	3/40		100.0 %	0.14 [0.01, 2.68]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.14 [0.01, 2.68]**
Total events: 0 (Rituximab+MTX), 3 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
3 72 weeks					
Edwards 2004 (WA16291)	7/40	15/40		100.0 %	0.47 [0.21, 1.02]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.47 [0.21, 1.02]**
Total events: 7 (Rituximab+MTX), 15 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.91 (P = 0.056)					
4 104 weeks					
Edwards 2004 (WA16291)	17/40	26/40		100.0 %	0.65 [0.43, 1.00]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.65 [0.43, 1.00]**
Total events: 17 (Rituximab+MTX), 26 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.95 (P = 0.051)					
Test for subgroup differences: Chi^2 = 1.47, df = 2 (P = 0.48), I^2 =0.0%					

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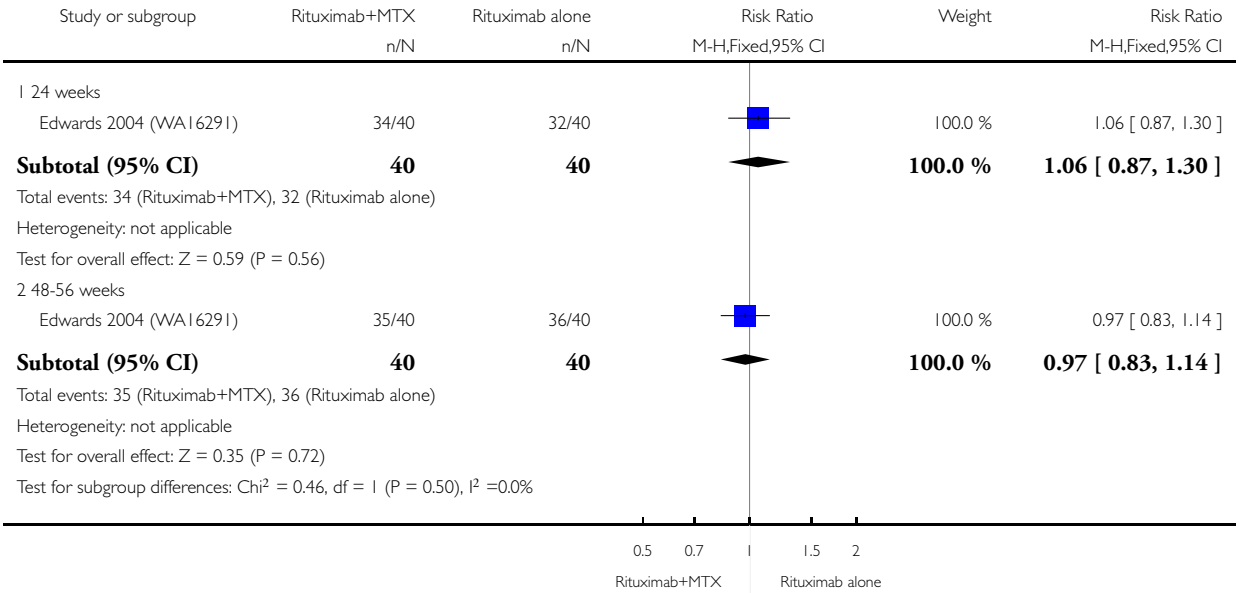
Analysis 21.12. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 12 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 12 Any Adverse Event



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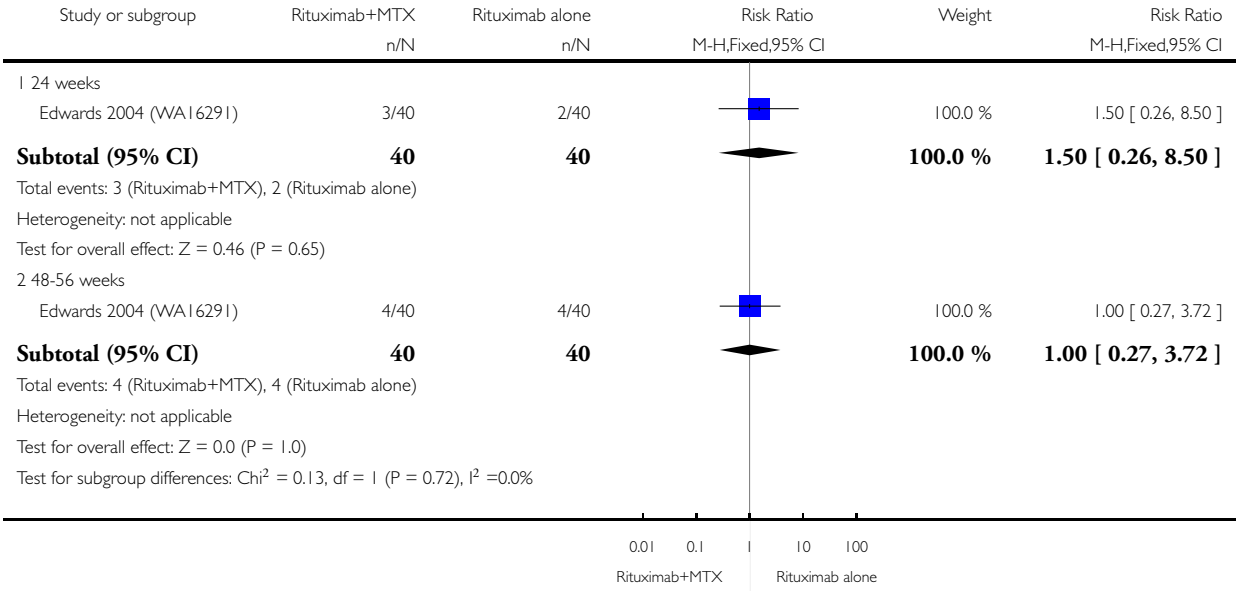
Analysis 21.13. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 13 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 13 Serious Adverse Events



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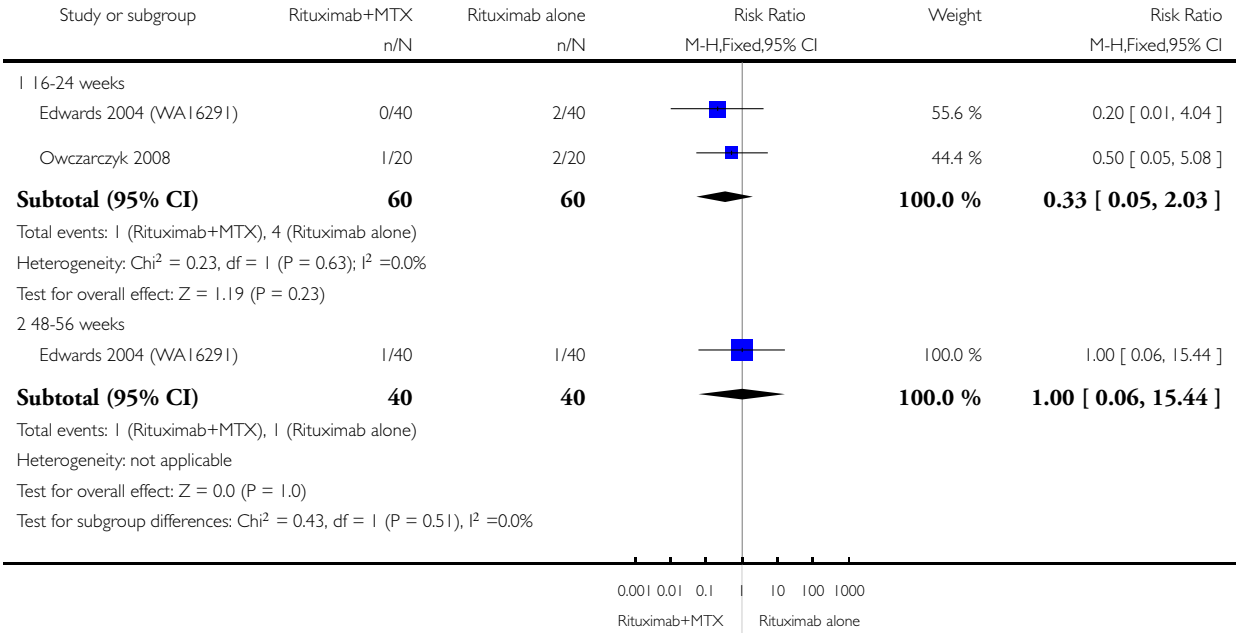
Analysis 21.14. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 14 Serious Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 14 Serious Infections



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Analysis 21.15. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 15 Death.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 15 Death

Study or subgroup	Rituximab+MTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/40	1/40		100.0 %	0.33 [0.01, 7.95]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.33 [0.01, 7.95]**
Total events: 0 (Rituximab+MTX), 1 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Not applicable					

Analysis 21.16. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 16 Any Event Associated with 1st Infusion.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 16 Any Event Associated with 1st Infusion

Study or subgroup	Rituximab+MTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 16-24 weeks					
Edwards 2004 (WA16291)	13/40	18/40		90.0 %	0.72 [0.41, 1.27]
Owczarczyk 2008	3/20	2/20		10.0 %	1.50 [0.28, 8.04]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**0.80 [0.47, 1.36]**
Total events: 16 (Rituximab+MTX), 20 (Rituximab alone)					
Heterogeneity: Chi^2 = 0.67, df = 1 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 0.82 (P = 0.41)					
Test for subgroup differences: Not applicable					

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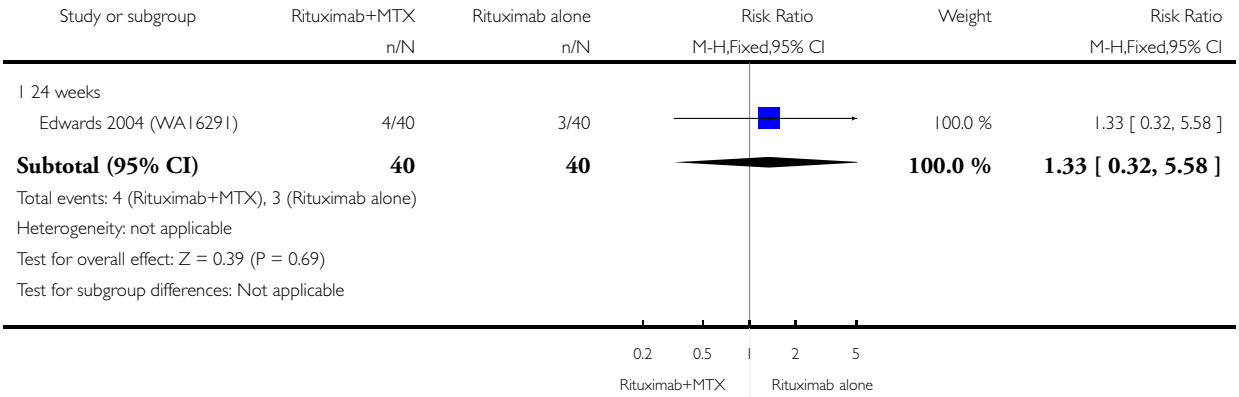
Analysis 21.17. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 17 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 17 Arthralgia



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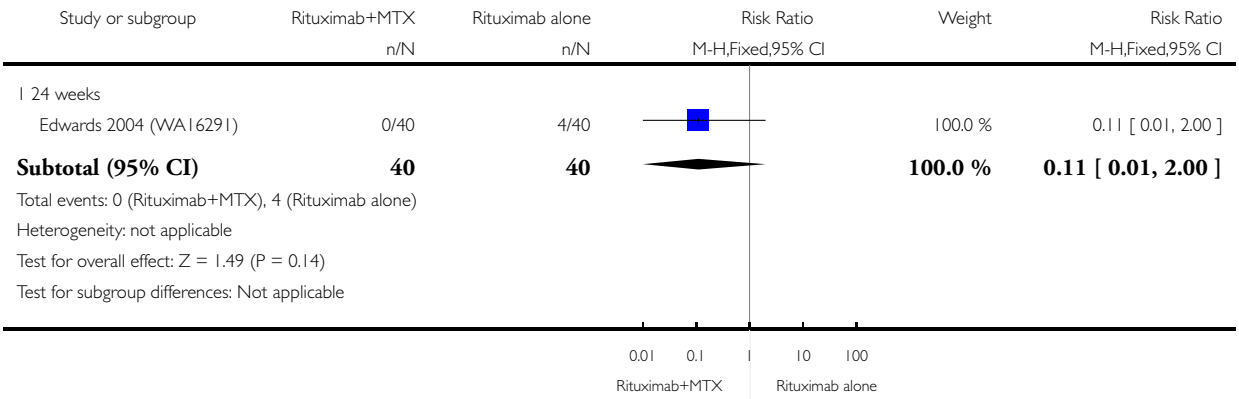
Analysis 21.18. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 18 Back pain.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 18 Back pain

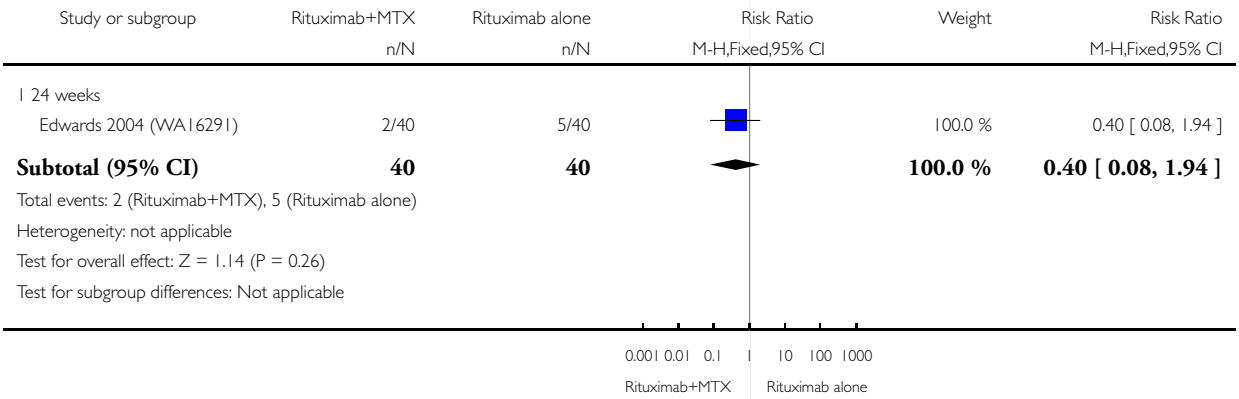


Analysis 21.19. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 19 Cough.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 19 Cough



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Analysis 21.20. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 20 Dyspnea.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 20 Dyspnea

Study or subgroup	Rituximab+MTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/40	4/40		100.0 %	0.11 [0.01, 2.00]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.11 [0.01, 2.00]**
Total events: 0 (Rituximab+MTX), 4 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.49 (P = 0.14)					
Test for subgroup differences: Not applicable					

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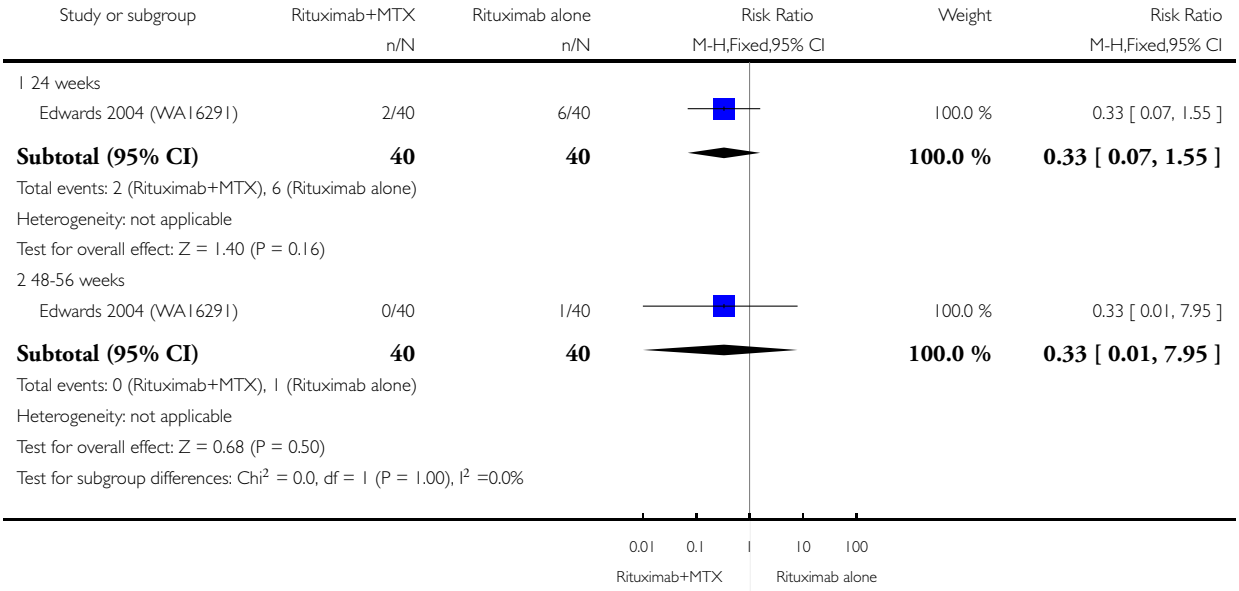
Analysis 21.21. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 21 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 21 Exacerbation of RA



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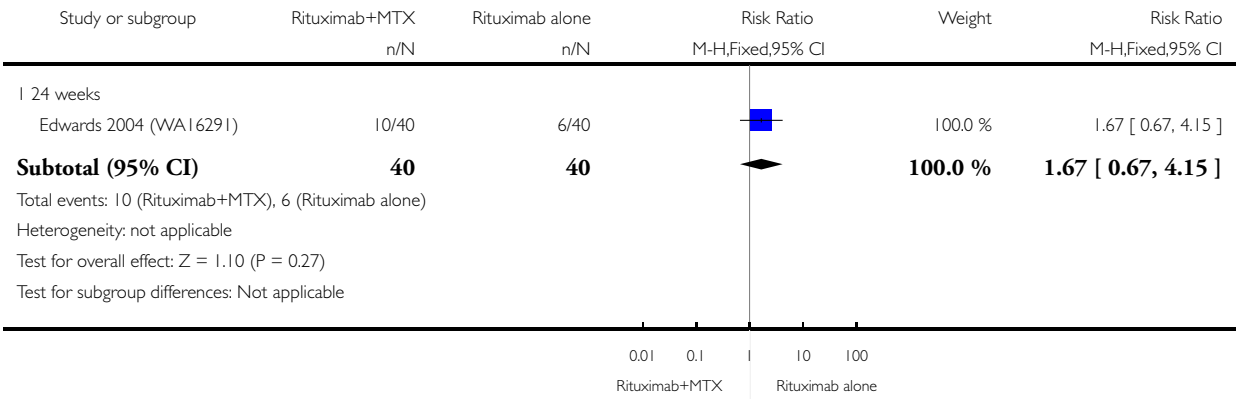
Analysis 21.22. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 22 Hypertension.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 22 Hypertension

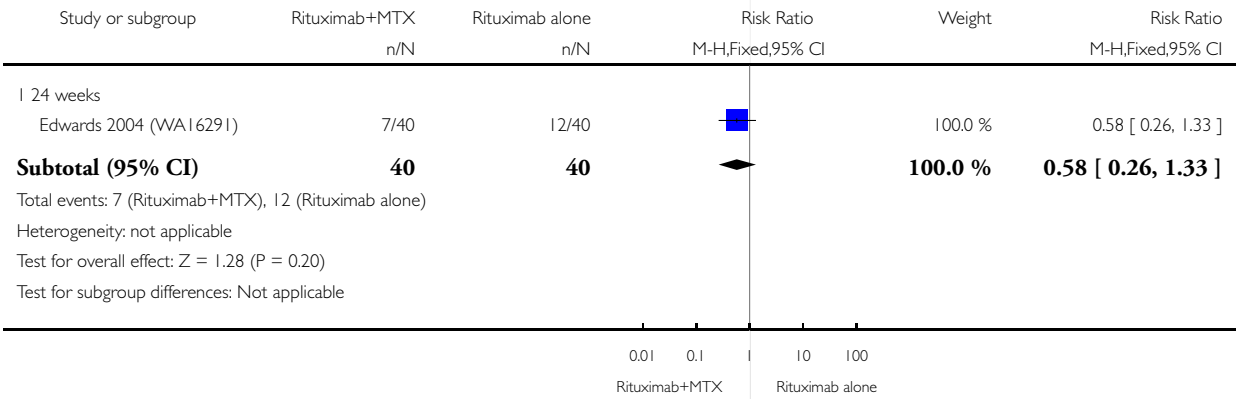


Analysis 21.23. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 23 Hypotension.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 23 Hypotension



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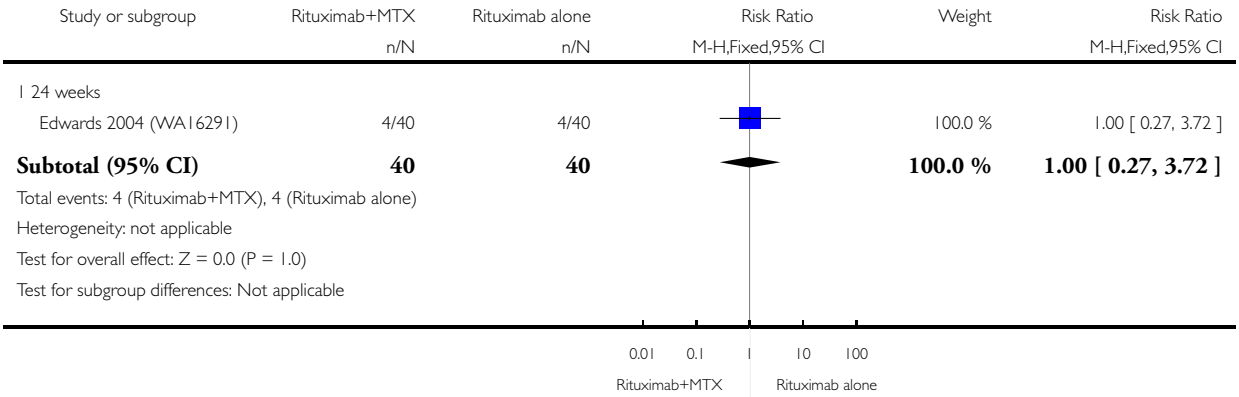
Analysis 21.24. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 24 Nasopharyngitis.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 24 Nasopharyngitis



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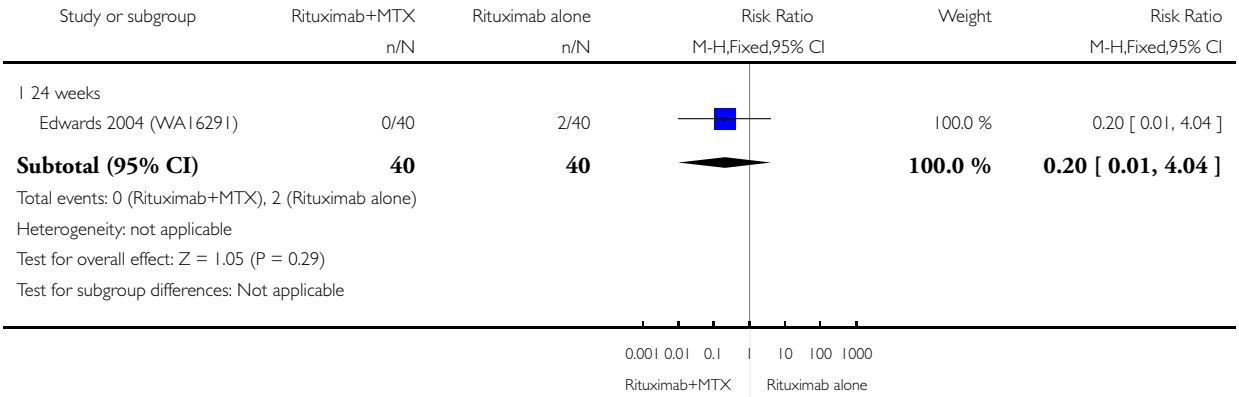
Analysis 21.25. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 25 Nausea.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 25 Nausea

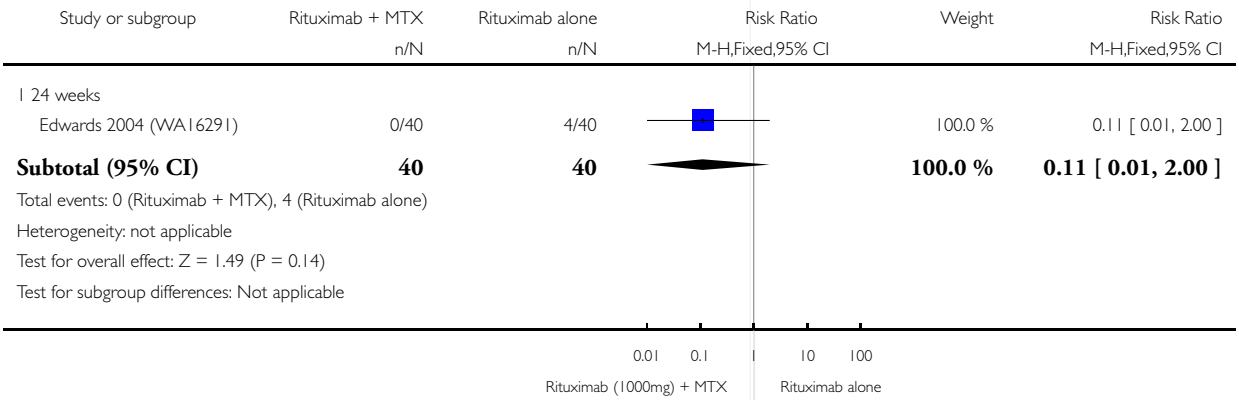


Analysis 21.26. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 26 Pruritus.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 26 Pruritus



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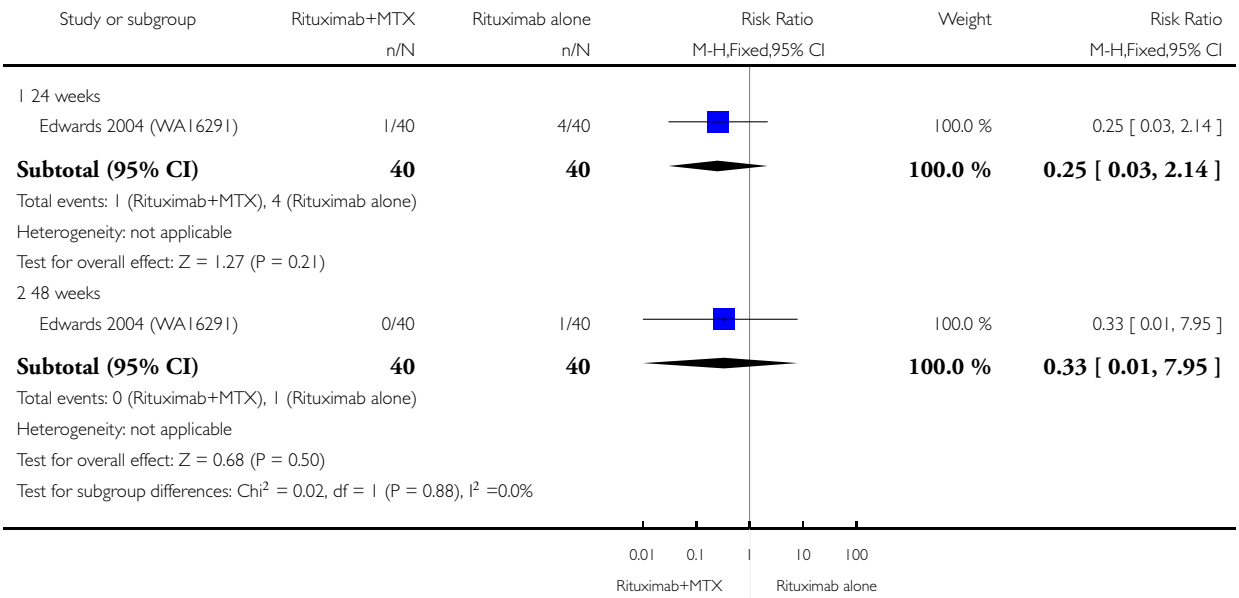
Analysis 21.27. Comparison 21 Concomitant treatment MTX versus none (sensitivity analysis), Outcome 27 Rash.

Review: Rituximab for rheumatoid arthritis

Comparison: 21 Concomitant treatment MTX versus none (sensitivity analysis)

Outcome: 27 Rash



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Analysis 22.1. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 1 ACR 20.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 1 ACR 20

Study or subgroup	Rituximab+CTX n/N	RTX monotherapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	31/41	26/40		100.0 %	1.16 [0.87, 1.55]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**1.16 [0.87, 1.55]**
Total events: 31 (Rituximab+CTX), 26 (RTX monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 48 weeks					
Edwards 2004 (WA16291)	20/41	13/40		100.0 %	1.50 [0.87, 2.59]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**1.50 [0.87, 2.59]**
Total events: 20 (Rituximab+CTX), 13 (RTX monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.46 (P = 0.14)					
3 104 weeks					
Edwards 2004 (WA16291)	5/41	3/40		100.0 %	1.63 [0.42, 6.36]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**1.63 [0.42, 6.36]**
Total events: 5 (Rituximab+CTX), 3 (RTX monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
Test for subgroup differences: Chi^2 = 0.81, df = 2 (P = 0.67), I^2 =0.0%					

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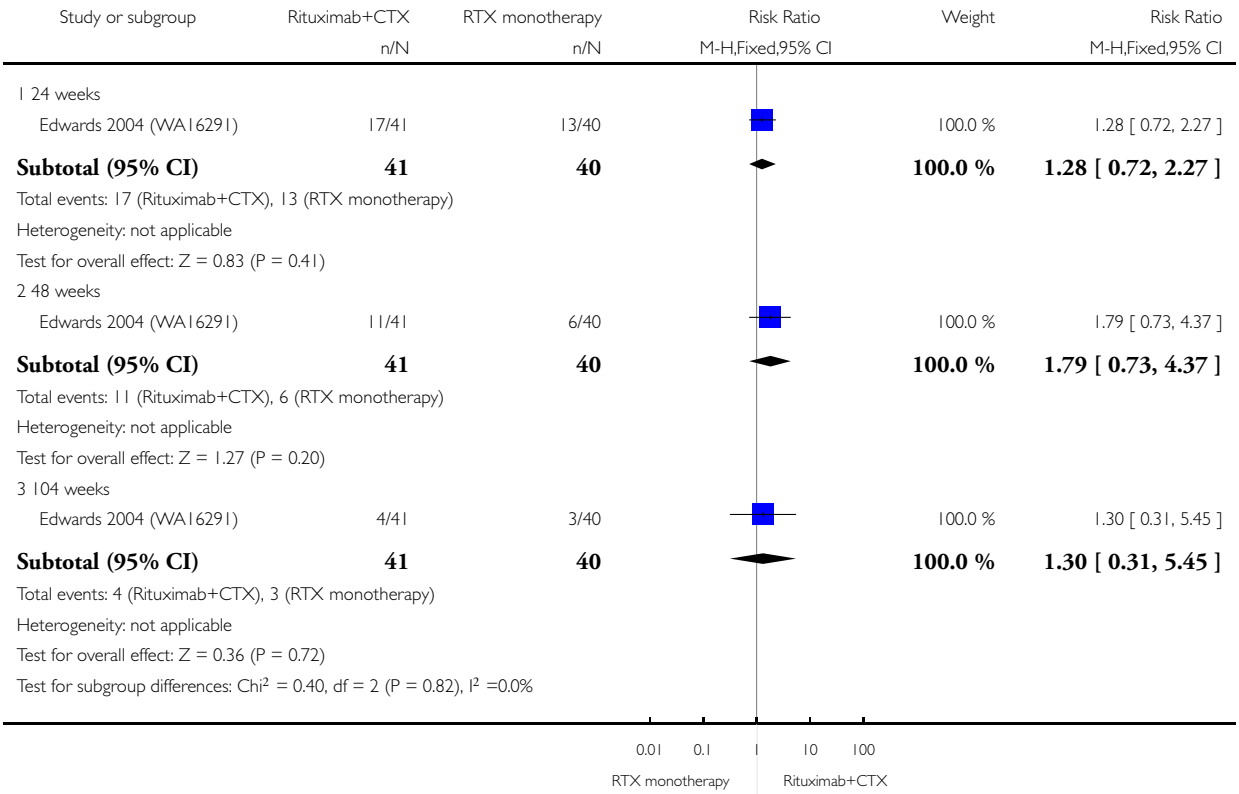
Analysis 22.2. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 2 ACR 50



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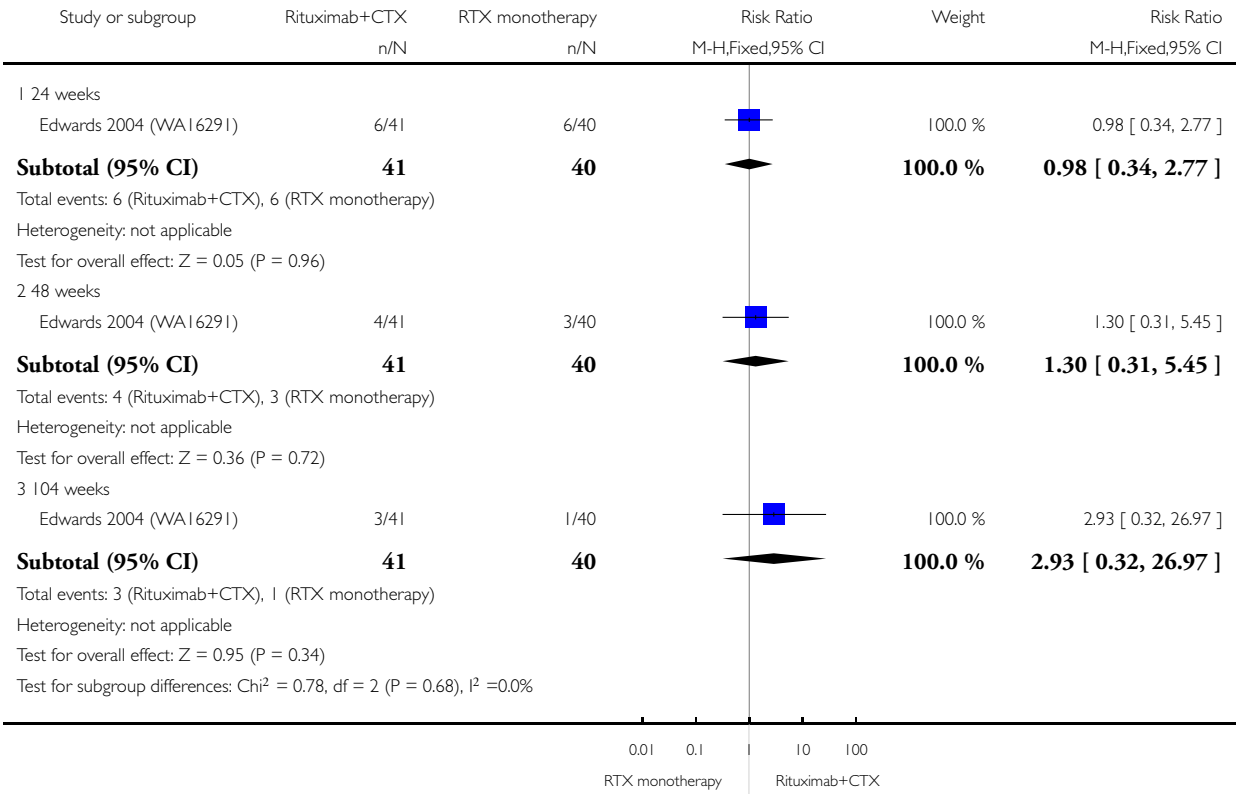
Analysis 22.3. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 3 ACR 70.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 3 ACR 70



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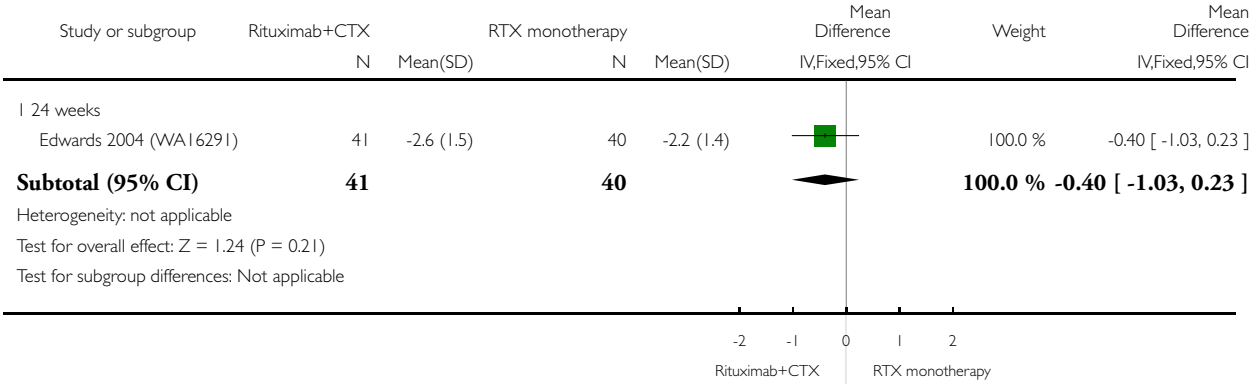
Analysis 22.4. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 4 DAS 28.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 4 DAS 28

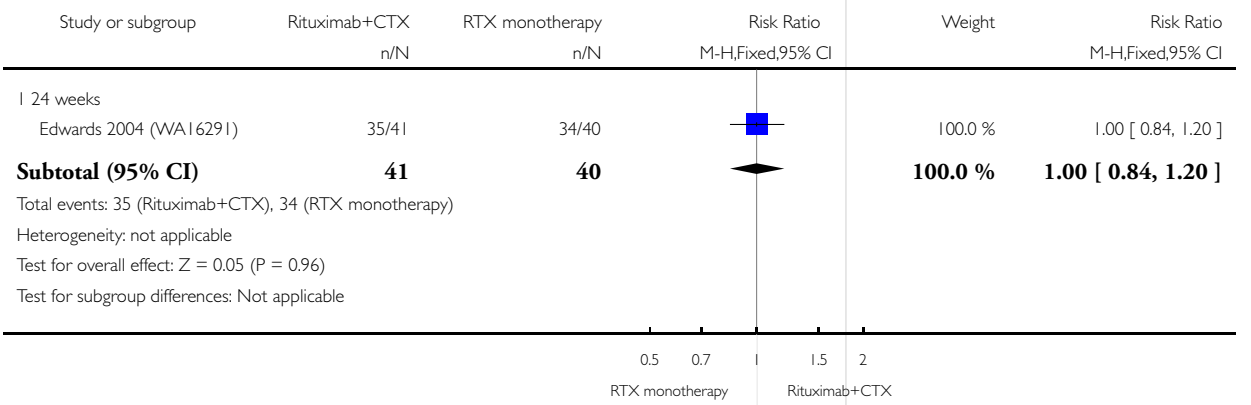


Analysis 22.5. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 5 Moderate or good EULAR response.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 5 Moderate or good EULAR response



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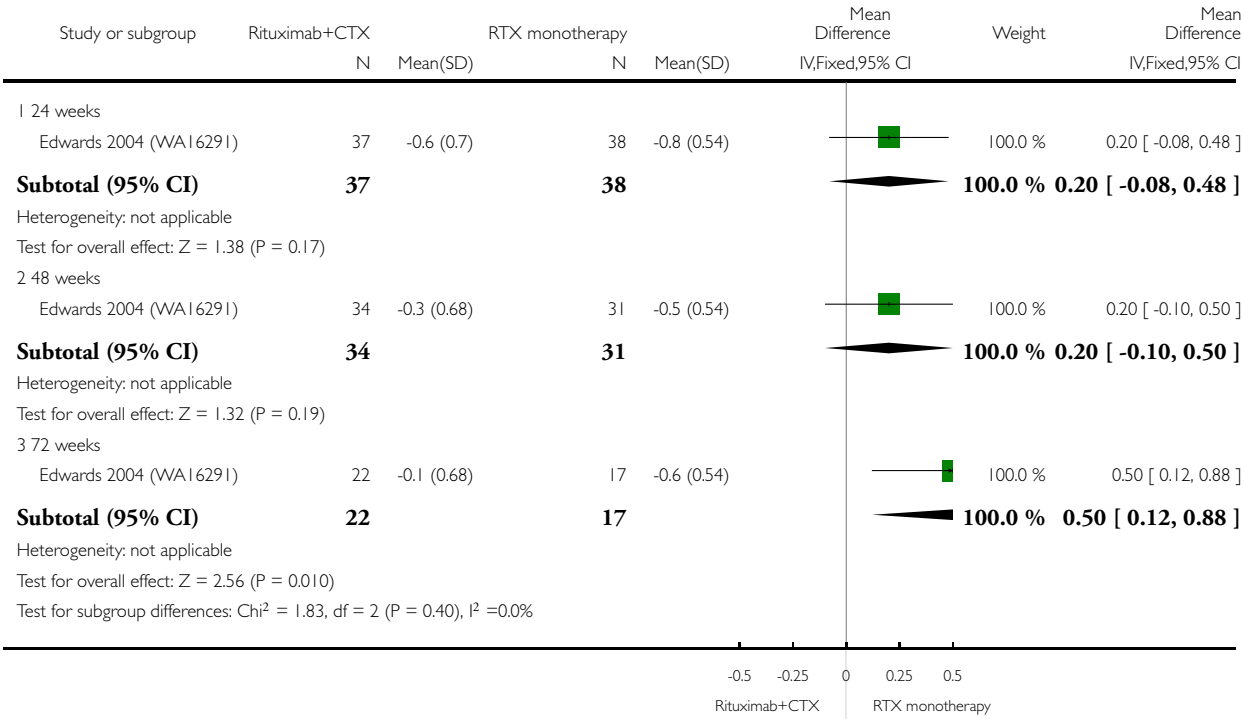
Analysis 22.6. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 6 HAQ-DI.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 6 HAQ-DI



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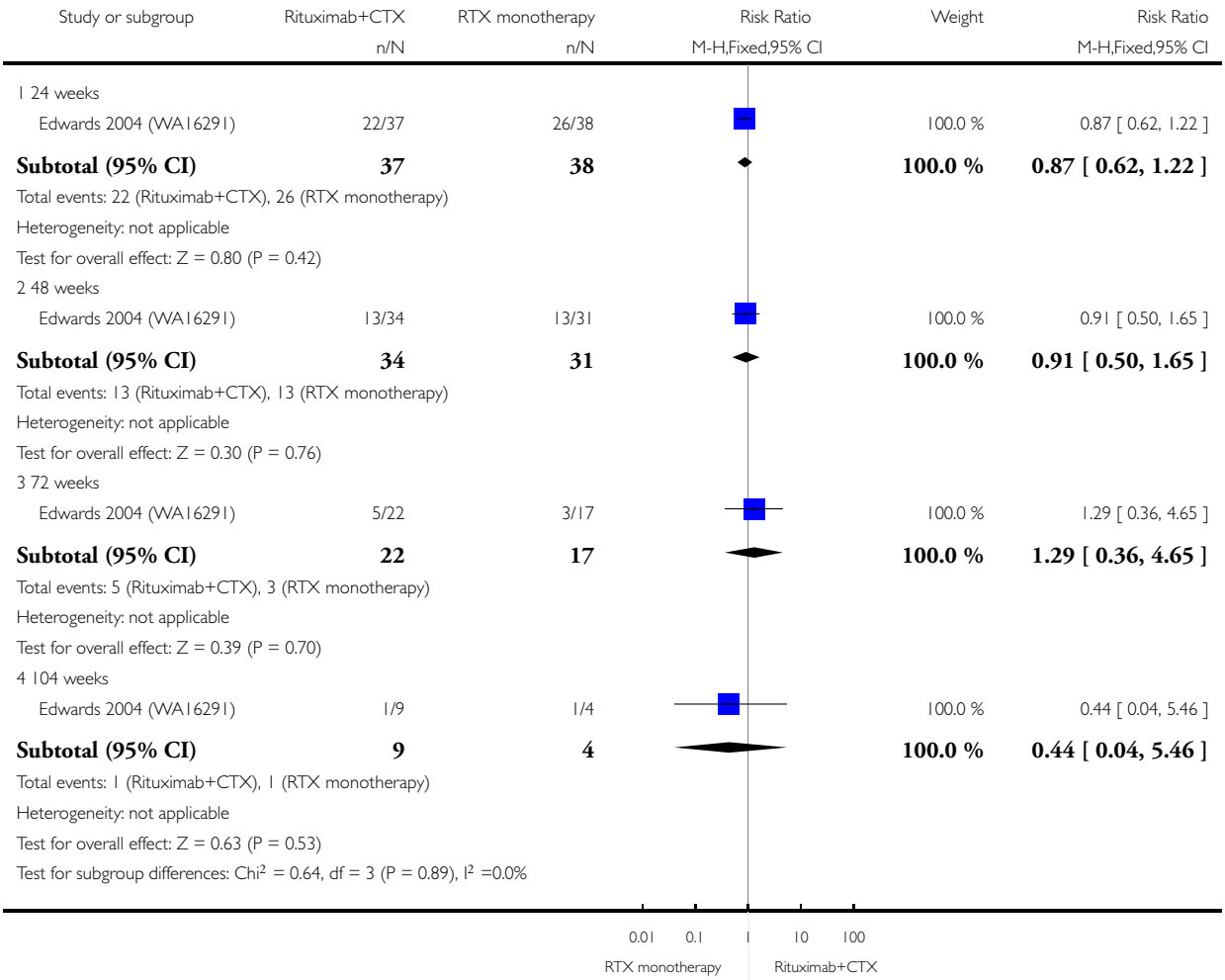
Analysis 22.7. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 7 HAQ-DI MCID=-0.22.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 7 HAQ-DI MCID=-0.22



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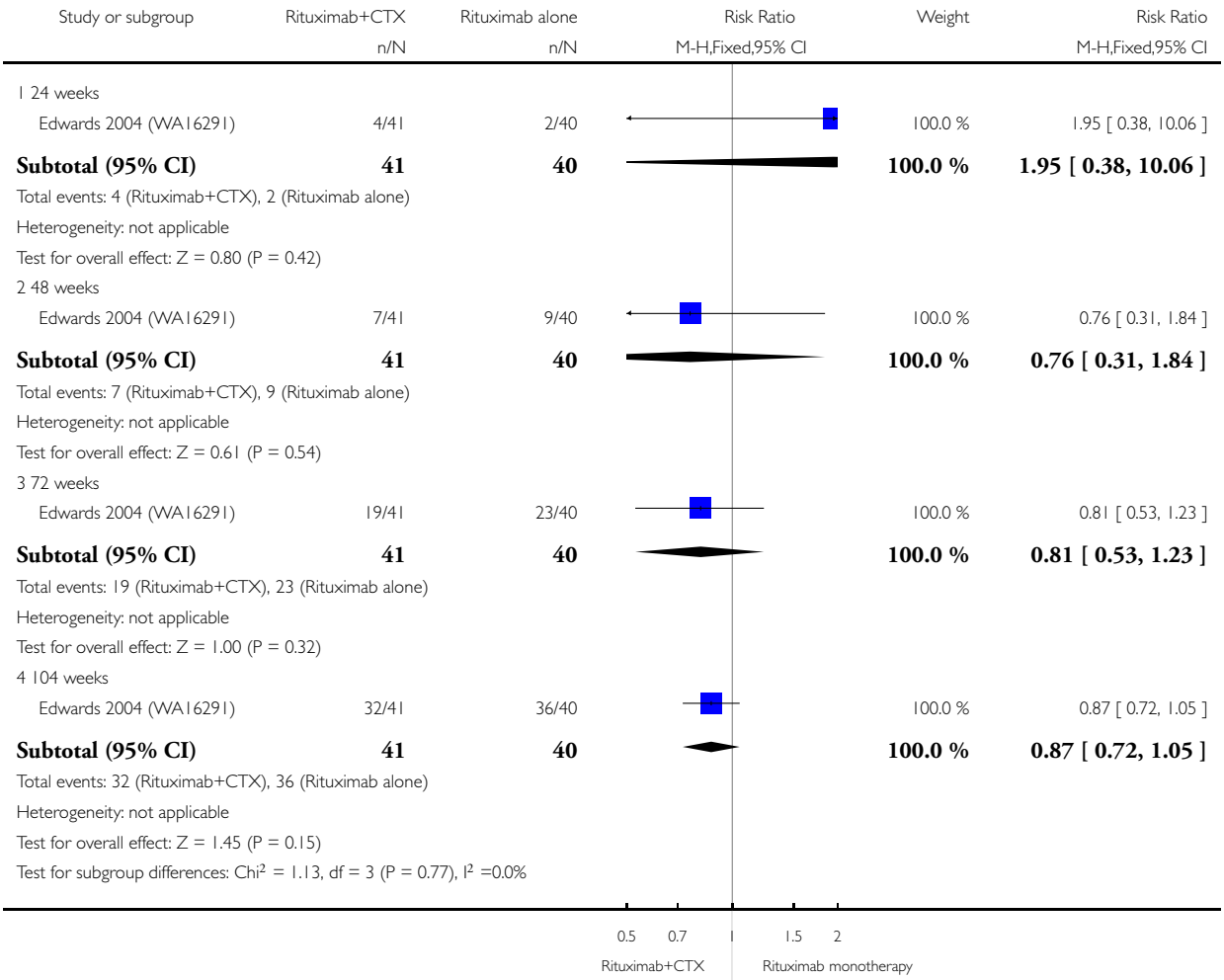
Analysis 22.8. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 8 Total discontinuations.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 8 Total discontinuations



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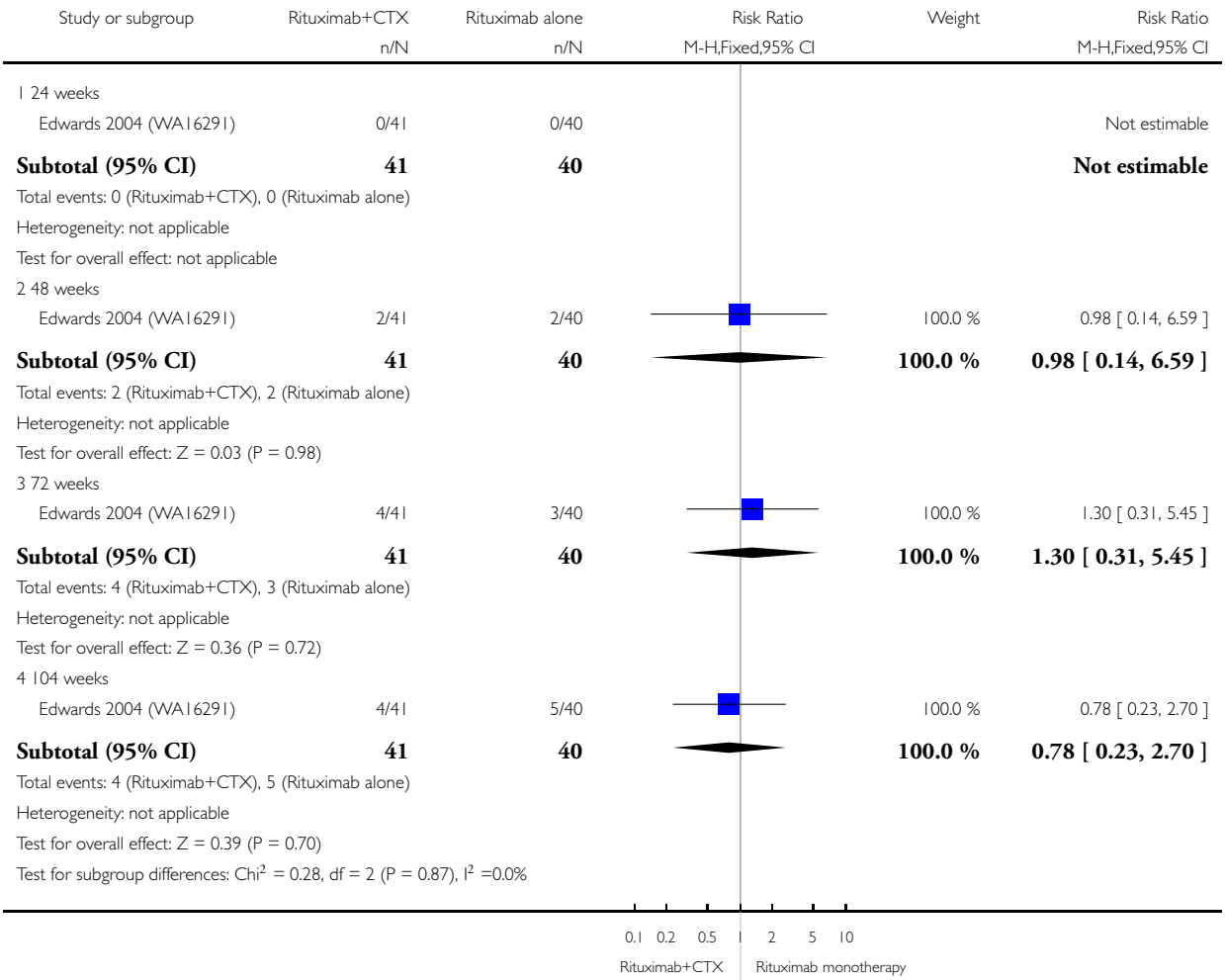
Analysis 22.9. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 9 Withdrawals due to lack of efficacy.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 9 Withdrawals due to lack of efficacy



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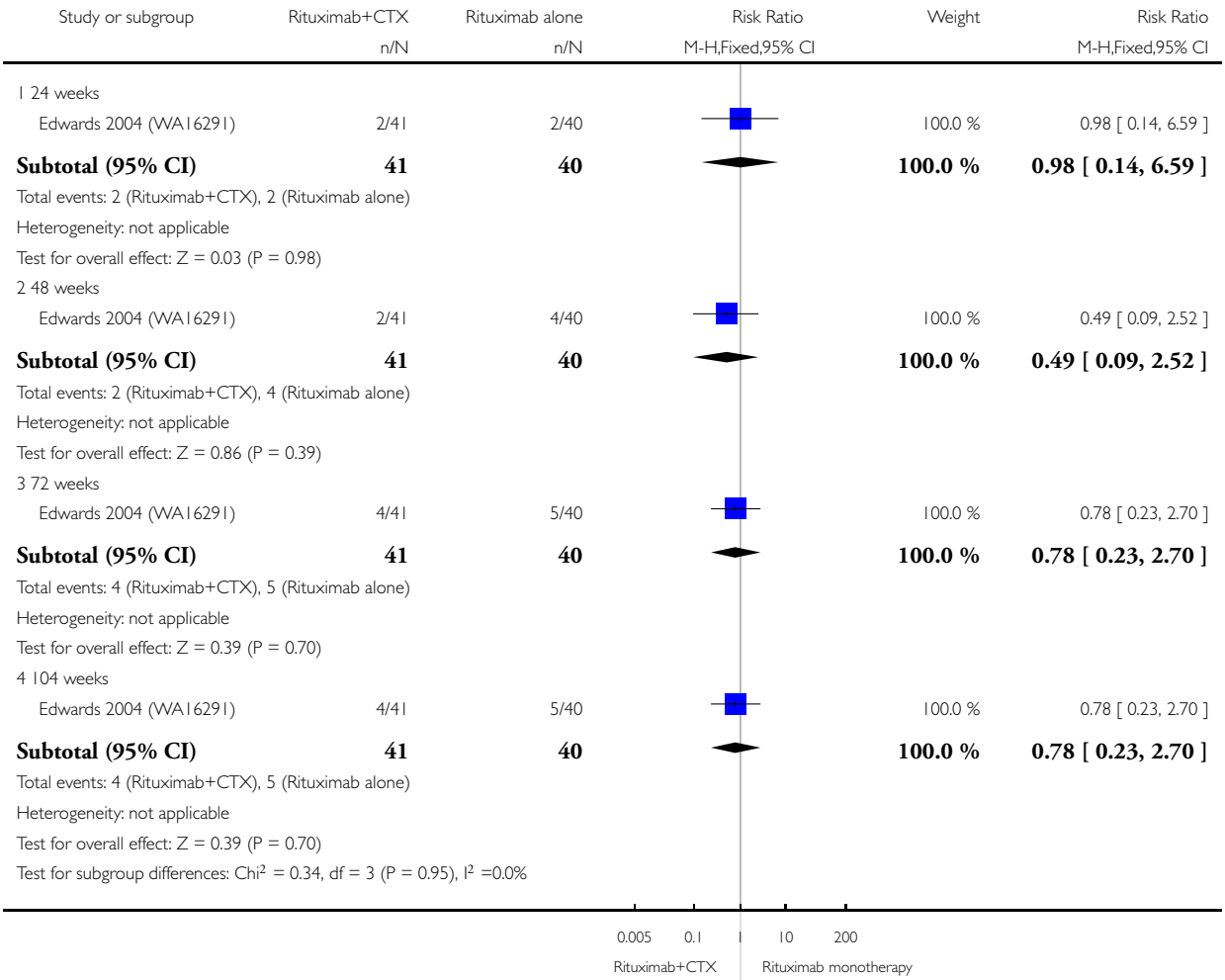
Analysis 22.10. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 10 Withdrawals due to adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 10 Withdrawals due to adverse Events



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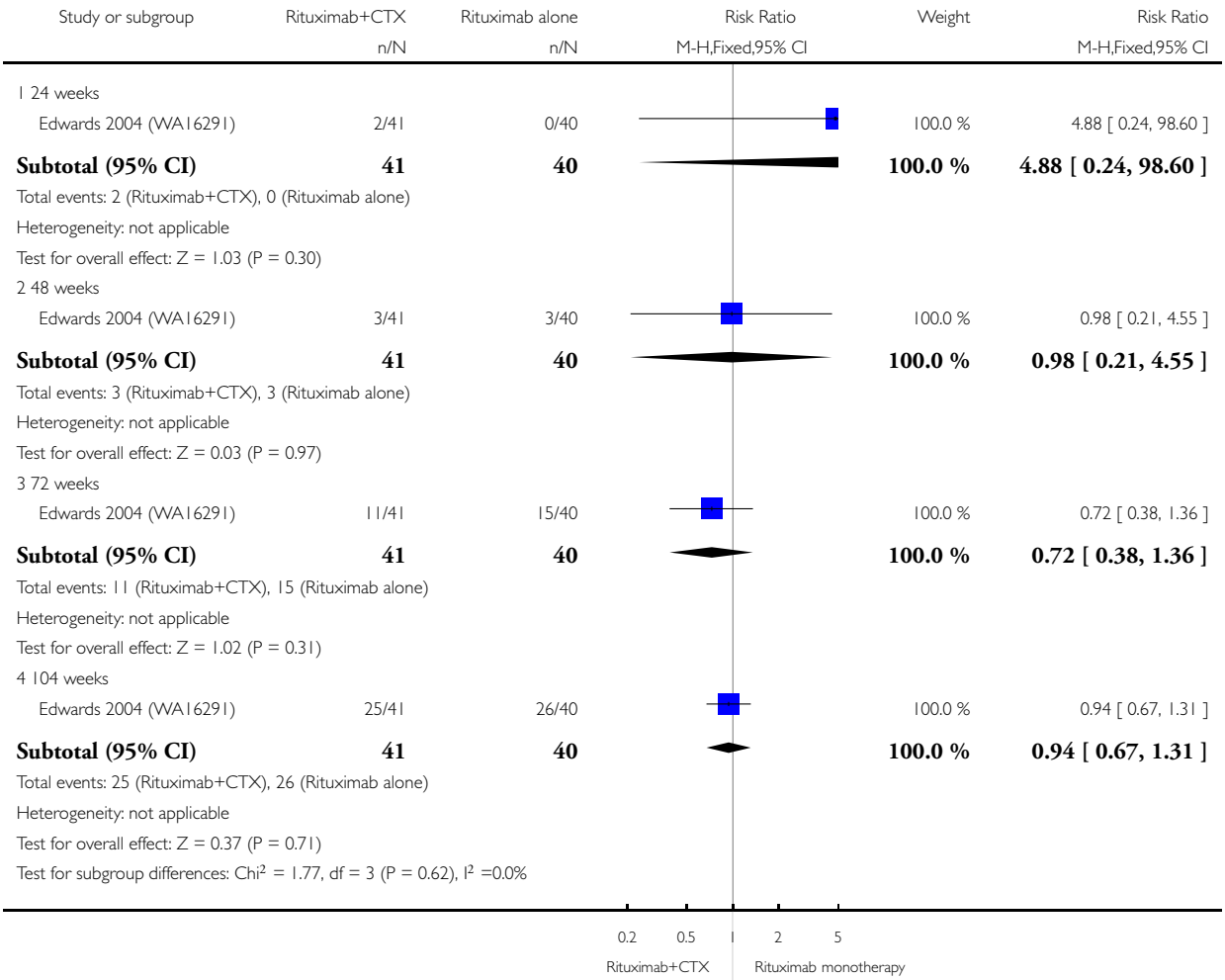
Analysis 22.11. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 11 Withdrawals due to other reasons.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 11 Withdrawals due to other reasons



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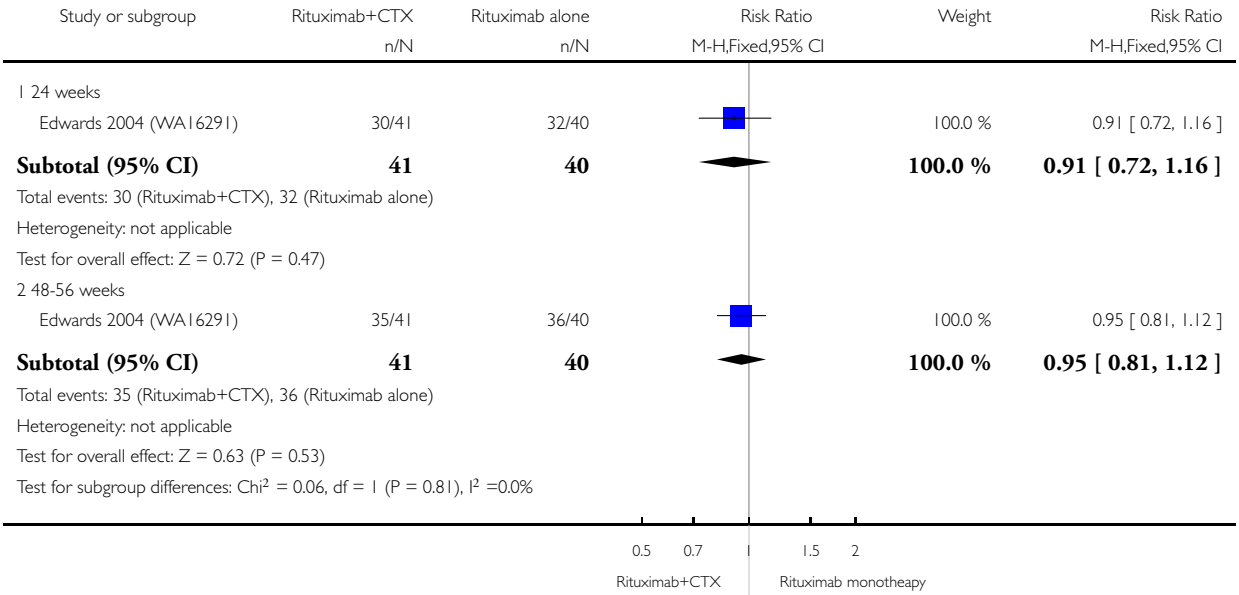
Analysis 22.12. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 12 Any Adverse Event.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 12 Any Adverse Event



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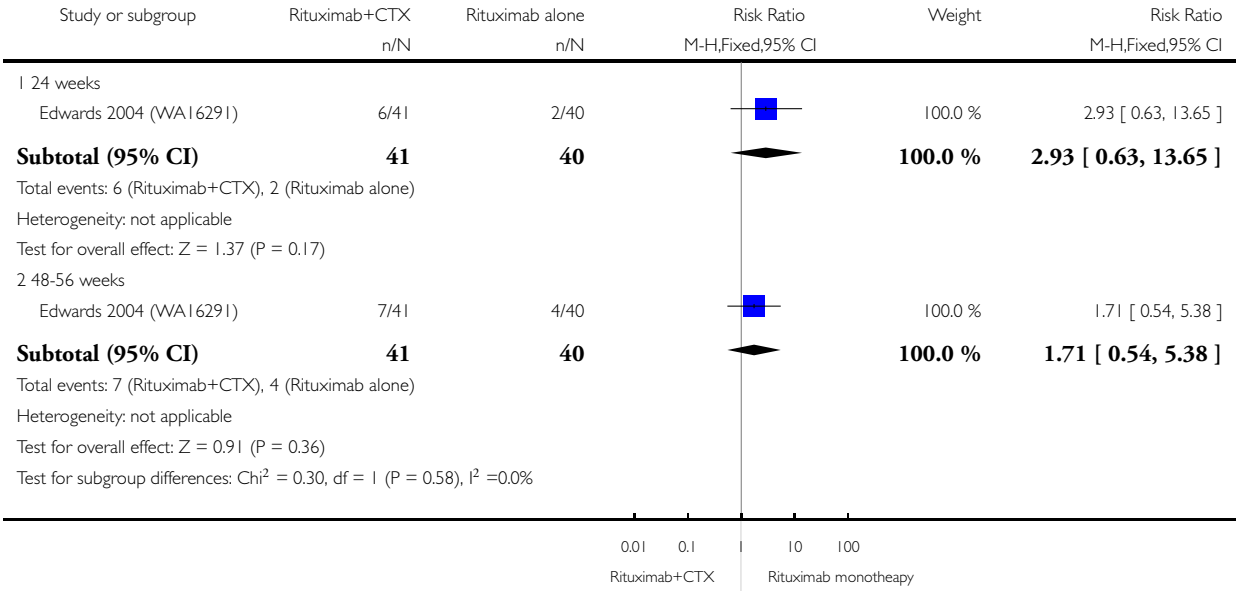
Analysis 22.13. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 13 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 13 Serious Adverse Events



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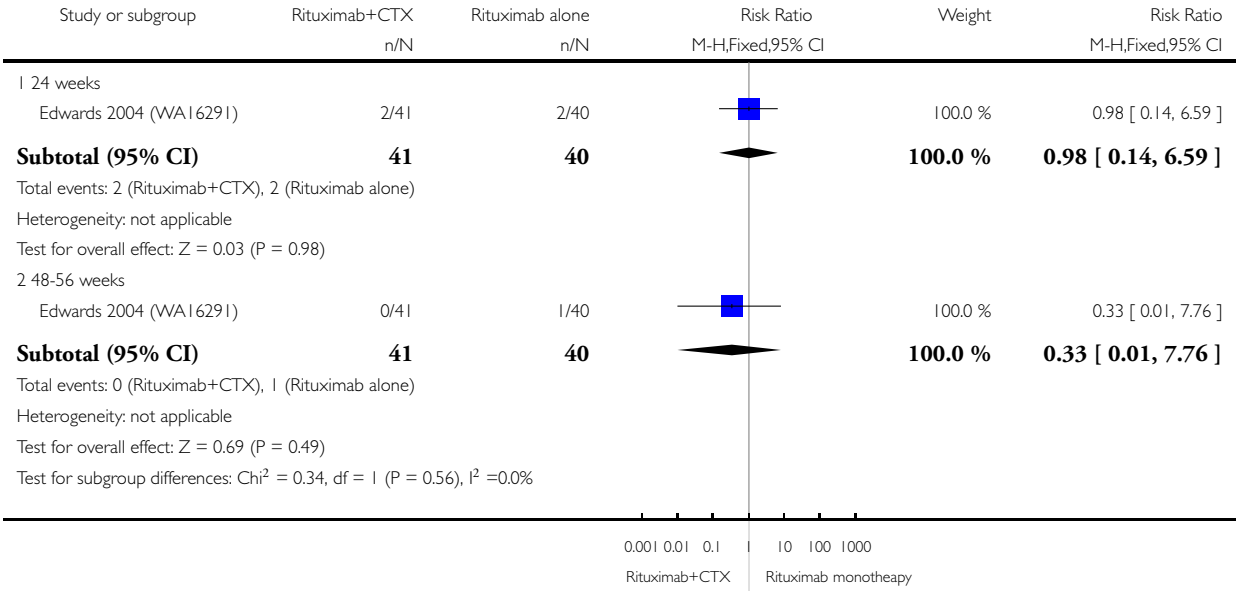
Analysis 22.14. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 14 Serious Infections.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 14 Serious Infections



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Analysis 22.15. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 15 Death.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 15 Death

Study or subgroup	Rituximab+CTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	0/41	1/40		100.0 %	0.33 [0.01, 7.76]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.33 [0.01, 7.76]**
Total events: 0 (Rituximab+CTX), 1 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					

Analysis 22.16. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 16 Any Event Associated with 1st Infusion.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 16 Any Event Associated with 1st Infusion

Study or subgroup	Rituximab+CTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	13/41	18/40		100.0 %	0.70 [0.40, 1.24]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.70 [0.40, 1.24]**
Total events: 13 (Rituximab+CTX), 18 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.21 (P = 0.22)					
Test for subgroup differences: Not applicable					

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Analysis 22.17. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 17 Arthralgia.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 17 Arthralgia

Study or subgroup	Rituximab+CTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	1/41	3/40		100.0 %	0.33 [0.04, 3.00]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.33 [0.04, 3.00]**
Total events: 1 (Rituximab+CTX), 3 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					
Test for subgroup differences: Not applicable					

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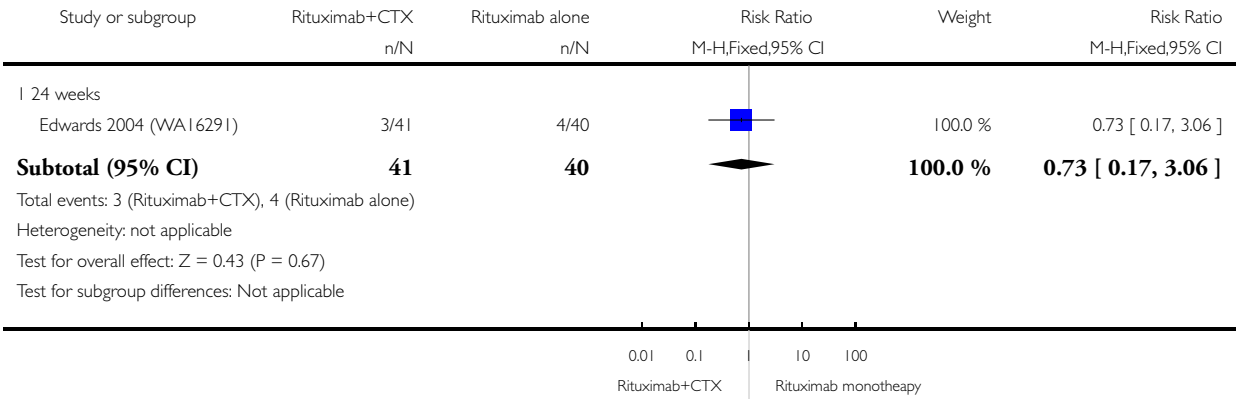
Analysis 22.18. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 18 Back pain.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 18 Back pain

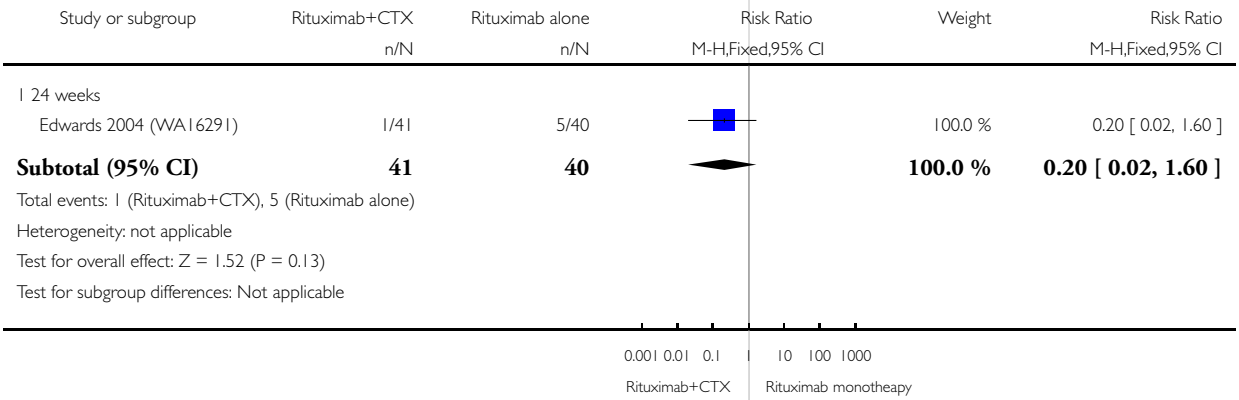


Analysis 22.19. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 19 Cough.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 19 Cough



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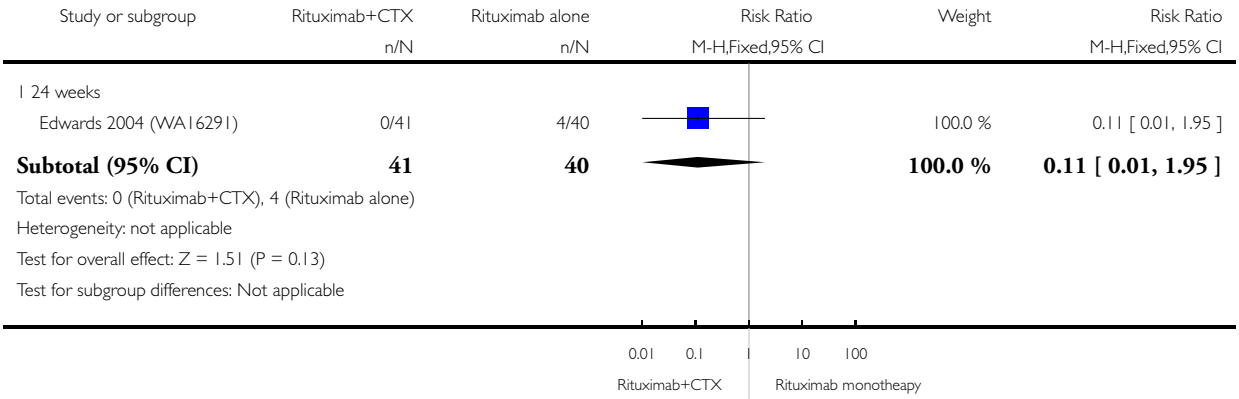
Analysis 22.20. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 20 Dyspnea.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 20 Dyspnea



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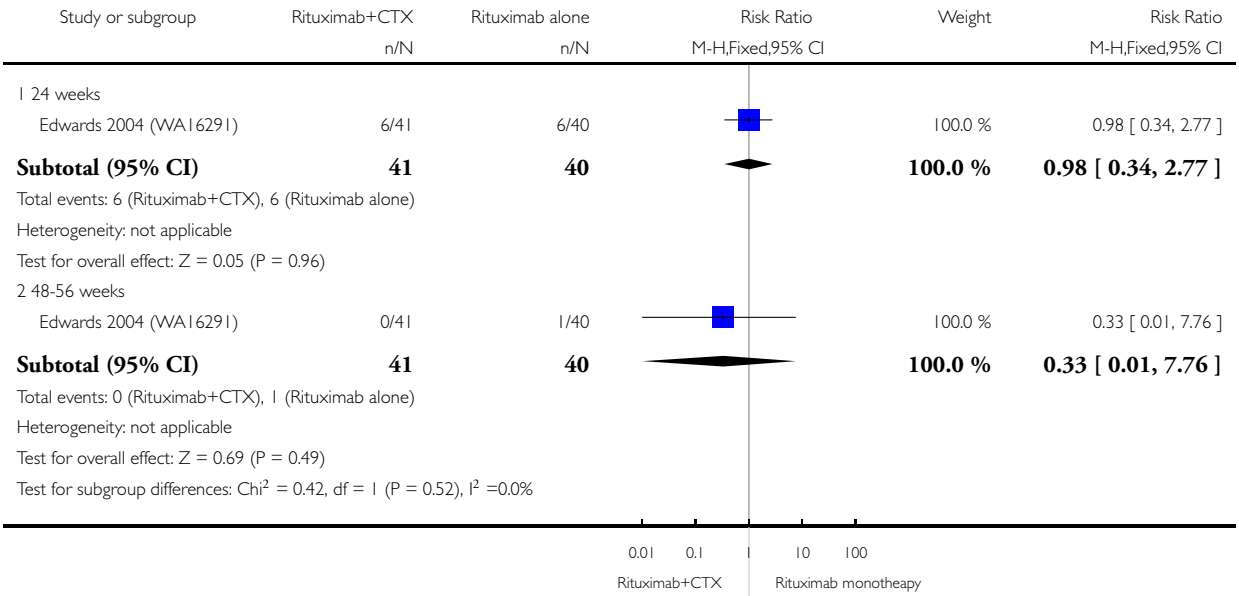
Analysis 22.21. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 21 Exacerbation of RA.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 21 Exacerbation of RA



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Analysis 22.22. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 22 Hypertension.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 22 Hypertension

Study or subgroup	Rituximab+CTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	3/41	6/40		100.0 %	0.49 [0.13, 1.82]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.49 [0.13, 1.82]**
Total events: 3 (Rituximab+CTX), 6 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					
Test for subgroup differences: Not applicable					

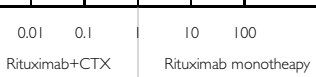
Analysis 22.23. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 23 Hypotension.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 23 Hypotension

Study or subgroup	Rituximab+CTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	12/41	12/40		100.0 %	0.98 [0.50, 1.91]
Subtotal (95% CI)	**41**	**40**		**100.0 %**	**0.98 [0.50, 1.91]**
Total events: 12 (Rituximab+CTX), 12 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.07 (P = 0.94)					
Test for subgroup differences: Not applicable					



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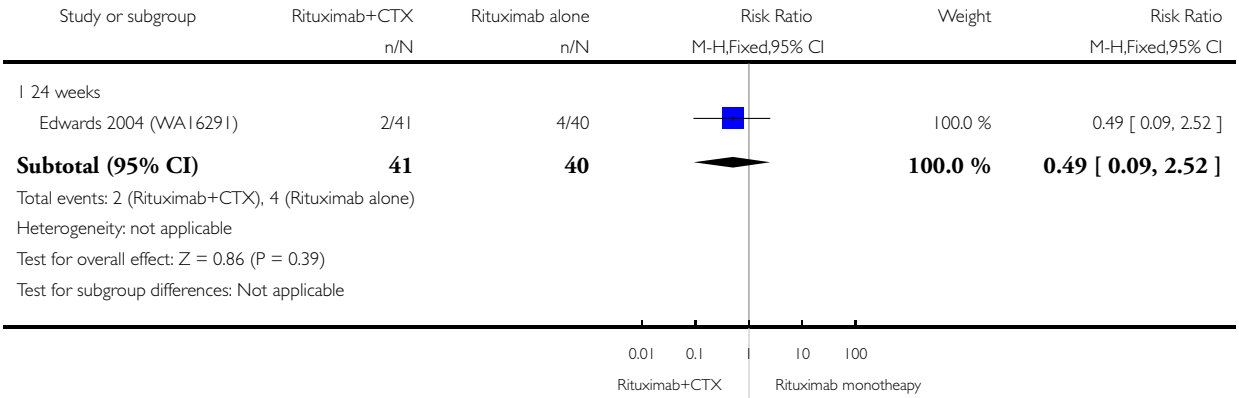
Analysis 22.24. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 24 Nasopharyngitis.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 24 Nasopharyngitis



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Analysis 22.25. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 25 Nausea.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 25 Nausea

Study or subgroup	Rituximab+CTX n/N	Rituximab alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Edwards 2004 (WA16291)	4/40	2/40		100.0 %	2.00 [0.39, 10.31]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**2.00 [0.39, 10.31]**
Total events: 4 (Rituximab+CTX), 2 (Rituximab alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					
Test for subgroup differences: Not applicable					

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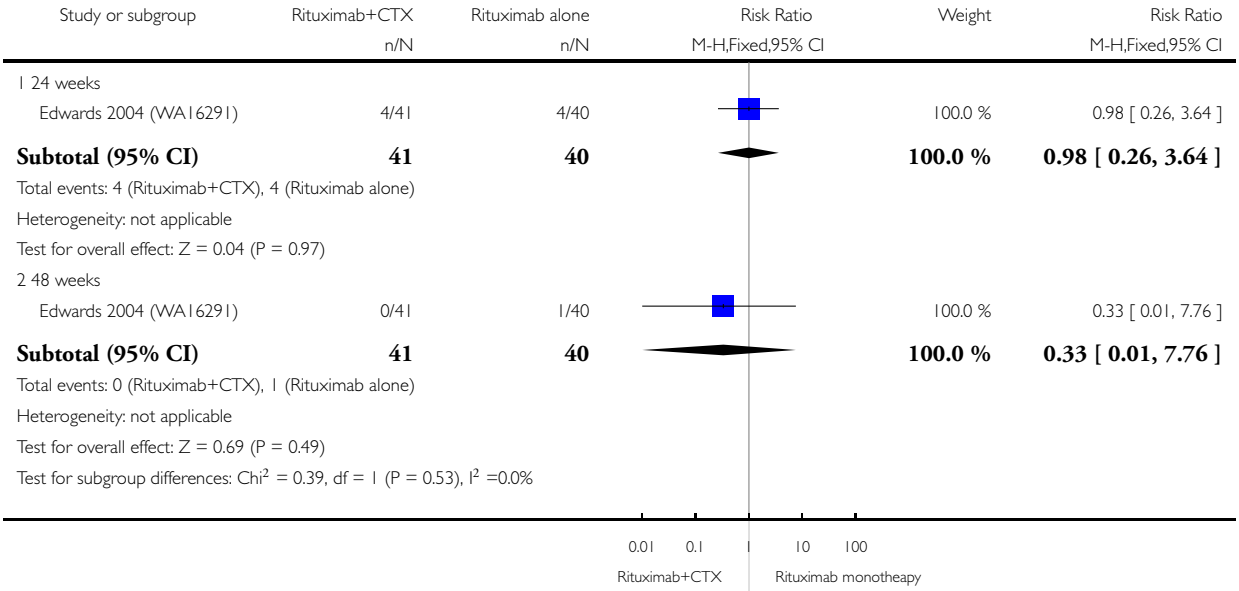
Analysis 22.26. Comparison 22 Concomitant treatment CTX versus none (sensitivity analysis), Outcome 26 Rash.

Review: Rituximab for rheumatoid arthritis

Comparison: 22 Concomitant treatment CTX versus none (sensitivity analysis)

Outcome: 26 Rash



ADDITIONAL TABLES

Table 1. Baseline patient characteristics

Study	Arms	n	Age, mean + SD*	Females, %	Disease duration, mean years	Rheumatoid factor, mean IU/litre	Previous DMARDs, mean no	Prior anti-TNFα treatment, %	MTX dose, mean mg/week
Cohen 2006 (REFLEX)	PBO + MTX	209	52.8 ± 12.6	81	11.7 ± 7.7	317.4 ± 870.2	2.4 ± 1.8	90†	16.7 ± 9.9
	RTX 2 (100 mg courses) + MTX	308	52.2 ± 12.2	81	12.1 ± 8.3	324.3 ± 613.5	2.6 ± 1.8	92†	16.4 ± 8.8
Edwards 2004	PBO + MTX	40	54 ± 11	80	11 ± 7	-	2.6 ± 1.3	-	12.5 to 15‡

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Table 1. Baseline patient characteristics (*Continued*)

(WA16291)									
	RTX 2 (100 mg courses) + MTX	40	53 ± 10	75	12 ± 7	-	2.5 ± 1.4	-	12.5 to 15‡
	RTX 2 (100 mg courses)	40	54 ± 10	73	9 ± 6	-	2.5 ± 1.6	-	12.5 to 15‡
	RTX 2 (100 mg courses) + CTX	41	54 ± 12	83	10 ± 6	-	2.6 ± 1.4	-	12.5 to 15‡
Emery 2006 (DANCER)	PBO + MTX	149	51.1	80	9.3	437	2.2	26	15.6
	RTX 2 (500 mg courses) + MTX	124	51.4	83	11.1	421	2.5	33	16
	RTX 2 (100 mg courses) + MTX	192	51.1	80	10.8	437	2.5	28	14.9
Emery 2010 (SERENE)	PBO + MTX	172	52.2 ± 12.4	85.5	7.5 ± 7.6	75.0% positive	1.1 ± 1.1[c]	-	16.6 ± 4.3
	RTX 2 (500 mg courses) + MTX	167	51.9 ± 12.9	79.6	7.1 ± 7.0	75.4% positive	1.2 ± 1.3[c]	-	15.4 ± 4.0
	RTX 2 (1000 mg courses) + MTX	170	51.3 ± 12.6	81.2	6.6 ± 7.3	73.5% positive	1.1 ± 1.1[c]	-	16.1 ± 4.3
Greenwald 2011 (TAME)	MTX + TNFi	18	50.4	94	10.7 ± 7.5	178.6 ± 242.8	-	100	17.5 ± 4.2
	RTX 2 (500 mg courses) + MTX +	32	49.7	85	10.3 ± 6.7	341.9 ± 521.0	-	97	16.1 ± 4.2

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Table 1. Baseline patient characteristics (*Continued*)

	TNFi								
Owczarczyl 2008	RTX	20	55 ± 9	-	12 ± 8	329 ± 724	-	1.47 ± 1.17	-
	RTX + MTX	20	53 ± 12	-	9 ± 9.6	479 ± 574	-	0.45 ± 0.75	-
Rubbert-Roth 2010 (MIR-ROR)	RTX (500 mg courses) + MTX	134	53.6 ± 12.8	82.1	9 + 7.4	235.5 ± 4. 16	2.0 ± 1.5	27.6	15.2 ± 4.7
	RTX 2 (1000mg courses) + MTX	93	51.3 ± 12.2	82.8	7.7 + 7.4	232.4 ± 366.1	1.8 ± 1.4	24.6	15.2 ± 4.7
Tak 2010 (IMAGE)	PBO + MTX	249	48.1 ± 12.7	77	0.91 (1.1)	87% positive	70% DMARD-naive	-	-
	RTX 2 (500 mg courses) + MTX	249	47.9 ± 13.4	82	0.99 (1.1)	87% positive	72% DMARD-naive	-	-
	RTX 2 (1000 mg courses) + MTX	250	47.9 ± 13.3	85	0.92 (1.3)	85% positive	69% DMARD-naive	-	-

*when reported

†Inadequate efficacy of anti-TNF agents (%)

‡ Median dose per week

[a] Patients were followed 36 weeks in the group receiving rituximab plus MTX and 12 weeks in the group receiving MTX monotherapy

[b] An upper age limit of 65 years was used because of known attenuation of vaccine response in older patients

[c] Excludes MTX

DMARD = Disease Modifying Anti-Rheumatic Drug; mg = milligrams; MTX = methotrexate; PBO = placebo; RTX = rituximab.

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APPENDICES

Appendix 1. Search strategy

MEDLINE

1. exp arthritis, rheumatoid/
2. (felty$ adj2 syndrome).tw.
3. (caplan$ adj2 syndrome).tw.
4. rheumatoid nodule.tw.
5. (sjogren$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still$ disease.tw.
8. bechterew$ disease.tw.
9. (arthritis adj2 rheumat$).tw.
10. or/1-9
11. Antibodies, Monoclonal/
12. Immunologic Factors/
13. rituximab.tw.
14. rituxan.tw.
15. mabthera.tw.
16. or/11-15
17. 10 and 16
18. clinical trial.pt.
19. randomized.ab.
20. placebo.ab.
21. dt.fs.
22. clinical trials/
23. randomly.ab.
24. trial.ti.
25. groups.ab.
26. or/18-25
27. animals/
28. humans/
29. 27 and 28
30. 27 not 29
31. 26 not 30
32. 17 and 31

EMBASE

1 exp arthritis, rheumatoid/
2 (felty$ adj2 syndrome).tw.
3 (caplan$ adj2 syndrome).tw.
4 rheumatoid nodule.tw.
5 (sjogren$ adj2 syndrome).tw.
6 (sicca adj2 syndrome).tw.
7 still$ disease.tw.
8 bechterew$ disease.tw.
9 (arthritis adj2 rheumat$).tw.
10 or/1-9
11 rituximab/
12 rituximab.tw.
13 rituxan.tw.
14 mabthera.tw.
15 or/11-14

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16 10 and 15
17 random$.ti,ab.
18 factorial$.ti,ab.
19 (crossover$ or cross over$ or cross-over$).ti,ab.
20 placebo$.ti,ab.
21 (doubl$ adj blind$).ti,ab.
22 (singl$ adj blind$).ti,ab.
23 assign$.ti,ab.
24 allocat$.ti,ab.
25 volunteer$.ti,ab.
26 crossover procedure.sh.
27 double blind procedure.sh.
28 randomized controlled trial.sh.
29 single blind procedure.sh.
30 or/17-29
31 exp animal/ or nonhuman/ or exp animal experiment/
32 exp human/
33 31 and 32
34 31 not 33
35 30 not 34
36 16 and 35

CINAHL

1 exp Arthritis, Rheumatoid/
2 (felty$ adj2 syndrome).tw.
3 (caplan$ adj2 syndrome).tw.
4 rheumatoid nodule.tw.
5 (sjogren$ adj2 syndrome).tw.
6 (sicca adj2 syndrome).tw.
7 bechterew$ disease.tw.
8 (arthritis adj2 rheumat$).tw.
9 or/1-8
10 rituximab/
11 rituximab.tw.
12 rituxan.tw.
13 mabthera.tw.
14 or/10-13
15 9 and 14
16 from 15 keep 1-30

The Cochrane Library

#1MeSH descriptor Arthritis, Rheumatoid explode all trees in MeSH products
#2felty near/2 syndrome in All Fields in all products
#3caplan near/2 syndrome in All Fields in all products
#4rheumatoid nodule in All Fields in all products
#5sjogren* near/2 syndrome in All Fields in all products
#6sicca near/2 syndrome in All Fields in all products
#7still* next disease in All Fields in all products
#8bechterew* next disease in All Fields in all products
#9arthritis near/2 rheumat* in All Fields in all products
#10(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11MeSH descriptor Antibodies, Monoclonal, this term only
#12MeSH descriptor Immunologic Factors, this term only
#13rituximab:ti,ab
#14rituxan:ti,ab

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#15mabthera:ti,ab
#16(#11 OR #12 OR #13 OR #14 OR #15)
#17(#10 AND #16)

Web of Science

#1 rheumatoid arthritis or felty syndrome or sicca syndrome or caplan syndrome or still* disease or sjogren* syndrome or bechterew* disease or rheumatoid nodule*)
#2 rituximab or rituxan or mabthera
#3 trial* or random* or placebo* or control* or double or treble or triple or blind* or mask* or allocat* or prospective* or volunteer*or comparative or evaluation or follow-up or followup
#4 #1 AND #2 AND #3

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 1, 2015

Date	Event	Description
3 May 2008	Amended	CMSG ID C172-P

CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-authors (MSA)

Draft review (MLO, MAU, LM, MSA)

Run search (LF, GP)

Identify relevant titles and abstracts from searches (MLO, MAU, NP, SKM, PS)

Obtain copies of trials (MLO, NP)

Selection of trials (MLO, MAU, NP, MSA)

Extract data from trials (MLO, MAU, LM, SKM, PS)

Enter data into RevMan (MLO)

Carry out analysis (MLO, MSA)

Interpret data (MLO, MAU, LM, NP MSA)

Draft final review (MLO, MSA, NP, MAU)

Update review (MLO, LM, MSA)

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DECLARATIONS OF INTEREST

Dr Suarez-Almazor is the recipient of a K24 career award from the National Institute for Musculoskeletal and Skin Disorders.

SOURCES OF SUPPORT

Internal sources

- University of Texas. MD Anderson Cancer Center, USA.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Eligibility criteria

1. The allowed minimum trial duration was changed from 6 months to 4 months.
2. The allowed minimum patient age was changed from 16 to 18 years.
3. The allowed doses of rituximab were changed from 300 mg/m^2, 350 mg/m^2, 500 mg/m^2 and 600 mg/m^2 to any dose.

Major outcomes

1. The list was modified to reflect the standard outcomes used in reviews from the Cochrane Musculoskeletal Group.

Search methods for identification of studies

1. Pharmaceutical companies that manufacture rituximab (Roche in Canada, Genetech and Biogen Idec in the USA) were not contacted.
2. Clinical trials registries and websites of the regulatory agencies were also searched.

Prioritisation of comparisons

Studies reported multiple comparisons (rituximab alone or combined) and doses. Due to the space limitations, we have prioritised reporting of rituximab (two 1000 mg doses) in combination with methotrexate since this is the most commonly use combination and approved dose. We also report additional data in the results section of the review as supplementary information on: (i) rituximab monotherapy versus methotrexate monotherapy, (ii) rituximab (two 500 mg doses) in combination with methotrexate versus methotrexate, (iii) rituximab (two 1000 mg doses) in combination with cyclophosphamide versus rituximab monotherapy, and (iv) rituximab in combination with methotrexate and a TNF inhibitor versus methotrexate in combination with a TNF inhibitor.

Subgroup analyses

1. Disease duration (more or less than 4 years).
2. Previous treatment (methotrexate-naive, prior DMARD failure, or prior DMARD and TNF inhibitor failure).
3. Study quality (low or high risk of bias) on the response to rituximab.
4. Whether RF or anti-CCP status predicts response to treatment.

Sensitivity analysis

1. Dosages (1000 mg versus 500 mg doses).
2. Concomitant treatment (methotrexate or cyclophosphamide or none - rituximab monotherapy).

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