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Rituximab for people with multiple sclerosis (Review)

Filippini G, Kruja J, Del Giovane C

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[Intervention Review]

Rituximab for people with multiple sclerosis

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ABSTRACT

Background

Multiple sclerosis (MS) is the most common neurological cause of disability in young adults. Off-label rituximab for MS is used in most countries surveyed by the International Federation of MS, including high-income countries where on-label disease-modifying treatments (DMTs) are available.

Objectives

To assess beneficial and adverse effects of rituximab as 'first choice' and as 'switching' for adults with MS.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, and trial registers for completed and ongoing studies on 31 January 2021.

Selection criteria

We included randomised controlled trials (RCTs) and controlled non-randomised studies of interventions (NRSIs) comparing rituximab with placebo or another DMT for adults with MS.

Data collection and analysis

We followed standard Cochrane methodology. We used the Cochrane Collaboration's tool for assessing risk of bias. We rated the certainty of evidence using GRADE for: disability worsening, relapse, serious adverse events (SAEs), health-related quality of life (HRQoL), common infections, cancer, and mortality. We conducted separate analyses for rituximab as 'first choice' or as 'switching', relapsing or progressive MS, comparison versus placebo or another DMT, and RCTs or NRSIs.

Main results

We included 15 studies (5 RCTs, 10 NRSIs) with 16,429 participants of whom 13,143 were relapsing MS and 3286 progressive MS. The studies were one to two years long and compared rituximab as 'first choice' with placebo (1 RCT) or other DMTs (1 NRSI), rituximab as 'switching' against placebo (2 RCTs) or other DMTs (2 RCTs, 9 NRSIs). The studies were conducted worldwide; most originated from high-income countries, six from the Swedish MS register. Pharmaceutical companies funded two studies. We identified 14 ongoing studies.

Rituximab as 'first choice' for relapsing MS

Rituximab versus placebo: no studies met eligibility criteria for this comparison.

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Rituximab versus other DMTs: one NRSI compared rituximab with interferon beta or glatiramer acetate, dimethyl fumarate, natalizumab, or fingolimod in active relapsing MS at 24 months' follow-up. Rituximab likely results in a large reduction in relapses compared with interferon beta or glatiramer acetate (hazard ratio (HR) 0.14, 95% confidence interval (CI) 0.05 to 0.39; 335 participants; moderate-certainty evidence). Rituximab may reduce relapses compared with dimethyl fumarate (HR 0.29, 95% CI 0.08 to 1.00; 206 participants; low-certainty evidence) and natalizumab (HR 0.24, 95% CI 0.06 to 1.00; 170 participants; low-certainty evidence). It may make little or no difference on relapse compared with fingolimod (HR 0.26, 95% CI 0.04 to 1.69; 137 participants; very low-certainty evidence). The study reported no deaths over 24 months. The study did not measure disability worsening, SAEs, HRQoL, and common infections.

Rituximab as 'first choice' for progressive MS

One RCT compared rituximab with placebo in primary progressive MS at 24 months' follow-up. Rituximab likely results in little to no difference in the number of participants who have disability worsening compared with placebo (odds ratio (OR) 0.71, 95% CI 0.45 to 1.11; 439 participants; moderate-certainty evidence). Rituximab may result in little to no difference in recurrence of relapses (OR 0.60, 95% CI 0.18 to 1.99; 439 participants; low-certainty evidence), SAEs (OR 1.25, 95% CI 0.71 to 2.20; 439 participants; low-certainty evidence), common infections (OR 1.14, 95% CI 0.75 to 1.73; 439 participants; low-certainty evidence), cancer (OR 0.50, 95% CI 0.07 to 3.59; 439 participants; low-certainty evidence), and mortality (OR 0.25, 95% CI 0.02 to 2.77; 439 participants; low-certainty evidence). The study did not measure HRQoL.

Rituximab versus other DMTs: no studies met eligibility criteria for this comparison.

Rituximab as 'switching' for relapsing MS

One RCT compared rituximab with placebo in relapsing MS at 12 months' follow-up. Rituximab may decrease recurrence of relapses compared with placebo (OR 0.38, 95% CI 0.16 to 0.93; 104 participants; low-certainty evidence). The data did not confirm or exclude a beneficial or detrimental effect of rituximab relative to placebo on SAEs (OR 0.90, 95% CI 0.28 to 2.92; 104 participants; very low-certainty evidence), common infections (OR 0.91, 95% CI 0.37 to 2.24; 104 participants; very low-certainty evidence), cancer (OR 1.55, 95% CI 0.06 to 39.15; 104 participants; very low-certainty evidence), and mortality (OR 1.55, 95% CI 0.06 to 39.15; 104 participants; very low-certainty evidence). The study did not measure disability worsening and HRQoL.

Five NRSIs compared rituximab with other DMTs in relapsing MS at 24 months' follow-up. The data did not confirm or exclude a beneficial or detrimental effect of rituximab relative to interferon beta or glatiramer acetate on disability worsening (HR 0.86, 95% CI 0.52 to 1.42; 1 NRSI, 853 participants; very low-certainty evidence). Rituximab likely results in a large reduction in relapses compared with interferon beta or glatiramer acetate (HR 0.18, 95% CI 0.07 to 0.49; 1 NRSI, 1383 participants; moderate-certainty evidence); and fingolimod (HR 0.08, 95% CI 0.02 to 0.32; 1 NRSI, 256 participants; moderate-certainty evidence). The data did not confirm or exclude a beneficial or detrimental effect of rituximab relative to natalizumab on relapses (HR 1.0, 95% CI 0.2 to 5.0; 1 NRSI, 153 participants; very low-certainty evidence). Rituximab likely increases slightly common infections compared with interferon beta or glatiramer acetate (OR 1.71, 95% CI 1.11 to 2.62; 1 NRSI, 5477 participants; moderate-certainty evidence); and compared with natalizumab (OR 1.58, 95% CI 1.08 to 2.32; 2 NRSIs, 5001 participants; moderate-certainty evidence). Rituximab may increase slightly common infections compared with fingolimod (OR 1.26, 95% CI 0.90 to 1.77; 3 NRSIs, 5187 participants; low-certainty evidence). It may make little or no difference compared with ocrelizumab (OR 0.02, 95% CI 0.00 to 0.40; 1 NRSI, 472 participants; very low-certainty evidence). The data did not confirm or exclude a beneficial or detrimental effect of rituximab on mortality compared with fingolimod (OR 5.59, 95% CI 0.22 to 139.89; 1 NRSI, 136 participants; very low-certainty evidence) and natalizumab (OR 6.66, 95% CI 0.27 to 166.58; 1 NRSI, 153 participants; very low-certainty evidence). The included studies did not measure SAEs, HRQoL, and cancer.

Authors' conclusions

For preventing relapses in relapsing MS, rituximab as 'first choice' and as 'switching' may compare favourably with a wide range of approved DMTs. A protective effect of rituximab against disability worsening is uncertain. There is limited information to determine the effect of rituximab for progressive MS.

The evidence is uncertain about the effect of rituximab on SAEs. They are relatively rare in people with MS, thus difficult to study, and they were not well reported in studies. There is an increased risk of common infections with rituximab, but absolute risk is small.

Rituximab is widely used as off-label treatment in people with MS; however, randomised evidence is weak. In the absence of randomised evidence, remaining uncertainties on beneficial and adverse effects of rituximab for MS might be clarified by making real-world data available.

PLAIN LANGUAGE SUMMARY

Rituximab for people with multiple sclerosis

Key messages

– Rituximab may offer moderate-to-large benefit against a range of other medicines in preventing relapses in relapsing multiple sclerosis (MS). Compared with no medicines, the desirable effects would be greater.

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– There is limited information to determine the effect of rituximab for preventing disability worsening in all forms of MS.

– Serious harmful effects are relatively rare in people with MS making them difficult to study, and they were also not well reported in studies.

What is the issue?

Rituximab is a medicine administered by intravenous (by a vein) infusion that can suppress certain immune cells. The immune system fights infections and consists of many immune cells; it is affected in MS.

Rituximab is currently used in many low- to middle-income countries that have major barriers for accessing approved medicines for MS. However, rituximab is not always reimbursed by health systems because it is not licensed for MS by marketing authorities.

Rituximab is considered a feasible treatment option as it is considered a highly effective treatment (similar to other approved medicines used to treat MS) but has considerably lower cost and less frequent dosing. Treatment with rituximab requires specialist care and infusion facilities, but other approved medicines do too.

What did we want to find out?

We aimed to investigate the beneficial and unwanted effects of rituximab for people with MS, when is used as a 'first choice' or as 'switching' (in other words, used when other medicines do not work well or become contraindicated).

We wanted to find out if rituximab was better than other medicines to prevent disability worsening and recurrence of relapse, and to improve well-being.

We also wanted to find out if rituximab was associated with any unwanted or harmful effects, for example, serious harmful effects, common infections, cancer, and mortality (death).

What did we do?

We searched for studies that investigated rituximab compared with all other approved medicines for MS. We searched the literature up to January 2021. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and quality.

What did we find?

We found 15 studies that involved about 16,000 people with MS and lasted one or two years. The biggest study was of 6421 people and the smallest study was of 27 people. The studies were conducted worldwide; most originated from high-income countries, six from the Swedish MS register. Pharmaceutical companies funded two included studies.

Main results

Rituximab as a first choice treatment in relapsing MS:

– likely results in a large reduction in the number of people who have relapses compared with interferon beta or glatiramer acetate (evidence from one study in 335 people);

– may reduce the number of people who have relapses compared with dimethyl fumarate and natalizumab, but the evidence is uncertain (evidence from one study).

There was no usable information on disability worsening, well-being, and serious harmful effects.

Rituximab as a first choice treatment in progressive MS:

– likely results in little to no difference in the number of participants who have disability worsening over 24 months compared with pretend treatment (evidence from one study of 439 people);

– the evidence is very uncertain about the effect of rituximab on well-being and serious harmful effects.

Rituximab as 'switching' for relapsing MS:

– likely results in a large reduction in the number of people who have relapses compared with interferon beta or glatiramer acetate (evidence from one study of 1383 people), and fingolimod (evidence from one study of 256 people). The evidence is very uncertain on the comparison of rituximab with natalizumab;

– the evidence is very uncertain on disability worsening;

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– likely increases slightly the number of people who have common infections compared with interferon beta or glatiramer acetate (evidence from one study of 5477 people), and natalizumab (evidence from two studies of 5001 people). The evidence is uncertain for the comparisons of rituximab with fingolimod and ocrelizumab.

There was no usable information on well-being and serious harmful effects.

Rituximab as 'switching' for progressive MS

Only three small studies investigated rituximab in secondary progressive MS. The evidence is uncertain about the effect of rituximab on disability worsening, well-being, and serious harmful effects.

What are the limitations of the evidence?

– Limited confidence about the effect of rituximab on disability worsening in all forms of MS.

– Limited information to determine the effect of rituximab for progressive forms of MS.

– Studies were short with a median duration of 24 months.

How up to date is the evidence?

This review is up to day to 31 January 2021.

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Summary of findings 1. Rituximab as 'first choice' versus other disease-modifying treatments for relapsing multiple sclerosis – results from non-randomised studies of intervention

Patient or population: relapsing multiple sclerosis
Settings: inpatient or outpatient
Intervention: rituximab as first choice treatment
Comparison: other disease-modifying treatments as first choice treatment

Intervention	Comparison intervention	Anticipated absolute effects*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Assumed risk with comparator	Corresponding risk with rituximab (95% CI)				
Disability worsening	—	—	—	—	—	—	The study[a] did not measure the outcome.
Chance of experiencing ≥ 1 relapses: visits over 24 months. Data collected from the Swedish MS registry and medical records.							
Rituximab	**Interferon beta or glatiramer acetate**	**270 per 1000**	**43 per 1000** (16 to 116)	**HR 0.14** (0.05 to 0.39)	335 (1 retrospective cohort study)[a]	⊕⊕⊕⊖ **Moderate** [b]	Downgraded 1 level for serious risk of bias. Rituximab likely results in a large reduction in relapses when compared with interferon beta or glatiramer acetate.
Rituximab	**Dimethyl fumarate**	**120 per 1000**	**36 per 1000** (10 to 120)	**HR 0.29** (0.08 to 1.00)	206 (1 retrospective cohort study)[a]	⊕⊕⊖⊖ **Low** [b,c]	Downgraded 1 level for serious risk of bias and 1 level for imprecision. Rituximab may reduce relapses when compared with dimethyl fumarate.
Rituximab	**Natalizumab**	**200 per 1000**	**52 per 1000** (13 to 200)	**HR 0.24** (0.06 to 1.00)	170 (1 retrospective cohort study)[a]	⊕⊕⊖⊖ **Low** [b,c]	Downgraded 1 level for serious risk of bias and 1 level for imprecision. Rituximab may reduce relapses when compared with natalizumab.
Rituximab	**Fingolimod**	**180 per 1000**	**50 per 1000** (8 to 285)	**HR 0.26** (0.04 to 1.69)	137 (1 retrospective cohort study)[a]	⊕⊖⊖⊖ **Very low** [b,d]	Downgraded 1 level for serious risk of bias and 2 levels for serious imprecision. The evidence is very uncertain about the effect of rituximab on relapses when compared with fingolimod.

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Serious adverse events	—	—	—	—	—	—	The study[a] did not measure the outcome.
Quality of life	—	—	—	—	—	—	The study[a] did not measure the outcome.
Common infections	—	—	—	—	—	—	The study[a] did not measure the outcome.
Cancer	—	—	—	—	—	—	The study[a] did not measure the outcome.
Mortality	No reported deaths in any comparison group over 24 months' follow-up. Death related to adverse events defined as CTCAE grade 5. Data collected from the Swedish MS registry and medical records.						

*The **assumed risk** was calculated in GRADEpro based on the number of participants with the event over the total sample size in the control group, for binary and time-to-event outcomes. The **risk in the rituximab group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** (odds ratio or HR) of the intervention (and its 95% CI).
CI: confidence interval; **CTCAE:** National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations: event rates in comparator based on the number of events in the included study.

[a] Granqvist 2018.
[b]Bias due to confounding by indication expected in the retrospective cohort study.
[c]The optimal information size criterion was not met (very few events).
[d]Results included both no effect and appreciable benefit or harm.

Summary of findings 2. Rituximab as 'first choice' versus placebo for progressive multiple sclerosis – results from randomised controlled trials

Patient or population: primary progressive multiple sclerosis

Settings: inpatient or outpatient

Intervention: rituximab as first choice treatment

Comparison: placebo

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Outcomes	Anticipated absolute effects*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with placebo	Corresponding risk with rituximab (95% CI)				
Disability worsening measured by EDSS over 24 months	**361 per 1000**	**286 per 1000** (202 to 385)	**OR 0.71** (0.45 to 1.11)	439 (1 RCT)[a]	⊕⊕⊕⊖ **Moderate** [b,c]	Downgraded 1 level for some imprecision. Rituximab likely resulted in little to no difference in the number of participants who had disability worsening over 24 months when compared with placebo.
Relapse measured by clinical assessment over 24 months	**34 per 1000**	**21 per 1000** (6 to 65)	**OR 0.60** (0.18 to 1.99)	439 (1 RCT)[a]	⊕⊕⊖⊖ **Low** [c,d]	Downgraded 2 levels for very serious imprecision. Rituximab may have resulted in little to no difference in recurrence of relapses when compared with placebo.
Serious adverse events measured by clinical assessment over 28 months	**136 per 1000**	**164 per 1000** (101 to 257)	**OR 1.25** (0.71 to 2.20)	439 (1 RCTs)[a]	⊕⊕⊖⊖ **Low** [c,e]	Downgraded 2 levels for very serious imprecision. Rituximab may slightly increase the number of participants who have serious adverse events compared with placebo.
Quality of life	—	—	—	—	—	The study[a] did not measure the outcome
Common infections measured by clinical assessment over 28 months	**653 per 1000**	**682 per 1000** (585 to 765)	**OR 1.14** (0.75 to 1.73)	439 (1 RCTs)[a]	⊕⊕⊖⊖ **Low** [e]	Downgraded 2 levels for very serious imprecision. Rituximab may increase common infections compared with placebo.
Cancer measured by clinical assessment over 28 months	**14 per 1000**	**7 per 1000** (1 to 47)	**OR 0.50** (0.07 to 3.59)	439 (1 RCT)[a]	⊕⊕⊖⊖ **Low** [e]	Downgraded 2 levels for very serious imprecision. Quote: "Rituximab group: 1 patient had breast cancer and 1 had adenocarcinoma. Placebo group: 1 patient had parathyroid tumour, 1 had prostate cancer".
Mortality measured by clinical assessment over 28 months	**14 per 1000**	**3 per 1000** (0 to 37)	**OR 0.25** (0.02 to 2.77)	439 (1 RCT)[a]	⊕⊕⊖⊖ **Low** [e]	Downgraded 2 levels for very serious imprecision. Rituximab may result in little to no difference in mortality compared with placebo.

*The **assumed risk** was calculated based on the number of participants with the event over the total sample size in the placebo group, for binary outcomes. The **risk in the rituximab group** (and its 95% confidence interval) is based on the assumed risk in the placebo group and the **relative effect** (OR) of the intervention (and its 95% CI).
CI: confidence interval; **EDSS:** Expanded Disability Status Scale; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

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High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Hawker 2009.
[b]Results included both appreciable benefit and no effect.
[c]We did not downgrade for risk of bias, even though the included study has some concerns.
[d]Results included both no effect and appreciable benefit or harm.
[e]Results included both no harm and appreciable harm.

Summary of findings 3. Rituximab as 'switching' versus placebo for relapsing multiple sclerosis – results from randomised controlled trials

Patient or population: relapsing multiple sclerosis
Settings: inpatient or outpatient
Intervention: rituximab as 'switching' treatment
Comparison: placebo

Outcomes	Anticipated absolute effects*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with placebo	Corresponding risk with rituximab (95% CI)				
Disability worsening	—	—	—	—	—	The study[a] did not measure the outcome.
Relapse measured by clinical assessment over 12 months	**400 per 1000**	**202 per 1000** (96 to 383)	**OR 0.38** (0.16 to 0.93)	104 (1 RCT)[a]	⊕⊕⊖⊖ **Low** [b,c]	Downgraded 1 level for serious risk of bias and 1 level for serious imprecision. Rituximab may result in a large reduction in recurrence of relapse over 12 months' follow-up when compared with placebo.
Serious adverse events measured by clinical assessment over 12 months	**143 per 1000**	**130 per 1000** (45 to 327)	**OR 0.90** (0.28 to 2.92)	104 (1 RCT)[a]	⊕⊖⊖⊖ **Very low** [b,d]	Downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on serious adverse events, when compared with placebo.

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Quality of life	—	—	—	—	—	The study[a] did not measure the outcome.
Common infections measured by clinical assessment over 12 months	**714 per 1000**	**695 per 1000** (481 to 848)	**OR 0.91** (0.37 to 2.24)	104 (1 RCT)[a]	⊕⊖⊖⊖ **Very low** [b,d]	Downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on infections, when compared with placebo.
Cancer measured by clinical assessment over 12 months	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 1.55** (0.06 to 39.15)	104 (1 RCT)[a]	⊕⊖⊖⊖ **Very low** [b,d]	Downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on the number of participants who have cancer, when compared with placebo.
Mortality measured by clinical assessment over 12 months	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 1.55** (0.06 to 39.15)	104 (1 RCT)[a]	⊕⊖⊖⊖ **Very low** [b,d]	Downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on mortality compared with placebo.

*The **assumed risk** was calculated based on the number of participants with the event over the total sample size in the placebo group for binary outcomes. The **risk in the rituximab group** (and its 95% CI) is based on the assumed risk in the placebo group and the **relative effect** (OR) of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Hauser 2008.
[b]High risk of bias for unblinding of personnel and incomplete outcome data. Unclear risk of bias for allocation concealment and blinding of participants.
[c]The optimal information size criterion was not met (few events).
[d]The optimal information size criterion was not met (very few events). Results included both no harm and appreciable harm.

Summary of findings 4. Rituximab as 'switching' versus other disease-modifying treatments for relapsing multiple sclerosis – results from non-randomised studies of intervention

Patient or population: relapsing multiple sclerosis
Settings: inpatient or outpatient
Intervention: rituximab as 'switching' treatment
Comparison: other disease-modifying treatments as 'switching'

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Intervention	Comparison intervention	Anticipated absolute effects*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Assumed risk with comparator	Corresponding risk with rituximab (95% CI)				
Disability worsening measured by EDSS over 24 months: data collected from the Swedish MS registry and medical records							
Rituximab	**Interferons or glatiramer acetate**	**90 per 1000**	**78 per 1000** (48 to 125)	**HR 0.86** (0.52 to 1.42)	853 (1 retrospective cohort study)[a]	⊕⊖⊖⊖ **Very low** [b,c]	Downgraded 2 levels for very serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on disability worsening when compared with interferon beta or glatiramer acetate
Relapse measured by clinical assessment over 24 months: data collected from the Swedish MS registry and medical records							
Rituximab	**Interferons or glatiramer acetate**	**270 per 1000**	**55 per 1000** (22 to 143)	**HR 0.18** (0.07 to 0.49)	1383 (1 retrospective cohort study)[a]	⊕⊕⊕⊖ **Moderate** [d]	Downgraded 1 level due to serious risk of bias. Rituximab likely results in a large reduction in recurrence of relapses when compared with interferons or glatiramer. The NNTB is 11 (95% CI 10 to 18).
Rituximab	**Fingolimod**	**176 per 1000**	**15 per 1000** (4 to 60)	**HR 0.08** (0.02 to 0.32)	256 (1 retrospective cohort study)[e]	⊕⊕⊕⊖ **Moderate** [d]	Downgraded 1 level due to serious risk of bias. Rituximab likely results in a large reduction in recurrence of relapses when compared with fingolimod. The NNTB is 6 (95% CI 6 to 9).
Rituximab	**Natalizumab**	**60 per 1000**	**60 per 1000** (12 to 266)	**HR 1.00** (0.20 to 5.00)	153 (1 retrospective cohort study)[f]	⊕⊖⊖⊖ **Very low** [c,d]	Downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on recurrence of relapses when compared with natalizumab.
Quality of life	—	—	—	—	—	—	None of the studies measured the outcome.
Serious adverse events	—	—	—	—	—	—	None of the studies measured the outcome.
Long-term adverse events: common infections over 24 months: data collected from MS registries and medical records.							

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Rituximab	**Interferon beta or glatiramer acetate**	**36 per 1000**	**60 per 1000** (40 to 89)	**OR 1.71** (1.11 to 2.62)	5477 (1 retrospective cohort study- the national Swedish MS Register linked to national healthcare and census registries)[g]	⊕⊕⊕⊖ **Moderate** [h]	Downgraded 1 level for serious risk of bias in measurement of the outcome. Rituximab likely increases infections when compared with interferons or glatiramer acetate.
Rituximab	**Fingolimod**	**56 per 1000**	**70 per 1000** (51 to 95)	**OR 1.26** (0.90 to 1.77)	5187 (3 retrospective multicentre cohort studies)[e,f,g]	⊕⊕⊖⊖ **Low** [i,j]	Downgraded 1 level for serious risk of bias and 1 level for imprecision. Heterogeneity: P = 0.24, I^2 = 30%. Rituximab may increase slightly common infections when compared with fingolimod.
Rituximab	**Natalizumab**	**50 per 1000**	**77 per 1000** (51 to 95)	**OR 1.58** (1.08 to 2.32)	5001 (2 retrospective multicentre cohort studies)[f,g]	⊕⊕⊕⊖ **Moderate** [j]	Downgraded 1 level for serious risk of bias. Heterogeneity: P = 0.39, I^2 = 0%. Rituximab likely increases the number of participants who have common infections when compared with natalizumab.
Rituximab	**Ocrelizumab**	**62 per 1000**	**1 per 1000** (0 to 26)	**OR 0.02** (0.00 to 0.40)	472 (1 retrospective multicentre cohort study). The Swedish MS register and medical records at the Rocky Mountain MS Clinic, Utah, US[k]	⊕⊖⊖⊖ **Very low** [j,l]	Downgraded 2 levels for very serious risk of bias and 1 level for imprecision. The evidence is very uncertain about the effect of rituximab on the number of participants who have common infections when compared with ocrelizumab.
Cancer	—	—	—	—	—	—	None of the studies measured the outcome.
Mortality over 24 months: defined as CTCAE grade 5. Data collected from the Swedish MS registry and medical records.							
Rituximab	**Fingolimod**	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 5.59** (0.22 to 139.89)	136 (1 retrospective multicentre cohort study)[f]	⊕⊖⊖⊖ **Very low** [d,i,m]	Downgraded 1 level for serious risk of bias, 1 level for indirectness, and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on mortality compared with fingolimod.

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Rituximab	**Natalizumab**	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 6.66** (0.27 to 166.58)	153 (1 retrospective multicentre cohort study)[f]	⊕⊖⊖⊖ **Very low** [d,i,m]	Downgraded 1 level for serious risk of bias, 1 level for indirectness, and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on mortality compared with natalizumab.

*The **assumed risk** was calculated in GRADEpro based on the number of participants with the event over the total sample size in the control group, for binary and time-to-event outcomes. The **risk in the rituximab group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** (OR or HR) of the intervention (and its 95% CI).

CI: confidence interval; **CTCAE:** National Cancer Institute. Common Terminology Criteria for Adverse Events version 4.0; **HR:** hazard ratio; **NNTB:** number needed to treat for an additional beneficial effect; **OR:** odds ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

Event rates in comparator based on the number of events in the included studies.

[a] Spelman 2018.
[b]Bias due to missing data since time to disability worsening was limited to participants with a minimum of three EDSS scores reported, i.e. 321/461 (70%) participants in the rituximab group and 532/922 (58%) participants in the interferon or glatiramer acetate group.
[c]The optimal information size criterion was not met (few events). Results included both no effect and appreciable benefit or harm.
[d]Bias due to residual confounding is expected in a retrospective cohort study.
[e] Alping 2016.
[f] Boremalm 2019.
[g] Luna 2020.
[h]Quote: "Data are not available on the validity of the registries to measure infections and on different reporting of infections between interventions" (Luna 2020).
[i]The optimal information size criterion was not met (very few events). Results included both no harm and appreciable harm.
[j]All retrospective cohort studies at serious risk of bias.
[k] Evertsson 2020.
[l]The optimal information size criterion was not met (few events).
[m]Indirectness of outcome, one suicide in the rituximab group.

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BACKGROUND

Description of the condition

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system. The global prevalence of MS is estimated at 36 per 100,000 people, which means there are 2.8 million adults living with MS worldwide. MS is present in all regions of the world, but prevalence is noticeably higher in Europe and the Americas. There are at least twice as many females (69%) with MS as there are males (31%). MS can occur at any age, but the mean age at which MS is diagnosed is from 30 to 33 years. MS is the most common neurological cause of disability for young adults (MSIF 2020).

MS is pathologically characterised by inflammation, demyelination, and axonal and neuronal loss. Clinically, it is characterised by recurrent relapses and disability worsening. The clinical course is classified as relapsing MS, secondary progressive MS, and primary progressive MS (Lublin 1996). These forms of MS were used to design trials of interventions over two decades. An updated classification of MS forms was produced in 2013 (Lublin 2014). The concept of disease activity was added, based on the presence of clinical relapse or new magnetic resonance imaging (MRI) lesions in the brain. The new classification included: 1. active or inactive relapsing MS, with or without worsening; and 2. active or inactive primary or secondary progressive disease, with or without progression (Lublin 2014). Worldwide, 85% of people with MS are initially diagnosed with relapsing MS and 12% with progressive MS. The remaining 3% are given an unknown disease type on diagnosis (MSIF 2020).

Description of the intervention

Rituximab is a monoclonal antibody approved for the treatment of adults with B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyarteritis, and pemphigus vulgaris (FDA 2020a). Neurologists have used rituximab off-label to treat neuromyelitis optica (Damato 2016), myasthenia gravis (Banerjee 2018), autoimmune encephalitis (Nepal 2020), autoimmune neuropathies and myopathies (Fasano 2017), and MS (European Commission 2017; Sarsour 2020). This drug is marketed by Genentech-Biogen in the US under the brand name Rituxan, and by Roche in Europe under the brand name MabThera.

Rituximab is administered by intravenous infusion at single doses of 500 mg or 1000 mg, two weeks apart. The maintenance dose is 500 mg or 1000 mg every six to 12 months. The alternative induction dose, or in cases of disease breakthrough, is 375 mg/m^2 every week for four weeks. However, a treatment protocol has not yet been established; induction and maintenance doses may change based on the type of MS, MRI lesion load, clinical response, and CD19-positive or CD20-positive cell counts. The summary of product characteristics states that rituximab should be administered under the close supervision of an experienced physician. Serum rituximab's half-life is reported to be 76.3 hours (Maloney 1997).

The most frequently observed short-term adverse events in people receiving rituximab are infusion-related reactions (FDA 2020a). The majority of these reactions occur during the first infusion or within 24 hours of the infusion. The final report of the Rheumatoid Arthritis Global Clinical Trial Program, based on over 11 years' follow-up, reported that rituximab remained well tolerated over time and for multiple courses (van Vollenhoven 2015). Under long-term therapy with rituximab or other B-cell-depleting drugs, and with alternative immunomodulatory agents for MS, immunoglobulin deficiency syndromes can occur that may be associated with severe infections (Hallberg 2019; Luna 2020; Tsao 2019; van Vollenhoven 2015). Hepatitis B virus (HBV) reactivation following chemotherapy that includes rituximab has been reported in people who have either had hepatitis B or are a carrier of HBV (Evens 2011; Pourcher 2020). Progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection caused by a virus, can occur in rituximab-treated people with haematological malignancies or other autoimmune diseases. Most people with haematological malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant (FDA 2020a). People with autoimmune diseases diagnosed with PML had prior or concurrent immunosuppressive therapy (Berger 2018; FDA 2020a). Most cases of PML were diagnosed within 12 months of their last infusion of rituximab (FDA 2020a). Rituximab is listed as having "no or very low risk for PML" by Yukitake 2018. Cardiac and vascular events (hypotension, hypertension, arrhythmias, and angina) have been reported with rituximab (FDA 2020a). Two registry studies in Sweden showed no evidence of an increased risk of cancer with rituximab use in 3585 people with rheumatic disease (Wadstrom 2017), and in 4187 people with MS (Alping 2020). However, the results of one observational study showed an association between malignant melanoma and breast cancer with rituximab use (Caldito 2021).

Several disease-modifying treatments (DMTs) have been discovered and approved for people with relapsing MS. Infused approved DMTs include: alemtuzumab, mitoxantrone, natalizumab, and ocrelizumab. Injectable approved DMTs include: interferon betas, glatiramer acetate, peginterferon beta-1a, and ofatumumab. Oral approved DMTs include: cladribine, dimethyl fumarate, diroximel fumarate, fingolimod, monomethyl fumarate, ozanimod, siponimod, and teriflunomide. Recently the US Food and Drug Administration (FDA) approved siponimod (FDA 2019a), ozanimod (FDA 2020b), and cladribine (FDA 2019b) for active secondary progressive MS.

Several national and international guidelines on the use of DMTs for MS are available (Table 1). Common to all guidelines is a moderate or low level of evidence available to assign strength to treatment recommendations, because there are few randomised studies that directly compared different DMTs as 'first choice' treatment or as 'switching'. Recommendations on the use of rituximab vary among guidelines, reflecting – among other things – the differences in regulatory agencies' recommendations and different regional or local health policies. For example, the use of rituximab has increased rapidly within Sweden for treating relapsing MS, since, under existing Swedish free right to prescription provisions, the treating hospital assumes responsibility and liabilities associated with off-label use of rituximab (Spelman 2018). The data from the national Swedish MS Registry showed an increasing prescription rate of rituximab in relation to other DMTs during the years 2011 to 2016. In June 2017, the proportion of people with MS starting rituximab as 'first choice' treatment was more than 50% (Berntsson 2018). Rituximab is recommended by the Middle East and North Africa Committee (MENACTRIMS) Consensus as an off-label treatment for highly active MS and as an escalation

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therapy for all levels of MS activity in special populations, such as refugees, or in countries where other appropriate options are not available (Yamout 2020). The European guideline does not include recommendations on the use of rituximab, as regulations on this treatment vary broadly between different European countries (Montalban 2018).

How the intervention might work

The inflammation in the central nervous system in MS stems from complex interactions between T cells and antigen-presenting cells, such as B cells and myeloid cells (macrophages, dendritic cells, and microglia) (Comi 2021; Zhong 2020). The pro-inflammatory role of B cells in MS involves antigen presentation to activate pathogenic T cells and macrophages, production of pro-inflammatory cytokines, and formation and maintenance of ectopic lymphoid organs in the central nervous system (Greenfield 2018; Hauser 2015; Sabatino 2019). B cells are highly selective for antigens bound to their cell receptor (BCR) (Greenfield 2018). The antigen–BCR complex is internalised and processed, its constituent peptides are then complexed with the major histocompatibility complex (MHC) class II molecules, and the antigen–MHC complex is transported to the cell surface where it can activate T cells (Th1 and Th17) by involvement of the T cell receptor and costimulatory molecules (Batista 2009). In MS, priming of T cells is caused by autoreactive B cells that demonstrate higher levels of antigen-presenting activity compared to B cells of healthy controls or individuals with other neuroinflammatory diseases (Jelcic 2018; Mathias 2017). The binding of autoantigen to BCR also causes aberrant B cells to produce pro-inflammatory and regulatory cytokines. B cells of people with MS cultured in vitro have been found to secrete higher levels of pro-inflammatory cytokines and lower levels of regulatory cytokines (Bar-Or 2010; Duddy 2007). In the milieu of pro-inflammatory cytokines, chemokines, and lymphotoxin signalling, B cells support the development of ectopic B-cell follicles that have been detected in the meninges of people with secondary progressive MS (Serafini 2004).

Rituximab binds selectively to the CD20 antigen expressed on the surface of pre-B cells, mature and memory B cells, and some plasmablasts, but not B-cell progenitors (pro-B cells) and differentiated plasma cells (i.e. B cells that do not express CD20) (Greenfield 2018; St Clair 2010). Therefore, administration of rituximab causes selective loss of circulating and tissue-based B cells that are responsible for antigen presentation and cytokine production, without affecting B-cell reconstitution or pre-existing humoral immunity. Mechanisms of B-cell lysis include primarily complement-dependent cytotoxicity (CDC) but also antibody-dependent cellular cytotoxicity (ADCC) (Greenfield 2018). Other modes of action of rituximab have been proposed (e.g. depletion of CD20 cells or Epstein-Barr herpesvirus (EBV) reservoir depletion) (Ineichen 2020).

Rituximab was detectable in the serum of people three to six months after completion of treatment (FDA 2020a). Following intravenous administration of rituximab, B lymphocytes typically remain depleted in peripheral blood for six to nine months (Greenfield 2018; Roll 2006). In non-blood tissues, including the central nervous system, the extent and duration of depletion is not fully known but is likely to be partial, to depend on the dose, and to be modulated by individual factors such as genetic background (Greenfield 2018).

Why it is important to do this review

The off-label use of rituximab to treat MS has been reported in most countries (70 of the 102 countries reported in the Multiple Sclerosis International Federation's (MSIF) Atlas of MS) (Laurson-Doube 2021). Several published observational data have strengthened the evidence for effectiveness and safety of rituximab in MS, and reported a discontinuation rate that was lower than that of other DMTs (Granqvist 2018; Salzer 2016). The identification of beneficial and adverse effects of rituximab for both relapsing MS and progressive forms of MS, including switching drug regimens, increases the importance of this review mainly for low- and medium-income countries.

Given that the period of patent protection has expired, it is extremely unlikely that a registration trial of rituximab for MS will ever been undertaken. Therefore, evidence on beneficial and adverse effects of rituximab for MS will not be provided by randomised trials. Considering that rituximab is widely used as off-label treatment in people with MS, we have a duty to people with MS, practitioners, and policymakers to provide these groups with a summary of available evidence that includes controlled non-randomised studies (Reeves 2019).

Ocrelizumab and ofatumumab, which are anti-CD20 monoclonal antibodies similar to rituximab, have been approved as treatments for relapsing and active progressive forms of MS, but these medicines are not available in low-income countries due to prohibitive costs. Rituximab is a relatively inexpensive treatment, cheaper than any other approved DMTs for MS, and it is a feasible option in resource-limited settings (Mathew 2020). With increasing incidence and prevalence of MS globally, especially in low- and middle-income countries, it is essential to ensure that people with MS have timely access to safe and effective treatments (Lancet Neurology 2019).

We considered that a new review was more appropriate, rather than updating the previous Cochrane Review (He 2013), because changes to the review methods were substantive. We decided to add non-randomised studies to the review that was previously restricted to randomised controlled trials (RCTs), to widen the evidence base, making use of the Risk Of Bias in Non-randomised Studies – of Interventions tool (ROBINS-I) in critical evaluation of the validity of non-randomised studies. We now added progressive forms of MS to the review that was previously restricted to relapsing MS. New DMTs have been approved since the early 2010s to treat relapsing and progressive MS, therefore, we added new comparisons including all DMTs that were used at 31 January 2021. We included important new outcomes (e.g. mortality, common infections, cancer) that were not addressed in the original review.

OBJECTIVES

To assess beneficial and adverse effects of rituximab as 'first choice' and as 'switching' for adults with MS.

Specific comparisons included:

- rituximab as 'first choice' treatment compared with placebo or other DMTs for relapsing forms of MS;
- rituximab as 'first choice' treatment compared with placebo or other DMTs for progressive forms of MS;

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- rituximab as 'switching' from another DMT compared with placebo or other DMTs for relapsing forms of MS;
- rituximab as 'switching' from another DMT compared with placebo or other DMTs for progressive forms of MS.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel RCTs and controlled non-randomised studies of interventions (NRSIs) of between-group design (i.e. open-label extension (OLE) studies, controlled clinical trials, controlled cohort studies, regression discontinuity designs, case-control studies, and registries). We had two main justifications for including NRSIs in the review. First, to provide evidence of the effects of rituximab for which only few RCTs were available. Second, to address long-term outcomes and different populations that are typical of real-world practice. We excluded studies of within-group design (e.g. before-after (pre–post) studies with no control group, interrupted time series, and case reports).

We excluded studies that did not record any relevant outcomes.

We applied no limitations with respect to the length of follow-up or methods of analysis. We included full-text publications, results published in non-commercial trial registries (e.g. ClinicalTrials.gov record), and abstracts if sufficient information was available on study design, characteristics of participants, interventions, and outcomes.

Types of participants

We included adults (aged 18 years or older), of either sex, who were treatment-naive or non-responsive to their current DMT. We accepted any definition of non-response that the included studies used because the criteria for treatment failure, either using clinical or imaging criteria, were still not agreed upon and different criteria were used in clinical routine practice. Diagnostic criteria for MS were the Poser criteria (Poser 1983), and the McDonald criteria and its revisions (McDonald 2001; Polman 2005; Polman 2011; Thompson 2018). We included all forms of MS (i.e. relapsing MS, secondary progressive MS, and primary progressive MS), regardless of disease duration and disability degree according to the Expanded Disability Status Scale (EDSS) (Kurtzke 1983).

Types of interventions

Rituximab as 'first choice' and as 'switching' treatment, as monotherapy or in combination treatments, irrespective of doses, timing, and frequency of treatment. We included combination treatments only if they were used in all the comparison groups.

We included studies comparing rituximab with placebo or with approved DMTs, interferons, peg interferon, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, cladribine, alemtuzumab, daclizumab, or ocrelizumab. We included studies that assessed switching to rituximab from another DMT compared to placebo or any other DMT, independently of the reason for switching, method, or time when the switch was made.

Types of outcome measures

We included short-term (12 to 24 months) and long-term (> 24 months) outcomes reported in the included studies.

Primary outcomes

Critical outcomes

- Disability worsening: number of participants with sustained disability worsening based on clinical follow-up visits. Worsening was defined as at least a 1-point increase on the EDSS (Kurtzke 1983), or a 0.5-point increase if the baseline EDSS score was more than 5.5, confirmed during two consecutive clinical examinations separated by an interval of at least six months free of attacks and carried out by the same physician. EDSS is an ordinal scale, where a score of 0 is no disability, 3 indicates mild disability, 6 walking stick requirement, 7 wheelchair use, and 10 is death from MS. An advantage of the EDSS over other disability measures is its international acceptance (e.g. by the European Medicines Agency (EMA)) as a primary endpoint in clinical trials (EMA 2015), and its broad use in trials that enables cross-study comparisons (Meyer-Moock 2014). We also assessed time-to-disability worsening.
- Recurrence of relapse: number of participants with clinical relapse, based on clinical follow-up visits. 'Relapse' was defined as the appearance of one or more new symptoms due to MS, or the deterioration of pre-existing symptoms, persisting more than 24 hours in the absence of fever, and preceded by a period of stability of at least one month (McDonald 2001). We also assessed time-to-relapse.
- Serious adverse events (SAEs): number of participants with SAEs, as defined by the authors of the study. If an insufficient number of studies reported the total number of SAEs and person-years, we used the number of participants with at least one SAE as defined in the study.

Secondary outcomes

Important prioritised outcomes

The following four outcomes, together with the critical outcomes, were prioritised to form the basis of the GRADE assessment and were summarised in the review's abstract and in the summary of findings tables.

- Quality of life: number of participants reporting quality of life impairment, assessed according to validated measures (e.g. the Multiple Sclerosis Quality of Life-54 tool (MSQOL-54), which is a multidimensional health-related quality of life measure (Vickrey 1995)). MSQOL-54 includes the generic 36-item Short-Form quality of life instrument, supplemented with 18 MS-specific items that were based on expert opinion and literature review. There is no single overall score for MSQOL-54. Two summary scores, physical health and mental health, can be derived from a weighted combination of scale scores (scale scores range from 0 to 100 and a higher scale score indicates improved quality of life).
- Number of participants with common infections.
- Number of participants with cancer.
- Mortality.

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Additional important outcomes

- Annualised relapse rate (ARR): mean number of new relapses per participant, adjusted for the duration of follow-up to annualise it. ARR is a frequently reported clinical outcome in trials on relapsing MS.
- Cognitive decline: number of participants with cognitive worsening, assessed according to validated neurocognitive batteries for MS (e.g. the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Benedict 2020; Langdon 2012).
- Number of participants with new or enlarging T2-weighted MRI lesions*. A T2-weighted MRI sequence provides information about the total number of lesions. T2 lesions appear as bright spots on the scan and could correlate to a panel of different MS pathological hallmarks. However, new T2 lesions are used as a measure of disease activity.
- Number of participants with new gadolinium-enhancing positive T1-weighted MRI lesions*. T1-weighted MRI lesions, mostly black holes, are believed to represent permanent tissue damage. Gadolinium-enhancing T1 lesions are a surrogate for blood–brain barrier breakdown.
- Number of participants who discontinued treatment due to adverse events. We also assessed time-to-discontinuation.
- Number of participants with grade 3 and grade 4 adverse events (US Department of Health and Human Services 2017).
- Number of participants with long-term adverse events: opportunistic infections, hypogammaglobulinaemia, cardiovascular events (hypotension, hypertension, arrhythmias, and angina), and HBV reactivation.
- Number of participants with short-term adverse events: infusion-related reactions.

*We judged MRI lesions as surrogate outcomes, but included them in the review in the presumption that changes in the surrogate reflect changes in relapse and disability that are important to patients.

Search methods for identification of studies

We applied no time, language, or publication status restrictions to the search for primary studies.

Electronic searches

We designed search strategies for electronic databases according to methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019). The Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group's Information Specialist designed and executed the search strategies. We searched the following databases and trials registries for primary studies, updated on 31 January 2021. The search strategies are documented in Appendix 1. For studies that are listed in trials registries and not yet published in full elsewhere, we included them as ongoing studies for the current review, and will add or update data in updates of the review once they are available as full-text reports.

Databases of medical literature

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (2021, Issue 1).
- MEDLINE (PubMed) (1966 to 31 January 2021).
- Embase (Embase.com) (1974 to 31 January 2021).
- CINAHL (via EBSCO) (1981 to 31 January 2021).

Trials registries and registry platforms to identify ongoing studies and results of completed studies

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int).
- US National Institutes of Health clinical trial register (www.clinicaltrials.gov).
- European Union Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

We reviewed the reference lists of relevant articles, review articles, and textbooks. We contacted study investigators to request missing data.

Data collection and analysis

Selection of studies

We used the search strategy described in the Search methods for identification of studies section to obtain titles and abstracts of studies. Two review authors (GF and JK) independently screened the titles and abstracts and discarded studies that were not applicable; however, they initially retained studies and reviews that might have included relevant data or information on eligible studies. Two review authors (GF and JK) independently assessed the retrieved abstracts and, when necessary, the full-text articles to determine which studies satisfied the inclusion criteria. The two review authors compared multiple reports of the same study and used the most comprehensive report. They linked multiple publications as companion reports, but excluded true duplicates. GF and JK resolved discrepancies in judgement by discussion, and reported excluded studies and their reasons for exclusion in the Characteristics of excluded studies table. We reported included studies in the Characteristics of included studies table. We created a PRISMA flow chart reporting the selection process (Moher 2009).

Data extraction and management

Two review authors (GF and JK) independently extracted data using a predefined data extraction form in an Excel spreadsheet. They resolved any disagreements by discussion. We requested additional data through correspondence with four study authors (Filippini 2021a; Filippini 2021b; Filippini 2021c; Filippini 2021d). Authors of two included studies provided us with additional outcome data.

Outcome data

We extracted the following data from each included study:

- number of participants who had disability worsening based on clinical follow-up visits;
- number of participants who had clinical relapses based on clinical follow-up visits;
- number who withdrew due to any adverse event;
- measures and results of critical and important outcomes that were reported in the included studies (e.g. hazard ratio (HR) for time-to-event outcomes).

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We extracted the authors' definition and measure used in the study to assess each reported outcome. For continuous outcomes, we extracted mean and standard deviation of the comparison groups, where possible. We extracted arm-level data when possible, otherwise we extracted effect sizes. For NRSIs, we extracted unadjusted and adjusted effect sizes. We extracted data at the authors' defined time points.

Other data

From each included study, we extracted data on the following:

- study: first author or acronym, number of centres and location, study setting, year of publication, years that the study was conducted (recruitment and follow-up), publication status (full-text publication, abstract publication, unpublished data);
- study design (RCT or NRSI), inclusion and exclusion criteria, number of randomised participants, withdrawals, early termination of trial;
- participants: age, sex, diagnostic criteria, type and duration of MS, important baseline data (EDSS score, percentage of participants with previous use of DMTs, MRI lesions);
- interventions: first choice or switching intervention, comparison, concomitant medications, duration of follow-up;
- conflict of interests of study authors;
- funding of the study.

One review author (GF) transferred data into Review Manager Web software (Review Manager Web).

Assessment of risk of bias in included studies

For the scope of this review, we assessed the effect of assignment to the intervention (intention-to-treat effect) for disability worsening, relapses, treatment discontinuation due to adverse events, and T1 and T2 MRI lesions. We also assessed the effect of adhering to the intervention (per-protocol effect) for all the other outcomes (numbers of participants with SAEs and further adverse events).

Randomised controlled trials

Two reviews authors (JK and GF) independently assessed the risk of bias for each study using the Cochrane Collaboration's tool for assessing risk of bias that include: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessor, incomplete outcome data, selective outcome reporting, and other bias, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We judged the risk of bias of each study and classified it as low, high, or unclear risk of bias. We judged incomplete outcome data at low risk of bias when numbers and causes of dropouts were balanced between arms (i.e. in the absence of a significant difference) and appeared to be unrelated to the outcome. We resolved any disagreements between the review authors by discussion.

Controlled non-randomised studies of interventions

Two reviews authors (JK, GF) independently assessed the risk of bias using the ROBINS-I (version August 2016) (Sterne 2016). Based on the inclusion and exclusion criteria for this review, we defined our generic target trial as rituximab versus placebo or versus other DMTs for the treatment of people with MS. Therefore, we used the ROBINS-I analogue of starting experimental intervention versus starting control intervention to evaluate risk of bias.

The ROBINS-I tool includes the following bias domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported result.

We applied the ROBINS-I tool to groups of outcomes according to 'effect of assignment' (including disability worsening, recurrence of relapse, treatment discontinuation due to adverse events, new or enlarging T2-weighted MRI lesions; new gadolinium-enhancing positive T1-weighted MRI lesions) and 'effect of adherence' (including all other outcomes). We assigned an overall risk of bias to each group based on the worst assessment across all bias domains using the recommended levels (low, moderate, serious, or critical risk of bias, or no information) (Sterne 2016). We resolved any disagreements between the review authors by discussion.

Baseline confounding by indication is likely to be the most frequent confounder in NRSIs that meet the inclusion criteria. For example, participants with high pretreatment MS activity are likely to be treated with a highly efficacious drug (e.g. fingolimod, natalizumab), whereas participants with low pretreatment MS activity are likely to be treated with a less powerful drug (e.g. interferon beta or glatiramer acetate). A cohort study comparing two or more DMTs for MS should control for baseline age, sex, MS duration, relapse within the previous year, EDSS score, MRI activity, and proportion of participants previously treated with DMTs. All these variables are prognostic for the outcomes included in the review and are also likely to influence choice of treatment. In some NRSIs, particularly those based on registries (i.e. routinely collected data), participants might have been observed for different follow-up periods due to differences in drug licensing and availability across different geographical and historical cohorts (Trojano 2017). This different follow-up period could confound the results, particularly regarding long-term outcomes. For each NRSI, we recorded whether the study controlled for these important confounding domains and used an analysis method to reduce confounding.

Adverse events

We extracted data on the prespecified adverse events and the total number of withdrawals due to adverse events.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Filippini 2021), and reported any deviations from it in the Differences between protocol and review section.

Measures of treatment effect

Randomised controlled trials

We extracted and report HRs with 95% confidence intervals (CIs) for time-to-event outcomes (time to disability worsening, time to relapse, and time to treatment discontinuation). For continuous outcomes (ARR, cognitive decline, and quality of life), we calculated the mean difference (MD) if studies used the same metric, or the standardised mean difference (SMD) if studies used different metrics, with 95% CIs. For dichotomous outcomes, we reported the odds ratio (OR) with 95% CI.

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Controlled non-randomised studies of interventions

For dichotomous outcomes, we reported OR with 95% CIs. For continuous outcomes (ARR, cognitive decline, and quality of life), we calculated the MD if studies used the same metric, or the SMD if studies used different metrics, with 95% CI. For time-to-event outcomes (time to disability worsening, time to relapse, and time to treatment discontinuation), we reported HRs with 95% CI.

Unit of analysis issues

Cluster-randomised trials and cross-over trials are not relevant to DMTs for MS.

Studies with multiple treatment groups

For multiple arm trials, the intervention groups of relevance were all those that could be included in a pairwise comparison of intervention groups which, if investigated alone, would have met the criteria for including studies in the review. For example, if we identified a study comparing rituximab versus glatiramer acetate versus rituximab plus glatiramer acetate, we used one comparison (rituximab versus glatiramer acetate), since it addressed the review's objective. Thus, data from the rituximab plus glatiramer treatment group were not relevant to the review. However, if the study compared rituximab versus glatiramer versus fingolimod, the two pairwise comparisons of rituximab versus glatiramer and rituximab versus fingolimod, were relevant to the review. In this case, we treated multiple arm studies as multiple independent two-arm studies.

We listed all treatment arms in the Characteristics of included studies table, even if they are not used in the review.

For multiple arm trials involving the same agent at different doses compared to a control treatment, we had planned to convert the treatment arms into a single arm by merging the different doses. We did not include studies involving the same agent at different doses without a comparison group.

Dealing with missing data

We used data that reflected the intention-to-treat analysis (the effect of assignment) for each included outcome except for adverse events, for which we assessed the risk of bias in relation to the effect of adherence (per protocol effect). We attempted to retrieve missing data from study authors. In order to assess the effect of missing outcome data where not reported or provided, we assumed that treated and control group participants who were missing both had an unfavourable outcome. If standard deviations were missing for continuous outcomes, we calculated them according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Assessment of heterogeneity

We quantified statistical heterogeneity using the I^2 statistic (Higgins 2003). We interpreted it using the following guide: I^2 statistic > 30% signifies moderate heterogeneity, I^2 > 75% signifies considerable heterogeneity (Deeks 2019).

Assessment of reporting biases

Reporting bias

As specified in the Types of studies section, we included results that were published in non-commercial trial registries. This was to ensure that we captured completed studies that had not been published elsewhere, in order to minimise publication bias. We included studies irrespective of their publication status, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2019). We had planned to evaluate potential publication bias using a funnel plot; however, there were fewer than 10 studies were available for meta-analysis (Page 2019).

Selective non-reporting bias

We expected that most of the included NRSIs did not have an available protocol, and that even protocols for RCTs might lack a detailed analysis plan. Therefore, we decided that if a study appeared to be carried out appropriately, we checked for consistencies between the outcome measurements and analyses described in the methods and those reported in the results of the included studies.

Data synthesis

We conducted an initial qualitative comparison of all the included studies to examine whether pooling of results was reasonable. This considered differences in study populations, inclusion and exclusion criteria, interventions, and outcome assessment. If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in meta-analyses.

We conducted separate analyses for RCTs and NRSIs, relapsing and progressive forms of MS, for rituximab as 'first choice' treatment (treatment naive) and rituximab as 'switching' from another DMT. When articles reported on a cohort (same database, e.g. the Swedish MS register) that overlapped with a cohort in another paper, we did not pool the comparators since participants in the rituximab group were the same across comparisons.

For RCTs, when meta-analysis was feasible, we used the random-effects model for pooling the data. For binary outcomes, we based the estimation of the between-study variance using the Mantel-Haenszel method. We used the inverse variance method for continuous outcomes, outcomes where HRs were available, or outcomes where only one study was included (fixed-effect model).

If a meta-analysis was feasible for controlled NRSIs, we analysed outcomes with adjusted effect estimates if these were adjusted for the same factors using the inverse-variance method, as recommended in Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2019). We used Review Manager Web software for analyses (Review Manager Web).

We excluded from all meta-analyses results from NRSI judged to be at 'critical' risk of bias using ROBINS-I.

Subgroup analysis and investigation of heterogeneity

We had planned subgroup analyses for active or inactive MS. These analyses were not performed because only two RCTs and three NRSIs provided the information. We did subgroup analyses for treatment comparisons: placebo or each individual DMT.

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Sensitivity analysis

We had planned a sensitivity analysis to remove from analyses those data at critical or high risk of bias. This was not performed because we judged four of five included RCTs at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in summary of findings tables, according to recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020). For the included NRSIs, we followed GRADE guidance 18 (Schünemann 2019). For time-to-event outcomes, we calculated absolute effects at specific time points, as recommended in GRADE guidance 27 (Skoetz 2020). We expressed the findings and certainty of the evidence as suggested in the informative statement guidance (Santesso 2020).

In the protocol, we had planned to present four summary of findings tables and additional tables for comparison versus placebo. In the review phase, due to the large number of treatment comparisons, we decided to restrict the results showed in the summary of findings to the effect estimates of rituximab as 'first choice' treatment and as 'switching' versus other DMTs for relapsing MS, critical and prioritised important outcomes (Summary of findings 1; Summary of findings 4). We decided to keep all possible treatment comparisons for which evidence were available because we believe that this information is important for clinicians and patients who use different treatments in the clinical practice. We reported completed tables, including results from RCTs, NRSIs, and for progressive MS, in Table 2.

We reported the following outcomes in the summary of findings tables:

- number of participants with disability worsening;
- number of participants with recurrence of relapses;
- number of participants with SAEs;
- number of participant reporting impairment in quality of life;
- number of participants with common infections;
- number of participants with cancer;
- number of deaths.

In the summary of findings tables, we prioritised long-term outcomes if they were available, otherwise we included short-term outcomes. We assessed the certainty of evidence for each outcome considering the risk of bias, indirectness, inconsistency, imprecision of effect estimates, and risk of publication bias. Using GRADEpro GDT software (GRADEpro GDT), we assigned one of four levels of certainty of evidence: high, moderate, low, or very low.

RESULTS

Description of studies

For a full description of studies, see the Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Results of the search

We identified 3574 records (MEDLINE 1380, Embase 1655, CINAHL 413, CENTRAL 70, clinical trials registries 56). After removing duplicates, we screened 3247 records based on their titles and abstracts, and we excluded 3152 records that we considered not pertinent. We evaluated the remaining 95 records and screened the full texts, or, if these were not available, abstract publications or trials registry entries.

We identified 32 eligible studies (50 records): 15 included studies (25 records) (Alcalá 2019; Alping 2016; Alping 2020; Boremalm 2019; Cheshmavar 2021; Etemadifar 2019; Evertsson 2020; Granqvist 2018; Hauser 2008; Hawker 2009; Komori 2016; Luna 2020; Naegelin 2019; Spelman 2018; Vollmer 2020a), 14 ongoing studies (22 records), and three studies awaiting classification (Berrios Morales 2016; Frisell 2019; Kalincik 2019). We excluded 63 studies (74 records) with reasons. See Figure 1 for the study flow diagram (Moher 2009).

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Figure 1. PRISMA flow diagram. Search updated to 31 January 2021. DMT: disease-modifying treatment.

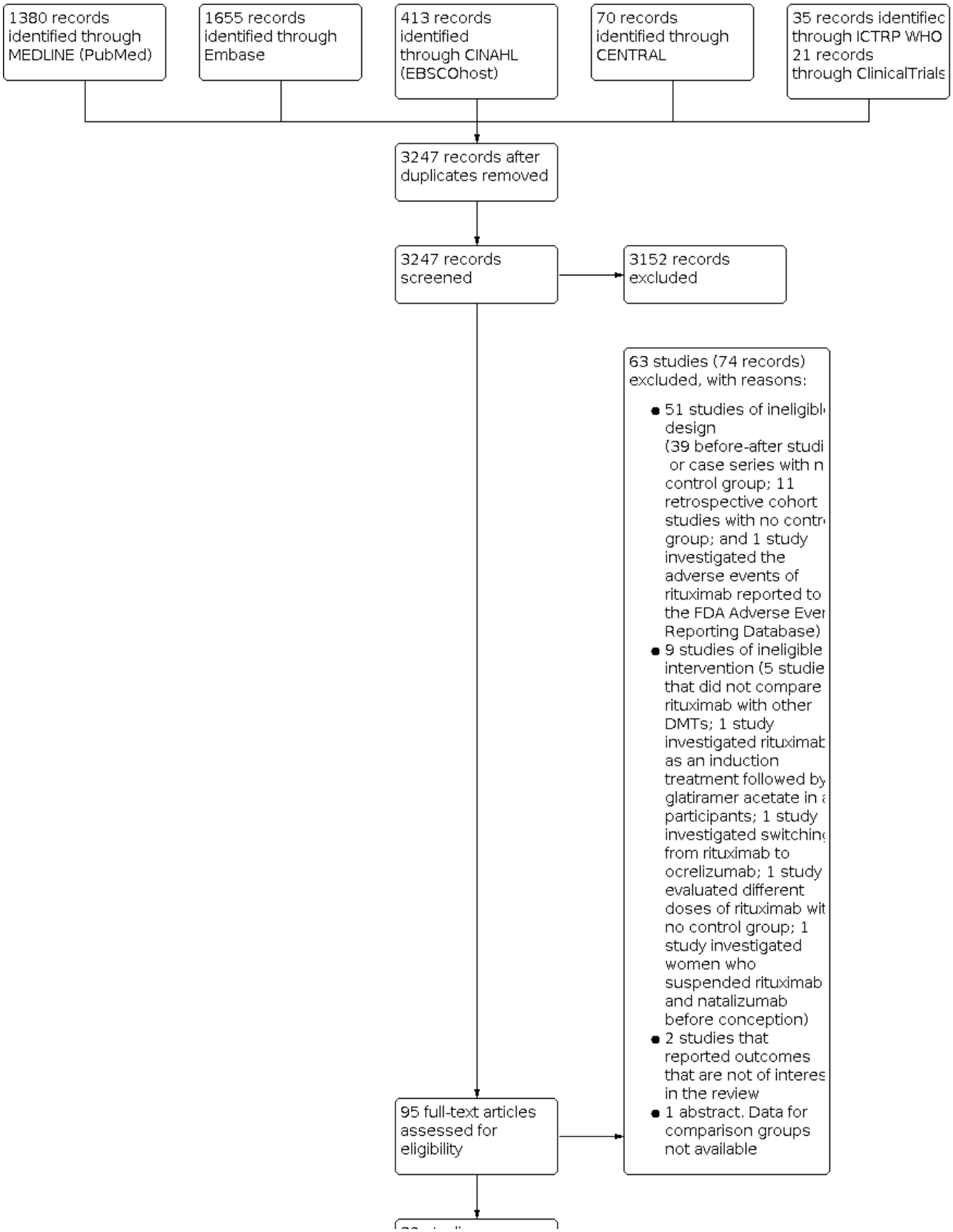

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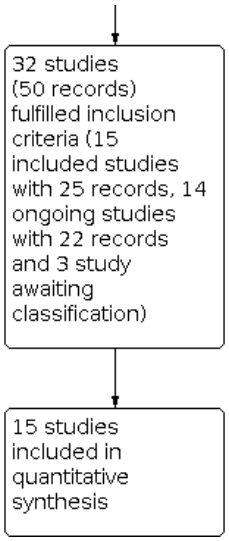
Figure 1. (Continued)



Included studies

We included 15 studies describing 16,429 participants of whom approximately 6000 received rituximab (Alcalá 2019; Alping 2016; Alping 2020; Boremalm 2019; Cheshmavar 2021; Etemadifar 2019; Evertsson 2020; Granqvist 2018; Hauser 2008; Hawker 2009; Komori 2016; Luna 2020; Naegelin 2019; Spelman 2018; Vollmer 2020a). These included studies were published between 2008 and 2020. Upon request, authors of one NRSI provided additional outcome data (Alping 2020): they provided us with the number of any invasive cancer outcome stratified by therapy and MS type. The Characteristics of included studies table provides details of included studies.

Design

We included five RCTs (Cheshmavar 2021; Etemadifar 2019; Hauser 2008; Hawker 2009; Komori 2016), and 10 controlled NRSIs (Alcalá 2019; Alping 2016; Alping 2020; Boremalm 2019; Evertsson 2020; Granqvist 2018; Luna 2020; Naegelin 2019; Spelman 2018; Vollmer 2020a).

Setting

One RCT (Komori 2016) and one controlled NRSI (Vollmer 2020a) originated from the USA, two RCTs originated from the USA and Canada (Hauser 2008; Hawker 2009), two RCTs originated from Iran (Cheshmavar 2021; Etemadifar 2019), six NRSIs originated from Sweden (Alping 2016; Alping 2020; Boremalm 2019; Granqvist 2018; Luna 2020; Spelman 2018), one NRSI originated from Sweden and the USA (Evertsson 2020), one NRSI originated from Spain (Alcalá 2019), and one NRSI originated from Switzerland and the Netherlands (Naegelin 2019).

Participants

One RCT (Hauser 2008) and seven NRSIs (Alcalá 2019; Alping 2016; Boremalm 2019; Evertsson 2020; Granqvist 2018; Luna 2020; Spelman 2018) included participants with relapsing MS. Three of these studies included participants meeting the definition of active relapsing MS (Alcalá 2019; Boremalm 2019; Granqvist 2018). Four RCTs (Cheshmavar 2021; Etemadifar 2019; Hawker 2009; Komori 2016) and one NRSI (Naegelin 2019) evaluated participants with progressive MS. Two of these studies included participants meeting the definition of active progressive MS (Cheshmavar 2021; Etemadifar 2019). Two NRSIs included participants as grouped relapsing and progressive MS (Alping 2020; Vollmer 2020a).

Interventions

One RCT evaluated rituximab as a 'first choice' treatment compared with placebo (Hawker 2009) and one NRSI evaluated rituximab as a 'first choice' compared with other DMTs (Granqvist 2018). Two RCTs evaluated rituximab compared with placebo in participants who had previously been treated with other DMTs (Hauser 2008; Komori 2016). Two RCTs (Cheshmavar 2021; Etemadifar 2019) and nine NRSIs (Alcalá 2019; Alping 2016; Alping 2020; Boremalm 2019; Evertsson 2020; Luna 2020; Naegelin 2019; Spelman 2018; Vollmer 2020a) evaluated rituximab compared with other DMTs in participants who had previously been treated with other DMTs. The majority of the included studies administered similar doses of rituximab.

Outcomes

For a detailed description of outcome measures reported in each included study, see Characteristics of included studies table.

Three RCTs provided critical and important beneficial outcomes (Cheshmavar 2021; Hauser 2008; Hawker 2009). We could not include outcome data from two RCTs. One did not report any of our prioritised outcomes (Etemadifar 2019). The other study was terminated early because an interim analysis on cerebrospinal fluid showed a lower-than-expected depletion of intrathecal B cells and 27 included participants were not followed up to measure outcomes (Komori 2016). Seven controlled NRSIs provided outcome data (Alcalá 2019; Alping 2016; Boremalm 2019; Granqvist 2018; Naegelin 2019; Spelman 2018; Vollmer 2020a). Three NRSIs did not measure beneficial outcomes (Alping 2020; Evertsson 2020; Luna 2020). We did not include outcomes from one NRSI that included 55 participants, 27 of whom received rituximab because of the critical risk of bias assessed with ROBINS-I (Alcalá 2019).

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We evaluated harm outcomes from all included RCTs. Eight included NRSIs reported harm outcomes (Alcalá 2019; Alping 2016; Alping 2020; Boremalm 2019; Evertsson 2020; Granqvist 2018; Luna 2020; Vollmer 2020a). One study compared the risk of cancer in a large population of people with MS treated with different DMTs (Alping 2020), and one examined the risk of serious infections associated with DMTs in one large population of people with MS (Luna 2020). One study did not measure harm outcomes (Spelman 2018), and one study reported the number of participants with adverse events in the rituximab group only (Naegelin 2019).

Outcome timing

Median outcome timing was 24 months (12 months from five studies, 18 months from one study, 24 months from eight studies, and 36 months from two studies).

Randomised controlled trials

Cheshmavar 2021 randomised 84 participants with active secondary progressive MS into two groups. The rituximab group received three courses of intravenous infusion of rituximab 1000 mg every six months, and the control group received glatiramer acetate 40 mg three times per week through subcutaneous injection. Timing of outcome assessments was 12 months.

Etemadifar 2019 randomised 80 participants with active secondary progressive MS into two groups. The rituximab group received intravenous infusion of rituximab 1000 mg repeated after two weeks, and then every six months with the same dosage if there was an increase in CD19 and CD20 levels, and the control group received intravenous pulse of cyclophosphamide 1000 mg every month until two years. Timing of outcome assessments was 24 months.

Hauser 2008 randomised 104 participants with relapsing MS into two groups. The rituximab group received a single course of intravenous infusion of rituximab 1000 mg on days one and 15, and the control group received a single course of intravenous infusion of placebo 1000 mg on days one and 15. Timing of outcome assessments were 24 and 48 weeks.

Hawker 2009 randomised 439 participants with primary progressive MS into two groups. The rituximab group received four courses of two intravenous infusion of rituximab 1000 mg each, two weeks apart, and the control group received four courses of two intravenous infusion of placebo 1000 mg each, two weeks apart. Sixty-five percent of participants had no prior treatment with DMTs. Timing of beneficial outcome assessments was 96 weeks. Adverse events were monitored until 122 weeks.

Komori 2016 randomised 27 participants with secondary progressive MS into two groups. The rituximab group received intrathecal injection of rituximab 25 mg (1:1 dilution in normal saline) followed by intravenous infusion of rituximab 200 mg at day 0 and 15, and 25 mg of intrathecal rituximab at months 1.5 and 12. The control group received intrathecal and intravenous placebo at month zero, followed by additional intravenous placebo at month 0.5 and another dose of intrathecal placebo at months 1.5 and 12. Timing of outcome assessments was 24 months.

Controlled non-randomised studies of interventions

Alcalá 2019 (the Grup d'Investigació i Tractament de l'Esclerosi Múltiple (GITEM) register) conducted a multicentre cohort study that retrospectively compared 28 participants with active relapsing MS, who switched from fingolimod to alemtuzumab, administered daily intravenously on five consecutive days at month zero, and on three consecutive days at month 12, with 27 participants with active relapsing MS, who switched from fingolimod to intravenous infusion of rituximab 1000 mg on day one and day 15. For maintenance, an isolated dose of rituximab 1000 mg was administrated when the percentage of total CD19 cells was 2% or more. Timing of outcome assessments was 12 months.

Alping 2016 conducted a multicentre cohort study, based on the Swedish MS register, that retrospectively compared 114 participants with relapsing MS who switched from natalizumab, due to John Cunningham (JC) virus antibody positivity, to rituximab or fingolimod. Participants who received intravenous infusions of rituximab 500 mg or 1000 mg every six months were compared to participants who received oral administration of fingolimod 0.5 mg once daily. Authors adjusted for confounding factors, including sex, age, time receiving natalizumab, washout time, baseline EDSS, follow-up time, and study centre. Timing of outcome assessments was 18 months.

Alping 2020 conducted a nationwide register-based cohort study, linking data from the Swedish MS register to the Swedish Cancer register and other national healthcare and census registers. Primary outcome was time to first invasive cancer. The study included 4187 first-ever initiations of rituximab, 1620 of fingolimod, and 1670 of natalizumab in 6136 people with MS matched for age, sex, and location to 37,801 people from a general population without MS.

Boremalm 2019 conducted a multicentre cohort study, based on the Swedish MS register, that retrospectively compared 241 participants with active relapsing MS who switched from interferon beta or glatiramer acetate, due to treatment failure, to rituximab or natalizumab or fingolimod. Participants who received intravenous infusions of rituximab 500 mg or 1000 mg every six months were compared to participants who received intravenous infusions of natalizumab 300 mg every four weeks and to participants who received oral administration of fingolimod 0.5 mg once daily. Authors adjusted for confounding factors, including sex, age at inclusion, duration of MS since debut, time receiving last DMT before switch, time from disease activity to switch, EDSS at baseline, and centre. Timing of outcome assessments was 24 months.

Evertsson 2020 conducted a multicentre cohort study, based on the Swedish MS register and the Rocky Mountain MS Clinic database, that retrospectively compared 472 people with relapsing MS. Participants who received a single intravenous infusion of rituximab 500 mg or 1000 mg followed by a single infusion of 500 mg every five to seven months were compared to participants who received two intravenous infusions of ocrelizumab 300 mg two weeks apart followed by a single infusion of 600 mg every five to seven months. Timing of outcome assessments was 12 months.

Granqvist 2018 conducted a propensity score-matched cohort study, based on the Swedish MS register, that retrospectively compared 488 participants with active relapsing MS who received a 'first choice' treatment of rituximab, interferon beta or glatiramer acetate, dimethyl fumarate, fingolimod, or natalizumab. The rituximab group received intravenous infusions of 500 or 1000 mg every six months. The interferon beta or glatiramer acetate group

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received subcutaneous injection of interferon beta 1b 0.25 mg every other day, intramuscular injection of interferon beta 1a 0.03 mg once per week, subcutaneous injection of interferon beta 1a 0.022 mg or 0.044 mg once per week, or subcutaneous injection of glatiramer acetate 20 mg daily. The dimethyl fumarate group received oral administration of dimethyl fumarate 120 mg once daily for seven days tapered upwards to 240 mg twice a day. The fingolimod group received oral administration of fingolimod 0.5 mg once daily. The natalizumab group received intravenous infusions of natalizumab 300 mg every 4 weeks. Matching criteria included age, sex, baseline EDSS score, MS duration after debut and diagnosis, relapse in the year before treatment initiation, region, and follow-up time. Timing of outcome assessments was 24 months.

Luna 2020 conducted a nationwide register-based cohort study linking the Swedish MS register to national healthcare and census registries using the national personal identity number. Primary outcome was serious infections that were defined as all infections resulting in hospitalisations. The study included 6421 participants with relapsing MS who initiated treatment with rituximab (3260 participants), interferon beta or glatiramer acetate (2217 participants), fingolimod (1535 participants), and natalizumab (1588 participants). HRs were adjusted for age, sex, educational level, country of birth, sick leave, disability pension, hospitalisations in the previous five years, history of infections, cancer, antidepressant use, antipsychotic use, major adverse cardiovascular events, arrhythmia, year of treatment start, region of treating clinic, relapses last year, MS duration, EDSS, MS Impact Scale-29, EuroQol 5-Dimension scale, and Symbol Digit Modalities test.

Naegelin 2019 conducted a multicentre case-control study that retrospectively compared 44 participants with secondary progressive MS who were treated with rituximab at two MS centres in Basel and Lugano, Switzerland, to 44 participants with secondary progressive MS, who were never treated with rituximab and were recruited from two cohorts, one at the MS centre in Basel and one at the MS centre in Amsterdam, the Netherlands. Timing of outcome assessments was 36 months. Doses of rituximab were not reported and the control group had never been treated with rituximab.

Spelman 2018 conducted a propensity score-matched cohort nationwide study based on the Swedish MS register between April 2005 and November 2015. Authors retrospectively compared 461 participants with relapsing MS, who switched from previous DMTs to rituximab, with 922 participants with relapsing MS who switched from previous DMTs to interferon-beta or glatiramer acetate. The rituximab group received intravenous infusions of 500 mg or 1000 mg every six months. The interferon beta or glatiramer acetate group received subcutaneous injection of interferon beta 1b 0.25 mg every other day, intramuscular injection of interferon beta 1a 0.03 mg once per week, subcutaneous injection of interferon beta 1a 0.022 mg or 0.044 mg once per week, or subcutaneous injection of glatiramer acetate 20 mg daily. Matching criteria included sex, age, EDSS and disease duration at baseline, number of prebaseline DMT starts, proportion of disease duration on treatment, the number of DMT starts as a proportion of disease duration, relapse activity in the 12- and 24-months prebaseline, the index year of the DMT start, and the number of assessments per year of follow-up. Timing of outcome assessments was 24 months.

Vollmer 2020a conducted a single-centre cohort study that retrospectively compared 1246 participants with all types of MS who received rituximab, fingolimod, dimethyl fumarate, or natalizumab. The rituximab group (182 participants) received an induction dose of intravenous infusions of 1000 mg at day one and day 14, and 500 mg every six months. Doses and frequency of fingolimod (271 participants), dimethyl fumarate (342 participants), natalizumab (451 participants) were not reported. The study controlled for confounding through statistical analyses for the primary outcome, a composite measure consisting of clinical relapse, gadolinium-positive lesions, or new T2 lesions on follow-up MRI. However, authors reported only unadjusted data for relapse and MRI lesions that were our predefined outcomes of interest. Timing of outcome assessments was 24 months.

Excluded studies

We excluded 63 studies that did not match our inclusion criteria. The Characteristics of excluded studies table provides details on these studies.

- Fifty-one studies were of ineligible design: 39 were before-after (pre–post) studies, cross-sectional studies, or case series with no control group (Airas 2020; Alcalá 2018; Alldredge 2018; Alvarez 2015; Bar-Or 2008; Bellinvia 2020; Bergman 2018; Bhargava 2019; Boremalm 2021; Cross 2012; D'Amico 2019; Das 2018; de Flon 2016; Disanto 2021; Dunn 2018; Durozard 2019; Ellrichmann 2019; EUCTR2013-002378-26; Hellgren 2020; Kuempfel 2019; Leonidou 2019; Maarouf 2020; Malucchi 2016; Mathew 2020; Mazdeh 2020; Midaglia 2020; Naismith 2010; Naser Moghadasi 2019; Nielsen 2012; Sahraian 2020; Salzer 2016; Schwake 2020; Shima 2020; Topping 2016; Tsao 2019; Wolf 2019; Yamout 2018; Zecca 2020; Zhovtis Ryerson 2018); 11 were retrospective cohort studies with no control group (Barmettler 2018; Barra 2016; Berntsson 2018; Boström 2016; Brown 2011; Ciplea 2020; Juto 2020; Persson 2020; Smith 2020; Torgauten 2021; Vollmer 2020b); and one study investigated the adverse events of rituximab reported to the FDA Adverse Event Reporting Database (Caldito 2021).
- Nine studies were of ineligible intervention: five studies did not compare rituximab with other DMTs (Hallberg 2019; He 2020; Langer-Gould 2018; Langer-Gould 2020; Wijnands 2018); one study investigated rituximab as an induction treatment followed by glatiramer acetate in all participants (Honce 2019); one study investigated switching from rituximab to ocrelizumab (NCT02980042); one study evaluated different doses of rituximab with no control group (NCT03979456); and one study investigated women who suspended rituximab and natalizumab before conception (Razaz 2020).
- Two studies reported outcomes that were not relevant. One reported only the JC antibody titres (Gottesman 2017), and the other study reported only "evidence of disease activity (EDA)" (Scotti 2018).
- One study was in abstract form only (Langer-Gould 2019). We wrote to the authors asking for additional data, but received no reply (Filippini 2021d). This was a retrospective multicentre cohort study conducted in the USA (Kaiser Permanent Southern California, KPSC) and Sweden. The KPSC cohort included 1175 people with MS treated with rituximab compared with glatiramer acetate. The Swedish cohort included 3165 people with MS treated with rituximab compared with fingolimod.

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Studies awaiting assessment

We kept three eligible studies under 'awaiting classification' because their data were only available in abstract form (Berrios Morales 2016; Frisell 2019; Kalincik 2019). Sufficient information was not available on study design, characteristics of participants, interventions, and outcomes. We will include the studies in the update of this review.

Ongoing studies

We identified 14 ongoing studies. Eleven are RCTs (EUCTR2017-000426-35-AT; EUCTR2020-002981-15-DK; IRCT20130812014333N125; NCT02545959; NCT02746744; NCT03315923; NCT03500328; NCT03535298; NCT04047628; NCT04121403; NCT04578639). One study is expected to be completed in August 2021, and plans to evaluate 200 participants (NCT02746744). Three large RCTs are planned for completion in 2023: NCT03500328 with 900 participants; NCT03535298 with 800 participants; and NCT04121403 with 264 participants. One RCT is planned for completion in 2025 (NCT04578639), and two RCTs in 2028 (EUCTR2020-002981-15-DK; NCT04047628). Another three RCTs are reported as completed in the study registries, but results are not published yet (IRCT20130812014333N125; NCT02545959; NCT03315923). The prospective completion date was not available for one RCT (EUCTR2017-000426-35-AT). Two ongoing NRSIs are planned for completion in 2022: NCT03193866 with 3526 participants from the Swedish registry, and NCT04283747 with 170 participants. One NRSI did not report the prospective completion date. The Characteristics of ongoing studies table provides details on these studies.

Risk of bias in included studies

Risk of bias in randomised controlled trials

We assessed risk of bias of the included RCTs using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2017). We rated the overall risk of bias to be unclear for Hawker 2009 and high for the other four included RCTs (Cheshmavar 2021; Etemadifar 2019; Hauser 2008; Komori 2016) (see Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included randomised controlled trials.

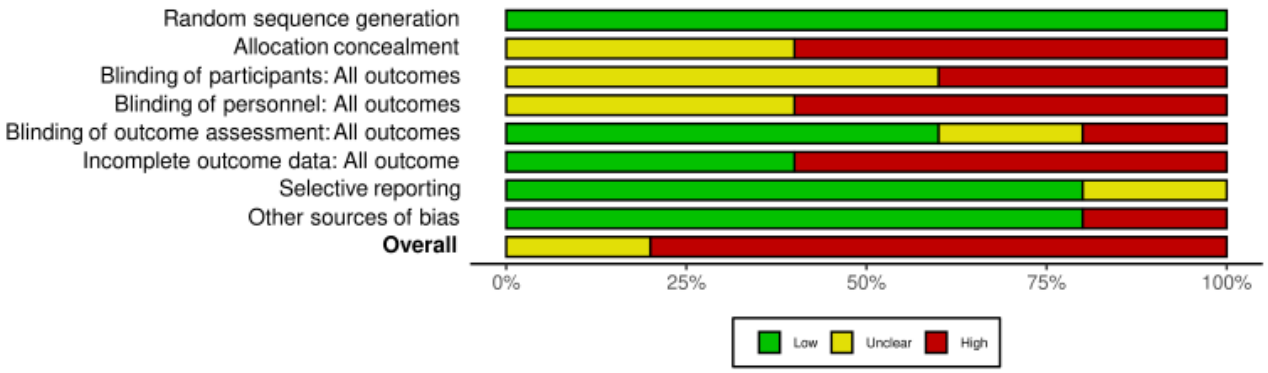

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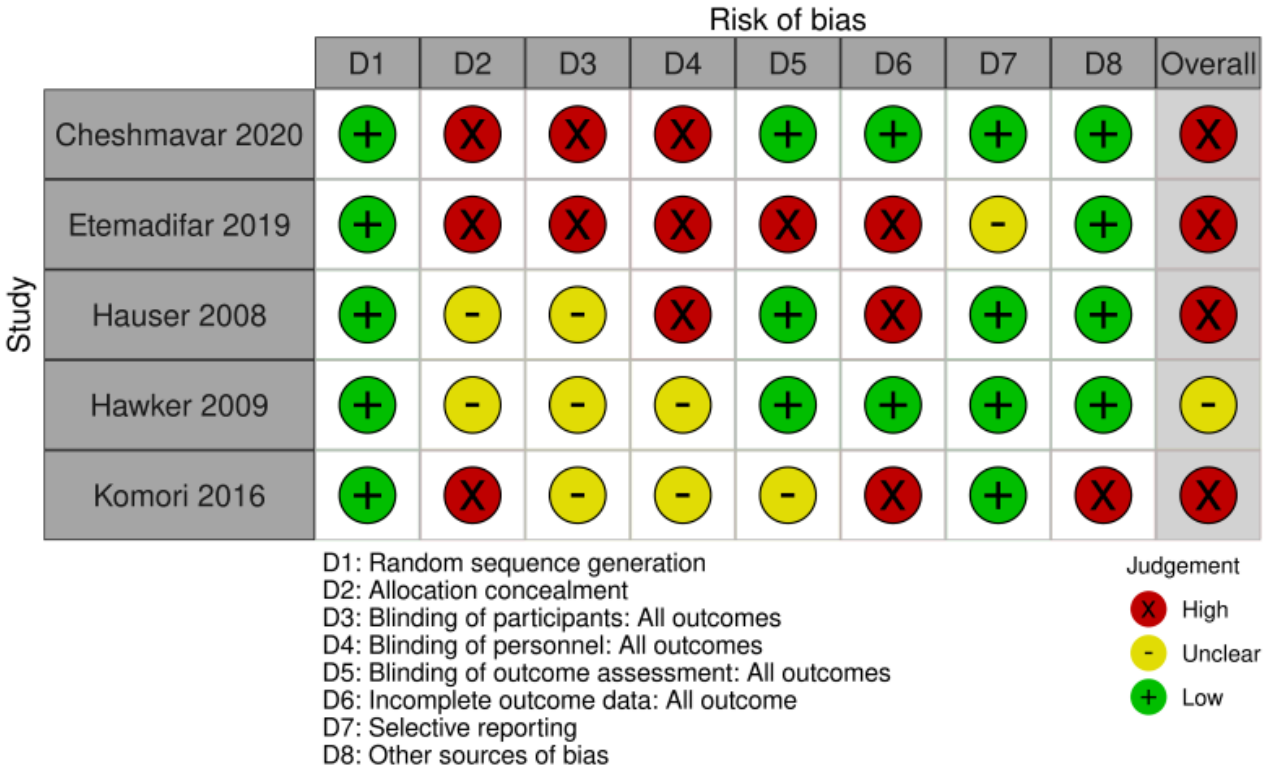
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included randomised controlled trial.



Allocation

We assessed this domain on a study level. All included studies were judged to be at low risk of selection bias for the domain of random sequence generation. We judged the risk of bias coming from the randomisation process to be of some concern for Hauser 2008 and Hawker 2009 because the authors provided no information on whether the allocation was concealed. Allocation was not concealed in the other three RCTs (Cheshmavar 2021; Etemadifar 2019; Komori 2016). Therefore, we judged risk of bias for this domain and these studies to be high.

Blinding

Participants were aware of the assigned intervention in Cheshmavar 2021 and Etemadifar 2019. Therefore, we judged risk for performance bias for these studies to be high. The other three RCTs provided no information on whether placebo infusion was indistinguishable from rituximab infusion in terms of taste, appearance, and duration of infusion (Hauser 2008; Hawker 2009; Komori 2016). Therefore, we judged risk for performance bias and these studies to be of some concern.

We judged risk for detection bias for all outcomes to be low for Cheshmavar 2021, Hauser 2008, and Hawker 2009, because assessment of outcomes was performed by an investigator who was blinded to the study group; to be of some concern for Komori 2016, because the authors provided no information on whether the assessment of outcomes was blinded; and to be high for Etemadifar 2019, because the comparison treatments (rituximab and cyclophosphamide) differed in the frequencies of administration and clinical examinations, every six months for the rituximab group and monthly for the cyclophosphamide group.

Incomplete outcome data

We judged risk of bias for missing outcome data to be low for all the outcomes in Cheshmavar 2021 and Hawker 2009, because outcome data were available for all participants. We judged attrition bias to be high in Etemadifar 2019, Hauser 2008, and Komori 2016, because numbers and causes of dropouts are not balanced between comparison groups (i.e. presence of a significant difference) and appeared to be related to the outcomes.

Selective reporting

We judged the risk of reporting bias to be low for all the outcomes in Cheshmavar 2021, Hauser 2008, Hawker 2009, and Komori 2016, because all these studies reported results in accordance with their published protocols (NCT03315923; NCT00097188; NCT00087529; NCT01212094). We judged reporting bias to be of some concern for Etemadifar 2019, because its study protocol was not available.

Other potential sources of bias

We judged the included RCTs to be at low risk of other bias except Komori 2016. We judged this study at high risk of other bias because the authors terminated the study prematurely based on an interim analysis on cerebrospinal fluid biomarkers and participants were not followed up to measure clinical outcomes.

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Risk of bias in controlled non-randomised studies of interventions

We assessed the risk of bias for the NRSIs using the ROBINS-I tool (Sterne 2016). We present the full judgement per study and outcomes, including the support for judgement in Appendix 2; and the risk of bias summaries in Figure 4 and Figure 5.

Figure 4. ROBINS-I summary: review authors' judgements about each risk of bias item for each included non-randomised study and for outcomes assessed to estimate the "effect of assignment to the intervention" (including disability worsening, relapses, treatment discontinuation due to adverse events, T1 and T2 magnetic resonance imaging lesions). Note: two studies did not report the outcomes and were not included in the figure (Alping 2020; Luna 2020).

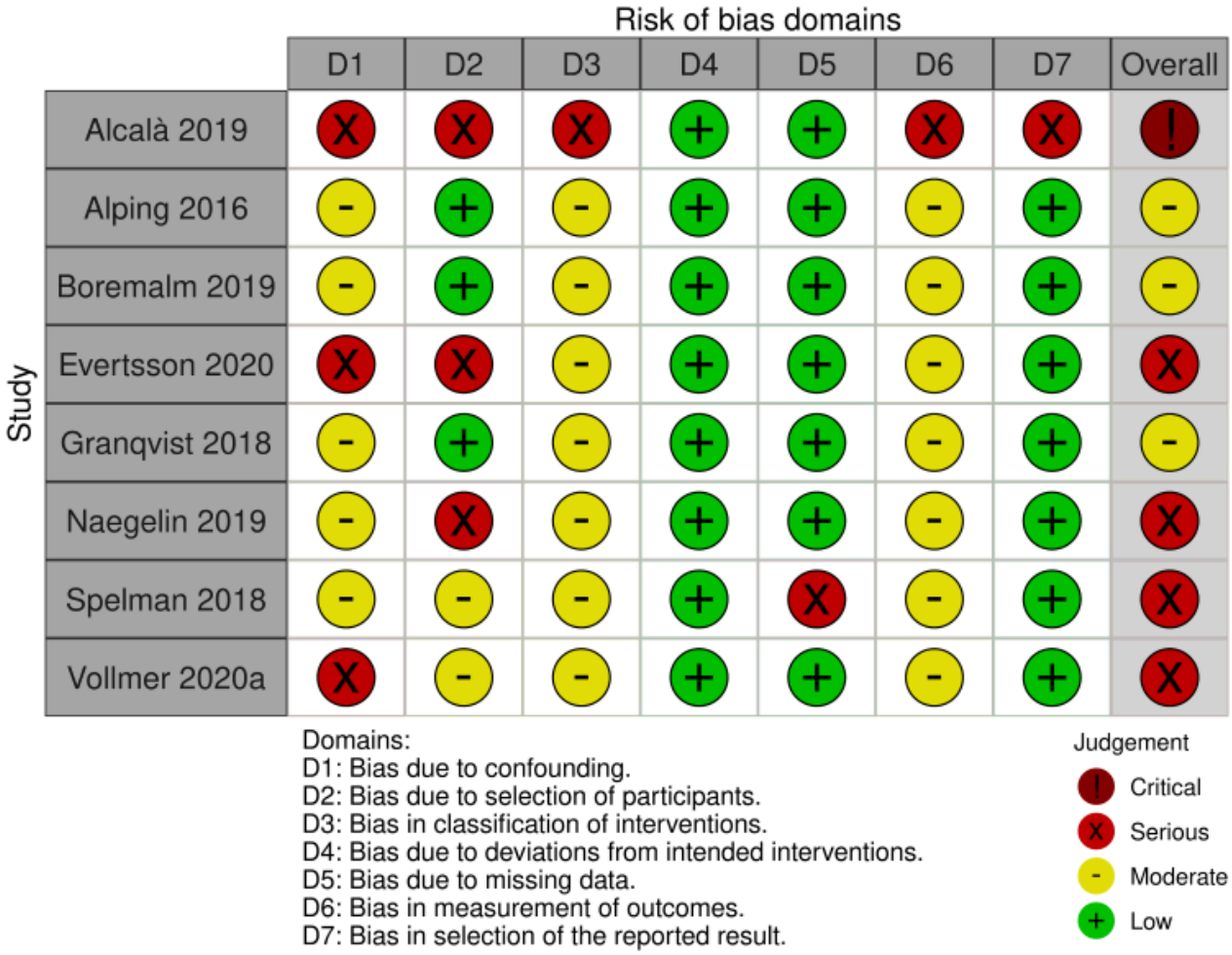

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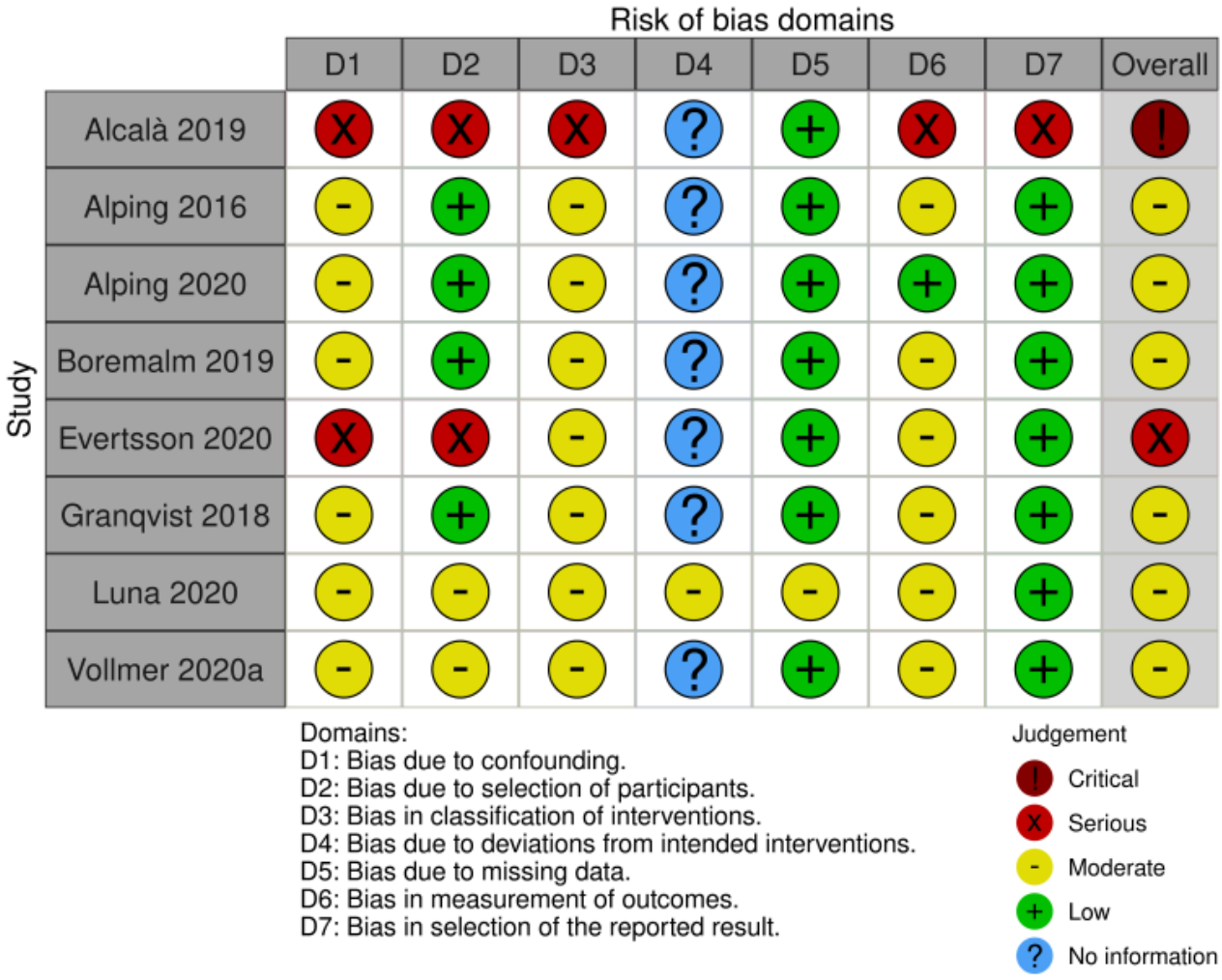
Figure 5. ROBINS-I summary: review authors' judgments about each risk of bias item for each included non-randomised study and for outcomes assessed to estimate the "effect of adherence to the intervention" (including serious adverse events and further adverse events). Note: two studies did not report the outcomes and were not included in the figure (Naegelin 2019; Spelman 2018).



Overall bias

Overall, we rated the risk of bias for outcomes assessed to estimate the 'effect of assignment to the intervention' (including disability worsening, recurrence of relapse, treatment discontinuation due to adverse events, new or enlarging T2-weighted MRI lesions; and new gadolinium-enhancing positive T1-weighted MRI lesions) to be critical in one study (Alcalá 2019), serious in four studies (Evertsson 2020; Naegelin 2019; Spelman 2018; Vollmer 2020a), and moderate in three studies (Alping 2016; Boremalm 2019; Granqvist 2018). Alping 2020 assessed the risk of cancer in a large population of people with MS treated with rituximab or other DMTs and did not report those outcomes. Luna 2020 examined the risk of serious infections associated with rituximab or other DMTs and did not report those outcomes.

We rated the risk of bias for outcomes assessed to estimate the 'effect of adherence to the intervention' (including SAEs and further adverse events) to be critical in one study (Alcalá 2019); serious in one study (Evertsson 2020); and moderate in six studies (Alping 2016; Alping 2020; Boremalm 2019; Granqvist 2018; Luna 2020; Vollmer 2020a). Assessment of risk of bias for SAEs and further adverse events was not applicable in two studies (Naegelin 2019; Spelman 2018). Naegelin 2019 reported common infections for the rituximab group only and did not report any other adverse events; Spelman 2018 did not report adverse events.

Bias due to confounding

We judged the risk of bias to be moderate in five studies for outcomes assessed to estimate the 'effect of assignment to the intervention' because the authors adjusted for most important confounding factors. Alping 2016 adjusted for the continuous variables age at inclusion, time receiving previous natalizumab treatment, and washout time, and the categorical variables sex, baseline EDSS, and study centre. MRI outcome was adjusted also

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for follow-up time. Boremalm 2019 adjusted for the continuous variables age at inclusion, MS duration since debut, EDSS at baseline, time receiving last DMT before switch, and time from disease activity to switch, and the categorical variables sex and centre (except for discontinuation of therapy because treatment allocation correlated to centre and too few had interrupted RTX treatment). Granqvist 2018 adjusted for age at inclusion, sex, baseline EDSS score, MS duration after debut and diagnosis, relapse in the year before treatment initiation, region, and follow-up time. Propensity scores were estimated for each DMT group in comparison with rituximab. Naegelin 2019 matched their groups by propensity scores based on sex, age, EDSS score, and MS duration at baseline. Spelman 2018 matched their groups by propensity scores based on sex, age, EDSS and disease duration at baseline, number of prebaseline DMTs start, the proportion of disease duration on treatment, the number of DMT starts as a proportion of disease duration, relapse activity in the 12- and 24-months prebaseline, the index year of the DMT start, and the number of assessments per year of follow-up. We judged the risk of bias due to confounding to be serious in three studies. Alcalá 2019 did not adjust for any confounding factors; Evertsson 2020 did not adjust for important confounding factors, including baseline EDSS, MS duration, and study centre; Vollmer 2020a reported unadjusted outcomes (relapse and MRI lesions).

We judged the risk of bias to estimate the 'effect of adherence to the intervention' to be moderate in six studies for SAEs and further adverse events (Alping 2016; Alping 2020; Boremalm 2019; Granqvist 2018; Luna 2020; Vollmer 2020a). We judged two studies at serious risk of bias (Alcalá 2019; Evertsson 2020).

Bias in selection of participants into the study

We judged the risk of bias to be low for Alping 2016, Boremalm 2019, and Granqvist 2018 for outcomes assessed to estimate the 'effect of assignment to the intervention'. In these studies, participants were identified through the web-based national Swedish MS registry and the number of participants excluded due to insufficient follow-up or compliance was low (1.7% in Alping 2016, 2.8% in Boremalm 2019, and 0.5% in Granqvist 2018). We judged two studies at moderate risk of bias. In Spelman 2018, the selection of participants into the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias. In Vollmer 2020a, the source population was all participants with MS who initiated intervention in a single centre. We judged three studies at serious risk of bias. In Alcalá 2019, an immortal time bias occurred and the authors did not adjust for the selection bias. In Evertsson 2020, the selection of participants into the study was based on characteristic of participants after the start of interventions and the authors did not adjust for the selection bias. In Naegelin 2019, selection of the participants into the study was likely related to interventions and outcome.

We judged the risk of bias to estimate the 'effect of adherence to the intervention' to be low in four studies for SAEs and further adverse events (Alping 2016; Alping 2020; Boremalm 2019; Granqvist 2018), moderate in two studies (Luna 2020; Vollmer 2020a), and serious in two studies (Alcalá 2019; Evertsson 2020).

Bias in classification of interventions

We judged the risk of bias to be moderate in seven studies for outcomes assessed to estimate the 'effect of assignment to the intervention' (Alping 2016; Boremalm 2019; Evertsson 2020; Granqvist 2018; Naegelin 2019; Spelman 2018; Vollmer 2020a); despite these studies collecting retrospective clinical data, the intervention and comparison groups were defined. We judged Alcalá 2019 at serious risk of bias because authors did not report dose, frequency, or intensity of the intervention in the comparison group.

We judged the risk of bias to estimate the 'effect of adherence to the intervention' to be moderate in seven studies for SAEs and further adverse events (Alping 2016; Alping 2020; Boremalm 2019; Evertsson 2020; Granqvist 2018; Luna 2020; Vollmer 2020a), and serious for Alcalá 2019.

Bias due to deviations from intended interventions

We judged the risk of bias for outcomes assessed to estimate the 'effect of assignment to the intervention' to be low in all included studies because deviations from intended intervention were part of usual practice.

We judged the risk of bias to estimate the 'effect of adherence to the intervention' to be unclear in seven studies for SAEs and further adverse events (Alcalá 2019; Alping 2016; Alping 2020; Boremalm 2019; Evertsson 2020; Granqvist 2018; Vollmer 2020a). These studies did not report any information on whether there was deviation from the intended intervention.

Bias due to missing data

We judged the risk of bias to be low in seven studies for outcomes assessed to estimate the 'effect of assignment to the intervention', because results were reasonably complete (Alcalá 2019; Alping 2016; Boremalm 2019; Evertsson 2020; Granqvist 2018; Naegelin 2019; Vollmer 2020a). We judged Spelman 2018 at serious risk of bias because the authors reported disability worsening for 70% of participants in the rituximab group and 58% of participants in the comparison group.

We judged the risk of bias to estimate the 'effect of adherence to the intervention' to be low in seven studies for SAEs and further adverse events (Alcalá 2019; Alping 2016; Alping 2020; Boremalm 2019; Evertsson 2020; Granqvist 2018; Vollmer 2020a), and moderate for Luna 2020 because the authors applied multiple imputation to account for missing data.

Bias in measurement of outcomes

We judged the risk of bias to be moderate in seven studies for outcomes assessed to estimate the 'effect of assignment to the intervention' because outcome assessors were not blinded to the intervention and geographical imbalances in the recording of outcomes may have been, given the lack of formal study visits (Alping 2016; Boremalm 2019; Evertsson 2020; Granqvist 2018; Naegelin 2019; Spelman 2018; Vollmer 2020a). We judged Alcalá 2019 at serious risk of bias because outcome assessors were aware of the intervention assigned, and the methods of outcome assessment were not comparable across the intervention groups.

We judged the risk of bias to estimate the 'effect of adherence to the intervention' to be low in one study for SAEs and further adverse events because outcomes were identified in the Swedish national cancer register and cancers occurring at any time after treatment were considered events (Alping 2020). We judged the risk of bias to be moderate in six studies for SAEs and further adverse

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events (Alping 2016; Boremalm 2019; Evertsson 2020; Luna 2020; Granqvist 2018; Vollmer 2020a), and serious in Alcalá 2019 because outcome assessors were aware of the intervention assigned, and the methods of outcome assessment were not comparable across the intervention groups.

Bias in selection of the reported results

We judged the risk of bias to be low in seven studies for outcomes assessed to estimate the 'effect of assignment to the intervention' because the authors reported outcome measures that corresponded to all intended outcomes reported in the methods section of their articles (Alping 2016; Boremalm 2019; Evertsson 2020; Granqvist 2018; Naegelin 2019; Spelman 2018; Vollmer 2020a). We judged the risk of bias to be serious for Alcalá 2019, because outcomes were reported in different ways in the methods and results sections of the article.

We judged the risk of bias to estimate the 'effect of adherence to the intervention' to be low in seven studies for SAEs and further adverse events (Alping 2016; Alping 2020; Boremalm 2019; Evertsson 2020; Granqvist 2018; Luna 2020; Vollmer 2020a), and serious for Alcalá 2019.

Effects of interventions

See: **Summary of findings 1** Rituximab as 'first choice' versus other disease-modifying treatments for relapsing multiple sclerosis – results from non-randomised studies of intervention; **Summary of findings 2** Rituximab as 'first choice' versus placebo for progressive multiple sclerosis – results from randomised controlled trials; **Summary of findings 3** Rituximab as 'switching' versus placebo for relapsing multiple sclerosis – results from randomised controlled trials; **Summary of findings 4** Rituximab as 'switching' versus other disease-modifying treatments for relapsing multiple sclerosis – results from non-randomised studies of intervention

We reported here the results of critical outcomes and important outcomes that we prioritised for presentation in the Summary of findings 1 and the Summary of findings 4. We also reported additional important outcomes. We presented the results for rituximab as 'first choice' and as 'switching', and ordered them by type of MS (relapsing or progressive), comparison (placebo or other DMT), and then by study design (RCT or NRSI).

In Table 2, we reported the other results that we have not presented in the summary of findings tables. In Table 3, we included a simple PICOS (Population, Intervention, Comparison, Outcomes, Study) table to briefly 'map' out the current evidence identified by our review.

Rituximab as 'first choice' versus placebo for relapsing multiple sclerosis

None of the included studies assessed rituximab as 'first choice' versus placebo for relapsing MS.

Rituximab as 'first choice' versus other disease-modifying treatments for relapsing multiple sclerosis

In Summary of findings 1, we provided a summary of the effect estimates of rituximab as 'first choice' treatment versus other DMTs for relapsing MS for critical and prioritised important outcomes, the certainty of NRSI evidence for each comparison, and reasons for downgrading it.

Randomised controlled trials

None of the included RCTs assessed rituximab as 'first choice' versus other DMTs for relapsing MS.

Controlled non-randomised studies of interventions

One retrospective multicentre cohort study compared 488 participants with newly diagnosed active relapsing MS who started their first treatment with rituximab (120 participants), interferon beta or glatiramer acetate (215 participants), dimethyl fumarate (86 participants), fingolimod (17 participants), or natalizumab (50 participants) (Granqvist 2018; the Swedish MS Register).

Critical outcomes

Disability worsening: the study did not measure the outcome.

Recurrence of relapses over 24 months: rituximab reduced the number of participants who had relapses when compared with the following agents (Analysis 1.1):

- moderate-certainty evidence for comparison with interferon beta or glatiramer acetate (HR 0.14, 95% CI 0.05 to 0.39; 1 NRSI, 335 participants); the absolute effect was 227 fewer people (95% CI 254 fewer to 154 fewer) per 1000 people having relapses with rituximab;
- low-certainty evidence for comparison with dimethyl fumarate (HR 0.29, 95% CI 0.08 to 1.00; 1 NRSI, 206 participants); the absolute effect was 84 fewer people (95% CI 110 fewer to 0 fewer) per 1000 people having relapses with rituximab;
- low-certainty evidence for comparison with natalizumab (HR 0.24, 95% CI 0.06 to 1.00; 1 NRSI, 170 participants); the absolute effect was 148 fewer people (95% CI 187 fewer to 0 fewer) per 1000 people having relapses with rituximab;
- very low-certainty evidence for comparison with fingolimod (HR 0.26, 95% CI 0.04 to 1.69; 1 NRSI, 137 participants).

SAEs: the study did not measure the outcome.

Important prioritised outcomes

Quality of life, common infections, cancer: the study did not measure these outcomes.

Mortality over 24 months: the study reported no deaths in any comparison group over 24 months' follow-up. Death related to adverse events was defined as grade 5 adverse events in the Common Terminology Criteria for Adverse Events (CTCAE).

Additional important outcomes

New gadolinium-positive MRI lesions over 24 months: rituximab probably resulted in a reduction in the number of participants who had new gadolinium-positive MRI lesions when compared with the following agents (Analysis 1.2):

- moderate-certainty evidence for comparison with interferon beta or glatiramer acetate (OR 0.10, 95% CI 0.02 to 0.43; 1 NRSI, 263 participants); the absolute effect was 150 fewer people (95% CI 166 fewer to 89 fewer) per 1000 people having new gadolinium-positive MRI lesions with rituximab;
- moderate-certainty evidence for comparison with dimethyl fumarate (OR 0.12, 95% CI 0.02 to 0.59; 1 NRSI, 177 participants); the absolute effect was 130 fewer people (95% CI 147 fewer to

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56 fewer) per 1000 people having new gadolinium-positive MRI lesions with rituximab;
- the evidence was very uncertain for comparison with natalizumab (OR 0.12, 95% CI 0.01 to 1.11; 1 NRSI, 147 participants) and with fingolimod (OR 0.33, 95% CI 0.01 to 10.00; 1 NRSI, 119 participants).

Treatment discontinuation due to adverse events over 24 months: the number of participants who discontinued initial treatment with rituximab was lower than that observed in participants treated with the following agents (Analysis 1.3):

- moderate-certainty evidence for comparison with interferon beta or glatiramer acetate (OR 0.02, 95% CI 0.00 to 0.16; 1 NRSI, 335 participants); the absolute effect was 271 fewer people (95% CI 275 fewer to 221 fewer) per 1000 people who discontinued rituximab;
- moderate-certainty evidence for comparison with dimethyl fumarate (OR 0.05, 95% CI 0.01 to 0.41; 1 NRSI, 206 participants); the absolute effect was 131 fewer people (95% CI 138 fewer to 77 fewer) per 1000 people who discontinued rituximab;
- low-certainty evidence for comparison with natalizumab (OR 0.20, 95% CI 0.02 to 2.28; 1 NRSI, 170 participants) and with fingolimod (OR 0.04, 95% CI 0.00 to 0.40; 1 NRSI, 137 participants).

Grade 3 and grade 4 adverse events over 24 months: the events were few and the evidence was uncertain about the number of participants who had grade 3 and grade 4 adverse events with rituximab when compared with the following agents:

- very low-certainty evidence for comparison with interferon beta or glatiramer acetate (OR 0.89, 95% CI 0.26 to 3.03; 1 NRSI, 335 participants), dimethyl fumarate (OR 2.93, 95% CI 0.32 to 26.69; 1 NRSI, 206 participants), natalizumab (OR 0.40, 95% CI 0.10 to 1.65; 1 NRSI, 170 participants), or fingolimod (OR 1.35, 0.07 to 26.21; 1 NRSI, 137 participants) (Analysis 1.4).

Rituximab as 'first choice' versus placebo for progressive multiple sclerosis

In Summary of findings 2, we provided a summary of the effect estimates of rituximab as 'first choice' treatment versus placebo for primary progressive MS for critical and prioritised important outcomes, the certainty of evidence, and reasons for downgrading it.

Randomised controlled trials

One RCT compared rituximab with placebo in 439 participants (65% treatment-naive) with primary progressive MS (Hawker 2009). None of the included RCTs assessed rituximab as 'first choice' in secondary progressive MS.

Critical outcomes

Disability worsening over 24 months: rituximab likely resulted in little to no difference in the number of participants who had disability worsening over 24 months compared with placebo (OR 0.71, 95% CI 0.45 to 1.11; 1 RCT, 439 participants; moderate-certainty evidence); the absolute effect was 75 fewer people (95% CI 158 fewer to 24 more) per 1000 people having disability worsening with rituximab (Analysis 2.1). Hawker 2009 reported that time to disability worsening was delayed in rituximab-treated progressive MS with gadolinium-positive MRI lesions (HR 0.41; P = 0.007), and people aged less than 51 years with gadolinium-positive MRI lesions (HR 0.33; P = 0.009) compared with placebo.

Recurrence of relapses over 24 months: rituximab may have resulted in little to no difference in recurrence of relapses when compared with placebo (OR 0.60, 95% CI 0.18 to 1.99; 1 RCT, 439 participants; low-certainty evidence; Analysis 2.2).

SAEs over 24 months: rituximab may have resulted in little to no difference in the number of participants who had SAEs (OR 1.25, 95% CI 0.71 to 2.20; 1 RCT, 439 participants; low-certainty evidence; Analysis 2.3).

Important prioritised outcomes

Quality of life: the study did not report the outcome.

Common infections over 24 months: rituximab may have resulted in little to no difference in the number of participants who had common infections compared with placebo (OR 1.14, 95% CI 0.75 to 1.73; 1 RCT, 438 participants; low-certainty evidence; Analysis 2.4). Infections reported in more than 10% of either group included upper respiratory infections, urinary tract infections, and nasopharyngitis (Hawker 2009).

Cancer over 24 months: the evidence was uncertain (OR 0.50, 95% CI 0.07 to 3.59; 1 RCT, 438 participants; low-certainty evidence; Analysis 2.5). Hawker 2009 reported that one participant had breast cancer and one had adenocarcinoma in the rituximab group, and one participant had parathyroid tumour and one had prostate cancer in the placebo group.

Mortality over 24 months: the evidence was uncertain (OR 0.25, 95% CI 0.02 to 2.77; 1 RCT, 438 participants; low-certainty evidence; Analysis 2.6). Hawker 2009 reported that three deaths occurred. One participant with a history of brainstem lesions and aspiration received two infusions of rituximab and withdrew early from the study after contracting pneumonia; he was subsequently hospitalised multiple times for recurrent aspiration and died approximately 10 weeks after the initial event. Two participants receiving placebo died; one had cardiopulmonary failure during the study, and the other contracted pneumonia and died after withdrawing from the trial.

Additional important outcomes

Treatment discontinuation due to adverse events over 24 months: the number of participants who discontinued initial treatment with rituximab was higher than that observed in participants assigned to placebo, but the 95% CIs were large, so our confidence in the estimate was very limited (OR 4.64, 95% CI 0.58 to 37.00; 1 RCT, 439 participants; Analysis 2.7).

Grade 3 and grade 4 adverse events over 24 months: there was no effect of rituximab compared with placebo; however, the evidence was uncertain (OR 1.10, 95% CI 0.73 to 1.66; 1 RCT, 439 participants; Analysis 2.8).

Infusion-related reactions: rituximab increased the number of participants who had infusion reactions within 24 hours after the first infusion (OR 6.79, 95% CI 4.31 to 10.69; 1 RCT, participants 439; Analysis 2.9), and after the second infusion (OR 1.66, 95% CI 0.98 to 2.82; 1 RCT, 439 participants; Analysis 2.10) compared with placebo. Infusion reactions decreased to rates comparable to

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placebo on successive courses. At week 74, reactions were lower in the rituximab group (4.9%) compared to placebo (7.2%). Infusion-associated adverse events were primarily mild to moderate in severity. Seventeen (3.9%) participants reported grade 3 infusion-associated events. There were no grade 4 infusion-associated events (Hawker 2009).

Controlled non-randomised studies of interventions

None of the included NRSIs assessed rituximab as 'first choice' versus placebo for progressive MS.

Rituximab as 'first choice' versus other DMTs for progressive multiple sclerosis

None of the included studies assessed rituximab as 'first choice' versus other DMTs for progressive MS.

Rituximab as 'switching' versus placebo for relapsing multiple sclerosis

In Summary of findings 3, we provided a summary of the effect estimates of rituximab as 'switching' versus placebo for relapsing MS for our prioritised critical and important outcomes, the certainty of evidence, and reasons for downgrading it.

Randomised controlled trials

One RCT included 104 participants with relapsing MS and compared rituximab as 'switching' with placebo (Hauser 2008).

Critical outcomes

Disability worsening: the study did not report the outcome.

Recurrence of relapses over 12 months: rituximab may have decreased the number of participants who had relapses compared with placebo (OR 0.38, 95% CI 0.16 to 0.93; 1 RCT, 104 participants; low-certainty evidence); the absolute effect was 198 fewer people (95% CI 304 fewer to 17 fewer) per 1000 people having relapses with rituximab (Analysis 3.1).

SAEs over 12 months: the evidence was very uncertain (OR 0.90, 95% CI 0.28 to 2.92; 1 RCT, 104 participants; very low-certainty evidence; Analysis 3.2).

Important prioritised outcomes

Quality of life: the study did not report the outcome.

Common infections over 12 months: the evidence was very uncertain (OR 0.91, 95% CI 0.37 to 2.24; 1 RCT, 104 participants; very low-certainty evidence; Analysis 3.3).

Cancer over 12 months: the evidence was very uncertain (OR 1.55, 95% CI 0.06 to 39.15; 1 RCT, 104 participants; very low-certainty evidence; Analysis 3.4). Hauser 2008 reported one person with a malignant thyroid neoplasm in the rituximab group and no cancer in the placebo group.

Mortality over 24 months: the evidence was very uncertain (OR 1.55, 95% CI 0.06 to 39.15; 1 RCT, 104 participants; very low-certainty evidence; Analysis 3.5). Hauser 2008 reported one death due to homicide in the rituximab group and no deaths in the placebo group.

Additional important outcomes

ARR, new gadolinium-positive MRI lesions, treatment discontinuation due to adverse events, grade 3 and grade 4 adverse events, and cardiovascular events: the evidence was very uncertain for the effect of rituximab on all these outcomes (Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10).

Opportunistic infections: Hauser 2008 reported no opportunistic infections in participants treated with rituximab or placebo over 12 months.

Infusion-related reactions: the number of participants who had infusion reactions within 24 hours after the first infusion of rituximab was higher than that observed in participants randomised to placebo (OR 5.40, 95% CI 2.23 to 13.09; 1 RCT, 104 participants; high-certainty evidence); the absolute effect was 383 more people (95% CI 198 more to 497 more) per 1000 people who had infusion reactions (Analysis 3.11). Infusion-associated adverse events were mild to moderate (grade 1 or 2) in severity. Four (7.4%) participants reported grade 3 events associated with infusion; these included headache, back pain, depression, limb pain, general pain, heat sensations, pruritus, and rash. There were no grade 4 events associated with infusion (Hauser 2008). Within 24 hours after the second infusion, fewer participants in the rituximab group than in the placebo group had adverse events (OR 0.38, 95% CI 0.16 to 0.93; 1 RCT, 104 participants; high-certainty evidence; Analysis 3.12).

Controlled non-randomised studies of interventions

None of the included NRSIs assessed rituximab as 'switching' versus placebo for relapsing MS.

Rituximab as 'switching' versus other DMTs for relapsing multiple sclerosis

In Summary of findings 4, we provided a summary of the effect estimates of rituximab as 'switching' versus other DMTs for relapsing MS for our prioritised critical and important outcomes, the certainty of NRSI evidence for each comparison, and reasons for downgrading it.

Randomised controlled trials

None of the included RCTs assessed rituximab as 'switching' versus other DMTs for relapsing MS.

Controlled non-randomised studies of interventions

Five retrospective multicentre cohort studies compared rituximab as 'switching' versus other DMTs in relapsing MS (Alping 2016; Boremalm 2019; Evertsson 2020; Luna 2020; Spelman 2018). We did not evaluate outcome data from one controlled NRSI because of the critical risk of bias (Alcalá 2019).

Critical outcomes

Disability worsening over 24 months: data for this outcome were available from one retrospective cohort nationwide study (Spelman 2018; the Swedish MS Register). There was very low-certainty evidence for comparison of rituximab with interferon beta or glatiramer acetate (HR 0.86, 95% CI 0.52 to 1.42; 1 NRSI, 853 participants; Analysis 4.1).

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Recurrence of relapses over 18 to 24 months: three studies from the Swedish MS Register reported relapse outcome (time to event) in participants who switched to rituximab from another DMT (Alping 2016; Boremalm 2019; Spelman 2018). Rituximab likely resulted in a large reduction in the number of participants who had relapses over 18 to 24 months when compared with the following agents (Analysis 4.2):

- moderate-certainty evidence for comparison with interferons or glatiramer (HR 0.18, 95% CI 0.07 to 0.49; 1 NRSI, 1383 participants); the absolute effect was 215 fewer people (95% CI 248 fewer to 127 fewer) per 1000 people having relapses with rituximab. The number needed to treat for an additional beneficial effect (NNTB) was 11 (95% CI 10 to 18);
- moderate-certainty evidence for comparison with fingolimod (HR 0.08, 95% CI 0.02 to 0.32; 1 NRSI, 256 participants); the absolute effect was 161 fewer people (95% CI 172 fewer to 116 fewer) per 1000 people having relapses with rituximab. The NNTB was 6 (95% CI 6 to 9).

The evidence was very uncertain about the effect of rituximab compared with natalizumab (HR 1.00, 95% CI 0.20 to 5.00; 1 NRSI, 153 participants; very low-certainty evidence).

SAEs: none of the identified studies reported the outcome.

Important prioritised outcomes

Quality of life: none of the identified studies reported the outcome.

Common infections over 24 months: four studies reported this outcome (Alping 2016; Boremalm 2019; Evertsson 2020; Luna 2020). Rituximab increased the number of participants who had common infections when compared with the following agents (Analysis 4.3):

- moderate-certainty evidence for comparison with interferon beta or glatiramer acetate (OR 1.71, 95% CI 1.11 to 2.62; 1 NRSI, 5477 participants); the absolute effect was 24 more people (95% CI 4 more to 53 more) per 1000 people having common infections with rituximab;
- moderate-certainty evidence for comparison with natalizumab (OR 1.58, 95% CI 1.08 to 2.32; 2 NRSIs, 5001 participants); the absolute effect was 27 more people (95% CI 4 more to 59 more) per 1000 people having common infections with rituximab.

There was low-certainty evidence for comparison of rituximab with fingolimod (OR 1.26, 95% CI 0.90 to 1.77; 3 NRSIs, 5287 participants) and very low-certainty evidence for comparison with ocrelizumab (OR 0.02, 95% CI 0.00 to 0.40; 1 NRSI, 472 participants). Ten/161 (6%) participants in the ocrelizumab group reported infections. There were no infections in 311 participants who received rituximab (Evertsson 2020).

Cancer: none of the identified studies reported the outcome.

Mortality over 24 months: Boremalm 2019 reported one suicide due to overdosing of sedative drugs in one participant with a severe concomitant psychiatric illness in the rituximab group. There were no deaths in the fingolimod group (OR 5.59, 95% CI 0.22 to 139.89; 1 NRSI, 136 participants; very low-certainty evidence), and no deaths in the natalizumab group (OR 6.66, 95% CI 0.27 to 166.58; 1 NRSI, 153 participants; very low-certainty evidence), over 24 months' follow-up (Analysis 4.4). Death related to adverse events was defined as grade 5 in the CTCAE.

Additional important outcomes

ARR over 24 months: one retrospective multicentre cohort study reported the ARR (Spelman 2018; the Swedish MS Register). Rituximab likely reduced ARR when compared with interferons or glatiramer acetate (MD −0.02, 95% CI −0.03 to −0.01; 1 NRSI, 1383 participants; moderate-certainty evidence; Analysis 4.5).

New or enlarging T2-weighted MRI lesions over 18 months: one retrospective multicentre cohort study provided data (Alping 2016; the Swedish MS Register). Rituximab may have reduced the number of participants who had new or enlarging T2 MRI lesions when compared with fingolimod (OR 0.01, 95% CI 0.00 to 0.06; 1 NRSI, 182 participants; low-certainty evidence; Analysis 4.6).

New gadolinium-positive MRI lesions over 24 months: two retrospective multicentre cohort studies provided outcome data for comparison of rituximab with fingolimod (Alping 2016; Boremalm 2019). Rituximab probably reduced the number of participants who had new gadolinium-positive MRI lesions (OR 0.09, 95% CI 0.03 to 0.30; P = 0.71, I^2 = 0%; 2 NRSI, 288 participants; moderate-certainty evidence); the absolute effect was 172 fewer people (95% CI 186 fewer to 126 fewer) per 1000 people who had new gadolinium-positive MRI lesions with rituximab (Analysis 4.7). The evidence was very uncertain about the effect of rituximab compared with natalizumab (OR 1.00, 95% CI 0.20 to 5.00; 1 NRSI, 138 participants; very low-certainty evidence; Analysis 4.7).

Treatment discontinuation due to adverse events over 24 months: Boremalm 2019 reported outcome data. There was very low-certainty evidence for the comparison of rituximab with fingolimod (OR 0.13, 95% CI 0.01 to 2.37; 1 NRSI, 136 participants), and with natalizumab (OR 0.30, 95% CI 0.02 to 5.96; 1 NRSI, 153 participants). Evertsson 2020 compared treatment discontinuation over the first 12 months in 311 participants treated with rituximab and 161 participants treated with ocrelizumab in one retrospective multicentre cohort study. The number of participants who discontinued treatment with rituximab was lower than that observed in participants treated with ocrelizumab (OR 0.26, 95% CI 0.11 to 0.62; 1 NRSI, 482 participants; moderate-certainty evidence); the absolute effect was 67 fewer people (95% CI 82 fewer to 33 fewer) per 1000 people who discontinued rituximab (Analysis 4.8).

Grade 3 and grade 4 adverse events over 24 months: two controlled NRSIs provided data for comparison of rituximab with fingolimod (Alping 2016; Boremalm 2019). Boremalm 2019 also reported data for comparison with natalizumab. The evidence was very uncertain about the effect of rituximab on the number of participants who had grade 3 and grade 4 adverse events when compared with fingolimod (OR 0.34, 95% CI 0.06 to 2.09; P = 0.80, I^2 = 0%; 2 NRSIs, 392 participants; very low-certainty evidence) and natalizumab (OR 0.23, 95% CI 0.01 to 4.41; 1 NRSI, 153 participants; very low-certainty evidence) (Analysis 4.9).

Cardiovascular events: two NRSIs reported outcome data for the comparison of rituximab with fingolimod (Alping 2016; Boremalm 2019). The evidence was very uncertain about the effect of rituximab on the number of participants who had cardiovascular events when compared with fingolimod (OR 0.31, 95% CI 0.05 to 1.85; P = 0.65, I^2 = 0%; 2 NRSIs, 392 participants; very low-certainty evidence; Analysis 4.10). There were no cardiovascular events

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in the comparison of rituximab with natalizumab (Analysis 4.10) (Boremalm 2019).

Infusion-related reactions: there were grade 1 adverse events related to the first infusion of rituximab in 26% of participants in the rituximab group, compared with a 7% incidence of adverse events at first dosing of fingolimod (OR 4.71, 95% CI 2.19 to 10.14; 1 NRSI, 256 participants; Analysis 4.11) (Alping 2016). Evertsson 2020 reported infusion-related adverse events in 0.6% of participants in the rituximab group compared with 1.2% in the ocrelizumab group. The events were few and the evidence was very low due to large imprecision (OR 0.51, 95% CI 0.07 to 3.69; 1 NRSI, 472 participants; Analysis 4.11).

Rituximab as 'switching' versus placebo for secondary progressive multiple sclerosis

A summary of the effect estimates of rituximab as 'switching' compared with placebo for secondary progressive MS (SPMS) is shown in Table 2.

Randomised controlled trials

One small RCT included 27 participants with secondary progressive MS (Komori 2016).

Critical outcomes

Disability worsening and relapses: the study did not report the number of participants who had these outcomes.

SAEs over 24 months: the evidence was very uncertain about the effect of rituximab on SAEs when compared with placebo (OR 0.36, 95% CI 0.06 to 2.00; 1 RCT, 27 participants; very low-certainty evidence; Analysis 5.1).

Important prioritised outcomes

Quality of life: the study did not report the outcome.

Common infections: the study did not report the outcome.

Cancer over 24 months: the evidence was very uncertain about the effect of rituximab on cancer when compared with placebo (OR 0.47, 95% CI 0.03 to 8.52; 1 RCT, 27 participants; very low-certainty evidence; Analysis 5.2). Komori 2016 reported one participant in each group coded as "Neoplasms benign, malignant and unspecified"(ClinicalTrials.gov Identifier: NCT0121209).

Mortality: the study did not report the outcome.

Additional important outcomes

Cardiovascular events over 24 months: the evidence was very uncertain about the effect of rituximab on cardiovascular events when compared with placebo (OR 0.47, 95% CI 0.03 to 8.52; 1 RCT, 27 participants; very low-certainty evidence; Analysis 5.3).

Controlled non-randomised studies of interventions

None of the included NRSIs assessed rituximab as 'switching' versus placebo for progressive MS.

Rituximab as 'switching' versus other DMTs for secondary progressive multiple sclerosis

A summary of the effect estimates of rituximab as 'switching' compared with other DMTs for secondary progressive MS is shown in Table 2.

Randomised controlled trials

Two RCTs included participants with secondary progressive MS. Cheshmavar 2021 compared rituximab with glatiramer acetate in 84 participants with active secondary progressive MS, and Etemadifar 2019 compared rituximab with cyclophosphamide in 80 participants with active secondary progressive MS.

Critical outcomes

Disability worsening and relapses: the included studies did not report the number of participants who had these outcomes.

SAEs: there were no SAEs over 12 months' follow-up in the comparison of rituximab with glatiramer acetate (Analysis 6.1). Etemadifar 2019 did not report the outcome.

Important prioritised outcomes

Quality of life: the included studies did not report the outcome.

Common infections over 12 to 24 months: the evidence was very uncertain about the effect of rituximab compared with glatiramer acetate over 12 months (OR 3.00, 95% CI 0.30 to 30.08; 1 RCT, 84 participants; very low-certainty evidence) and with cyclophosphamide over 24 months (OR 0.39, 95% CI 0.14 to 1.11; 1 RCT, 69 participants; very low-certainty evidence) (Analysis 6.2).

Cancer and mortality: the included studies did not report these outcomes.

Additional important outcomes

ARR, new gadolinium-positive MRI lesions, and treatment discontinuation due to adverse events over 12 months: the evidence was very uncertain about the effect of rituximab on all these outcomes when compared with glatiramer acetate (Analysis 6.3; Analysis 6.4; Analysis 6.5).

Opportunistic infections: there were no opportunistic infections in participants treated with rituximab or glatiramer acetate over 12 months (Analysis 6.6).

Controlled non-randomised studies of interventions

One small case-control study included 44 participants with secondary progressive MS who were treated with rituximab compared with 44 matched controls never treated with rituximab (Naegelin 2019).

Critical outcomes

Disability worsening over 36 months: we had very little confidence in the effect estimate (OR 0.49, 95% CI 0.26 to 0.93; 1 NRSI, 88 participants; very low-certainty evidence; Analysis 7.1).

Relapses and SAEs: the study did not report the number of participants who had these outcomes.

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Important prioritised outcomes

Quality of life, common infections, cancer, and mortality: the study did not report the outcomes.

Additional important outcomes

The study did not report the outcomes.

Rituximab as 'switching' versus other DMTs for grouped data as relapsing and progressive multiple sclerosis

A summary of the effect estimates of rituximab as 'switching' compared with other DMTs for grouped forms of MS is reported in Table 2.

Randomised controlled trials

None of the included RCTs assessed rituximab as 'switching' versus other DMTs for relapsing and progressive MS.

Controlled non-randomised studies of interventions

Two NRSIs reported grouped data as relapsing and progressive MS. Vollmer 2020a was a retrospective cohort study conducted in a single MS centre in the USA. The study compared rituximab with fingolimod, dimethyl fumarate, and natalizumab over 24 months' follow-up. In one nationwide register-based cohort study, Alping 2020 linked data from the Swedish MS register (www.neuroreg.se/) to the Swedish Cancer Register and other national healthcare and census registers. In this study, first-ever initiations of rituximab, fingolimod, and natalizumab were compared and the reported outcome was time to first invasive cancer over 36 months.

Critical outcomes

Disability worsening: the included studies did not report the outcome.

Recurrence of relapses over 24 months: the evidence from one NRSI was very uncertain because we judged the effect estimates at very serious risk of bias (only unadjusted data were available) and there was indirectness related to populations (Vollmer 2020a):

- very low-certainty evidence for comparison of rituximab with fingolimod (OR 0.35, 95% CI 0.14 to 0.88; 1 NRSI, 453 participants), dimethyl fumarate (OR 0.23, 95% CI 0.10 to 0.55; 1 NRSI, 524 participants), and natalizumab (OR 0.54, 95% CI 0.22 to 1.32; 1 NRSI, 633 participants) (Analysis 8.1).

SAEs: the included studies did not report the outcome.

Important prioritised outcomes

Quality of life: the included studies did not report the outcome.

Common infections over 24 months: the evidence was very uncertain in the comparison of rituximab with the following agents:

- very low-certainty evidence for comparison with fingolimod (OR 1.06, 95% CI 0.34 to 3.30; 1 NRSI, 453 participants), dimethyl fumarate (OR 2.39, 95% CI 0.63 to 9.00; 1 NRSI, 524 participants), and natalizumab (OR 4.22, 95% CI 1.00 to 17.84; 1 NRSI, 633 participants) (Analysis 8.2).

Cancer over 36 months: rituximab may have reduced the number of participants who had cancer compared with fingolimod (OR 0.60, 95% CI 0.35 to 1.03; 1 NRSI, 5807 participants; low-certainty evidence). The evidence was very uncertain in the comparison of rituximab with natalizumab (OR 0.74, 95% CI 0.42 to 1.31; 1 NRSI, 5857 participants; very low-certainty evidence; Analysis 8.3). Alping 2020 reported six breast cancers in the rituximab cohort, corresponding to an incidence rate of 8.9 per 10,000 person-years (95% CI 3.3 to 19.4), which was similar to the rate in the general population.

Mortality: the included studies did not report the outcome.

Additional important outcomes

New or enlarging T2-weighted MRI lesions over 24 months: the evidence is very uncertain about the effect of rituximab when compared with the following DMTs:

- very low-certainty evidence for comparison with fingolimod (OR 0.40, 95% CI 0.25 to 0.62; 1 NRSI, 453 participants), dimethyl fumarate (OR 0.46, 95% CI 0.30 to 0.72; 1 NRSI, 524 participants), natalizumab (OR 0.63, 95% CI 0.41 to 0.98; 1 NRSI, 633 participants) (Analysis 8.4).

New gadolinium-positive MRI lesions over 24 months: there was very low-certainty evidence in the comparison of rituximab with fingolimod (OR 0.04, 95% CI 0.00 to 0.27; 1 NRSI, 453 participants), dimethyl fumarate (OR 0.05, 95% CI 0.01 to 0.37; 1 NRSI, 524 participants), natalizumab (OR 0.09, 95% CI 0.01 to 0.67; 1 NRSI, 633 participants) (Analysis 8.5).

Treatment discontinuation due to adverse events over 24 months: there was low-certainty evidence for comparison with fingolimod (OR 0.28, 95% CI 0.13 to 0.60; 1 NRSI, 453 participants), and dimethyl fumarate (OR 0.30, 95% CI 0.15 to 0.60; 1 NRSI, 524 participants), and very low-certainty evidence for comparison with natalizumab (OR 1.10, 95% CI 0.48 to 2.52; 1 NRSI, 633 participants) (Analysis 8.6).

Cardiovascular events over 24 months: the evidence was very uncertain in the comparison with fingolimod (OR 0.16, 95% CI 0.01 to 3.04; 1 NRSI, 441 participants) and natalizumab (OR 0.82, 95% CI 0.03 to 20.29; 1 NRSI, 633 participants; Analysis 8.7). There were no cardiovascular events in the comparison with dimethyl fumarate (Analysis 8.7).

DISCUSSION

This review summarised the evidence on beneficial and adverse outcomes of rituximab as 'first choice' treatment or as 'switching' from another DMT for people with MS. Our priority outcomes of interest included disability worsening, recurrence of relapses, SAEs, quality of life, common infections, cancer, and mortality. We also assessed the effect of rituximab on additional important outcomes (cerebral MRI findings, treatment discontinuation, adverse events of grade 3 or grade 4 severity), which are reported in the Effects of interventions section.

The review included five RCTs (734 participants), and 10 controlled NRSIs (15,695 participants). Three RCTs compared rituximab with placebo, one with glatiramer acetate, and one with cyclophosphamide. The NRSIs compared rituximab with other active DMTs. Most studies were of short duration, with the median follow-up being 24 months, therefore the effects of rituximab beyond two years remain uncertain.

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Summary of main results

Rituximab as 'first choice' treatment in relapsing multiple sclerosis

One controlled NRSI (488 participants) assessed rituximab versus other DMTs. The results are as follows (Summary of findings 1):

- rituximab likely results in a large reduction in the number of participants who have relapses compared with interferon beta or glatiramer acetate, and may reduce the number of people who had relapses compared with dimethyl fumarate and natalizumab;
- the evidence is very uncertain about the effect of rituximab on relapses when compared with fingolimod;
- there were no deaths in the comparison of rituximab with the other DMTs;
- the study did not provide data regarding disability worsening, SAEs, quality of life, common infections, or cancer.

Rituximab as 'first choice' treatment in progressive multiple sclerosis

One RCT (439 participants) compared rituximab with placebo in primary progressive MS. The results are as follows (Table 2):

- rituximab likely results in little to no difference in the number of participants who have disability worsening over 24 months;
- the evidence is uncertain about the effect of rituximab on the other outcomes of interest.

Rituximab as 'switching' treatment in relapsing multiple sclerosis

Five controlled NRSIs compared rituximab as 'switching' versus other DMTs in relapsing MS. The results are as follows (Summary of findings 4):

- the evidence is very uncertain about the effect of rituximab on disability worsening when compared with interferon beta or glatiramer acetate (1 NRSI, 853 participants);
- rituximab likely results in a large reduction in the number of participants who have relapses compared with interferon beta or glatiramer acetate (1 NRSI, 1383 participants), and with fingolimod (1 NRSI, 256 participants);
- the evidence is very uncertain about the effect of rituximab on relapses when compared with natalizumab;
- rituximab likely increases slightly the number of participants who have common infections compared with interferon beta or glatiramer acetate (1 NRSI, 477 participants), with natalizumab (2 NRSIs, 5001 participants). The evidence is uncertain for the comparisons with fingolimod and ocrelizumab;
- the evidence is very uncertain about the effect of rituximab on mortality when compared with fingolimod and natalizumab;
- none of the identified studies measured SAEs, quality of life, or cancer.

Rituximab as switching treatment in progressive multiple sclerosis

Only three small studies investigated rituximab in secondary progressive MS. The evidence is uncertain about the effect of rituximab on disability worsening, SAEs, and quality of life. The studies did not provide usable information on relapses, common infections, cancer, or mortality (Table 2).

Overall completeness and applicability of evidence

All eligible RCTs and controlled NRSIs (up to 31 January 2021) of rituximab for treatment of MS were included in the review. Six out of 10 included NRSIs were retrospective multicentre cohort studies based on the nationwide Swedish Multiple Sclerosis Register linked to national healthcare registers. The Swedish MS register captures data on several aspects of MS care (Hillert 2020), and has especially high validity for therapy data (Alping 2019). Participation is voluntary, but coverage has been estimated to be greater than 80% (Hillert 2015).

With respect to the scope of our review, data and findings relevant to rituximab when switching from another DMT were available in 13 (87%) of the 15 included studies, and rituximab as a 'first choice' treatment in two studies. Most studies included people with relapsing MS who represented 80% of those included in the review.

We identified 14 ongoing studies, 11 are RCTs. The publication of the results of these studies will necessitate an update of this review.

Our review was intended to be a comprehensive review of effects of rituximab, but short duration of included studies and no or poor reporting of some outcomes were major limitations in determining the overall completeness and the balance between beneficial and adverse effects of rituximab. For example, there were no data on quality of life and cognitive decline that are important outcomes for patients and clinicians.

We focused on treatment discontinuation due to AEs to indirectly assess acceptability of rituximab compared with other DMTs; however, the true compliance rate is not known, as it was not a topic of our investigation.

With respect to applicability, findings in this review originated mostly from retrospective cohort studies conducted in Sweden and only five small RCTs. This is one of controversies about treatment with rituximab in MS concerning uncertainty on benefits and harms since randomised evidence is insufficient, and other approved DMTs are available. Rituximab is an off-label treatment for MS, and since its patent has expired, there is no interest of the pharmaceutical industry in promoting randomised trials (Greenfield 2018). However, rituximab is used in many countries globally (Delate 2020; Sarsour 2020; Wongseelashote 2018), and is considered a feasible option in low- and middle-income countries because it has considerably lower cost and less frequent administration (Lancet Neurology 2019; Mathew 2020). Treatment with rituximab requires specialist care and infusion facilities, but other approved DMTs also have these requirements.

Evidence on harms of treatment with rituximab in people with MS during the COVID-19 pandemic was not included in this review since it was published after the review search was conducted.

Quality of the evidence

The majority of the evidence was low or very-low certainty for the critical and important outcomes included in the review.

Our assessment of the risk of bias in five included RCTs is summarised in Figure 2 and Figure 3. Four (80%) RCTs were at

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a high risk of bias due to having two or more domains at high risk of bias. The certainty of the evidence in reported outcomes was further reduced because of the small information size and imprecise estimates.

We included 10 controlled NRSIs and assessed risk of bias with the ROBINS-I tool (Figure 4; Figure 5; Appendix 2). We did not include data from one NRSI in data synthesis because of critical risk of bias. We judged four (40%) NRSIs at serious risk of bias. The other included NRSIs were at moderate risk of bias. The evidence we have obtained from NRSIs was limited mainly due to the risk of confounding, selection bias, and retrospective data collection. Moreover, numbers of people and number of events in each comparison group were small, with imprecise estimates, for several outcomes in the included NRSIs. The outcome measures were also heterogeneous with wide variation in reporting across the included studies.

Potential biases in the review process

To avoid a possible risk of publication bias, we searched a range of databases and trials registries to identify ongoing studies and results of unpublished completed studies, and applied no time or language restriction to the search. However, it is possible that we have not identified other sources of unpublished observational eligible studies.

Two review authors independently identified eligible studies and assessed risk of bias. We requested additional data through correspondence with four study authors and obtained missing information from two of them.

Much of the non-randomised data in the review came from the Swedish MS Register. We wished to use most of the available information on the comparison of rituximab with other DMTs in the absence of direct randomised evidence. Six retrospective cohort studies based on the Swedish MS Register compared rituximab separately against each other DMT. We did not pool the comparators, and performed separate analyses of each comparison; however, there was likely double counting of the rituximab participants from one comparison to another.

We cannot exclude the possible presence of reporting bias.

Agreements and disagreements with other studies or reviews

In one previous Cochrane Review including only RCTs of rituximab for relapsing MS, authors concluded, based on low-certainty evidence, that there was insufficient evidence to support the use of rituximab for relapsing MS because there was only one small RCT versus placebo (He 2013). We widened the evidence base adding NRSIs to the review and used of ROBINS-I in critical evaluation of the validity of NRSIs. By using new criteria for considering studies for our review, we can suggest the following. People with relapsing MS receiving rituximab as 'first choice' treatment likely have significantly lower risks of experiencing new relapses over 24 months compared to interferons or glatiramer acetate, and may have lower risk of relapses compared with dimethyl fumarate and natalizumab. Moreover, rituximab used to escalate participants with relapsing MS from other DMTs or when other DMTs become contraindicated (switching), likely results in a large reduction in recurrence of relapses over 24 months, compared with interferons or glatiramer acetate and fingolimod. We now added progressive forms of MS to the review, which was previously restricted to relapsing MS (He 2013), and found that there is limited information to determine the effect of rituximab for progressive forms of MS.

Comparing other reviews with ours points out some challenges inherent in evidence synthesis in the context of reviews including randomised and non-randomised studies. Important issues we need to consider are differences in study selection and inclusion, assessment of study quality, methods for data synthesis, and interpretations and inferences made by the review authors. In fact, most of our findings cannot be compared to the results reported by other reviews (Castillo-Trivino 2013; Ghajarzadeh 2020; Hu 2019; Siddiqui 2020; Tian 2020), since the authors included mostly uncontrolled observational studies, the quality of evidence for the results arising from their reviews was often not assessed and methods for data synthesis differed from ours. For example, one narrative review examined 38 studies, five of which were RCTs and 33 were uncontrolled observational studies, of rituximab for relapsing MS and highly active relapsing MS (Siddiqui 2020). The authors reported that their results needed to be interpreted with caution because the quality of the included studies was poor, but they suggested that rituximab was beneficial for people with relapsing MS compared with placebo as well as with glatiramer acetate, interferons, fingolimod, and natalizumab without indicating the certainty of evidence for each comparison. Moreover, the review was sponsored by EMD Serono Inc., two of the co-authors were employees of the pharmaceutical company, and this might have influenced authors' conclusions or interpretations of their findings. Hu 2019 reported a significant reduction of disability worsening in 946 participants with relapsing MS treated with rituximab, but the result was based on a meta-analysis of data from 15 uncontrolled observational studies. Ghajarzadeh 2020 reported a meta-analysis of seven uncontrolled pre–post studies (399 participants with MS) and concluded that rituximab treatment was effective in controlling relapses and disability worsening in all forms of MS, but the authors did not assess the quality of evidence for the outcomes.

Our confidence in the effect estimate of rituximab on SAEs was limited since they were relatively rare in people with MS and observed over a short time period. There is extensive experience of long-term use of rituximab in people with rheumatoid arthritis with a good acceptance profile and adherence to the treatment (van Vollenhoven 2015); however, indirect comparison with MS is difficult owing to differences in patient populations, dose, administration regimens, and co-interventions.

In our review, we used treatment discontinuation due to adverse events as an indirect outcome to assess acceptability. Results from the included studies suggested that rituximab was superior to all other investigated DMTs in terms of treatment discontinuation over a median follow-up of two years. Some reviews on adherence to approved DMTs are available in the literature. One systematic review, including 151 studies, reported poor adherence to the traditional 'first choice' treatments for MS (e.g. interferon beta and glatiramer acetate) (Giovannoni 2012). The mean discontinuation rates after two years' treatment ranged from 22% to 43%, and the reasons most frequently mentioned for discontinuation were occurrence of adverse events or perceived lack of efficacy. Another systematic review of studies published between January 2010 and April 2018 showed that approximately one in five people with

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MS did not adhere to once- or twice-daily oral maintenance DMT regimens, and one in four people discontinued oral treatments before one year (Nicholas 2020). The authors reported a high heterogeneity among the included studies. Pust 2020 conducted semi-structured interviews with 23 people with MS: 11 receiving first-line treatment and 12 receiving second-line treatment. One key reason for non-adherence reported by people receiving first-line treatment was undesirable adverse effects, and for adherence was belief in medication effectiveness. In people with MS receiving second-line treatment, lack of perceived medication effectiveness was a key category related to discontinuation of treatment.

AUTHORS' CONCLUSIONS

Implications for practice

- A policy of provision of rituximab to people with multiple sclerosis (MS) in countries that have major barriers for accessing approved disease-modifying treatments (DMTs) for MS likely reduces the number of people who have relapses.
- Rituximab may reduce relapses when early highly effective therapy or escalation treatment from other DMTs are needed.
- A protective effect of rituximab against disability worsening is uncertain.
- There is limited information to determine the effect of rituximab for progressive forms of MS.
- The evidence is uncertain about the effect of rituximab on serious adverse events that are relatively rare in people with MS, and are thus difficult to study.
- There is an increased risk of common infections with rituximab, but the absolute risk is small.
- There is less risk of treatment discontinuation due to adverse events with rituximab compared with other DMTs. However, the true compliance rate with rituximab and other DMTs is not known.

Implications for research

Rituximab is widely used as off-label treatment in people with MS, but randomised evidence is weak, and likely it will remain so in the future as well.

- Better understanding is needed of comparative benefits and harms of rituximab and other highly effective DMTs over the long term.
- Future studies are needed to assess comparative effectiveness of acceptance and adherence to highly effective DMTs.
- In the absence of randomised evidence, data from registries and large observational studies should be publicly available. These may be relevant sources for providing complementary data regarding the long-term benefits of DMTs for MS.
- More thorough investigations are needed to assess reasons for treatment discontinuation and comparison for adverse events applicable to each DMT.

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The following people conducted the editorial process for this review:

- Sign-off Editor (final editorial decision): Robert Boyle, Imperial College London, UK
- Managing Editor (selected per reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the review): Joey Kwong, Cochrane Editorial and Methods Department
- Editorial Assistant (conducted editorial policy checks, supported editorial team): Leticia Rodrigues, Cochrane Editorial and Methods Department
- Copy Editor (copy-editing, production): Anne Lawson, Cochrane Copy Edit Support
- Peer-reviewers (provided comments, recommended an editorial decision): Benjamin Victor Ineichen, National Institutes of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, USA [clinical/content review]; Dai-shi Tian, Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China [clinical/content review]; Thomas Mathew, Department of Neurology, St John's National Academy of Health Sciences, Bangalore [clinical/content review]; Onur Boyman, University of Zurich and Department of Immunology, University Hospital Zurich [clinical/content review]; Nuala Livingstone, Cochrane Editorial and Methods Department [methods review]; Douglas Salzwedel, Cochrane Hypertension [search review]; Robin Featherstone, Cochrane Editorial and Methods Department [search review]; Amin Sharifan; one additional peer-reviewer also provided methods review but chose not to be publicly acknowledged.

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REFERENCES

References to studies included in this review

Alcalá 2019 *{published data only}*

* Alcalá C, Gascón F, Pérez-Miralles F, Domínguez J A, Gil-Perotín S, Casanova B. Treatment with alemtuzumab or rituximab after fingolimod withdrawal in relapsing-remitting multiple sclerosis is effective and safe. *Journal of Neurology* 2019;**266**(3):726-34.

Alping 2016 *{published data only}*

* Alping P, Frisell T, Novakova L, Islam-Jakobsson P, Salzer J, Björck A, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Annals of Neurology* 2016;**79**(6):950-8.

Alping 2020 *{published data only}*

* Alping P, Askling J, Burman J, Fink K, Fogdell-Hahn A, Gunnarsson M, et al. Cancer risk for fingolimod, natalizumab, and rituximab in multiple sclerosis patients. *Annals of Neurology* 2020;**87**(5):688-99.

Alping P, Piehl F, Frisell T. Cancer risk among Swedish multiple sclerosis patients: a nationwide cohort study comparing rituximab, fingolimod and natalizumab. *Multiple Sclerosis Journal* 2018;**24**(2):36.

Boremalm 2019 *{published data only}*

* Boremalm M, Juto A, Axelsson M, Novakova L, Frisell T, Svenningsson A, et al. Natalizumab, rituximab and fingolimod as escalation therapy in multiple sclerosis. *European Journal of Neurology* 2019;**26**(8):1060-7.

Salzer J, Boremalm M, Juto A, Novakova L, Axelsson M, Frisell T, et al. Comparison of rituximab and highly effective second line disease modifying therapies after breakthrough disease activity in relapsing-remitting multiple sclerosis. *Multiple Sclerosis Journal* 2017;**23**(3):323.

Cheshmavar 2021 *{published data only}*

* Cheshmavar M, Mirmosayyeb O, Badihian N, Badihian S, Shaygannejad V. Rituximab and glatiramer acetate in secondary progressive multiple sclerosis: a randomized clinical trial. Acta Neurologica Scandinavica 2021;**143**(2):178-87.

NCT03315923. Comparison of clinical effects of rituximab and glatiramer acetate in secondary progressive multiple sclerosis patients. clinicaltrials.gov/show/NCT03315923 (first received 20 October 2017).

Etemadifar 2019 *{published data only}*

* Etemadifar M, Ghourchian S, Mahinparvar N, Salari M, Etemadifar F, Nikanpour Y, et al. Cyclophosphamide versus rituximab in progressive forms of multiple sclerosis. *Acta Medica Iranica* 2019;**57**(8):484-91.

Evertsson 2020 *{published data only}*

* Evertsson B, Hoyt T, Christensen A, Nimer FA, Foley J, Piehl F. A comparative study of tolerability and effects on immunoglobulin levels and CD19 cell counts with ocrelizumab vs low dose of rituximab in multiple sclerosis. *Multiple Sclerosis Journal – Experimental, Translational and Clinical* 2020;**6**(4):2055217320964505.

Granqvist 2018 *{published data only}*

* Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. *JAMA Neurology* 2018;**75**(3):320-7.

Hauser 2008 *{published data only}*

* Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *New England Journal of Medicine* 2008;**358**(7):676-88.

NCT00097188. A study to evaluate rituximab in adults with relapsing remitting multiple sclerosis. clinicaltrials.gov/show/NCT00097188 (first received 19 November 2004).

Hawker 2009 *{published data only}*

Hawker K, O'Connor P, Freedman M. Efficacy and safety of rituximab in patients with primary progressive multiple sclerosis (PPMS): results of a randomized double-blind placebo-controlled multicenter trial. *Neurology* 2009;**72 (11 Suppl 3)**:A254.

* Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Annals of Neurology* 2009;**66**(4):460-71.

NCT00087529. A study to evaluate the safety and efficacy of rituximab in adults with primary progressive multiple sclerosis (OLYMPUS). clinicaltrials.gov/show/NCT00087529 (first received 13 July 2004).

Komori 2016 *{published data only}*

* Komori M, Lin YC, Cortese I, Blake A, Ohayon J, Cherup J, et al. Insufficient disease inhibition by intrathecal rituximab in progressive multiple sclerosis. *Annals of Clinical and Translational Neurology* 2016;**3**(3):166-79.

NCT01212094. Double blind combination of rituximab by intravenous and intrathecal injection versus placebo in patients with low-inflammatory secondary progressive multiple sclerosis (RIVITaLISe). clinicaltrials.gov/show/NCT01212094 (first received 30 September 2010).

Luna 2020 *{published data only}*

* Luna G, Alping P, Burman J, Fink K, Fogdell-Hahn A, Gunnarsson M, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. *JAMA Neurology* 2020;**77**(2):184-91.

Luna G, Piehl F, Frisell T. Infection risks among Swedish multiple sclerosis patients treated with rituximab compared to natalizumab, fingolimod, and injectable therapies: a nationwide cohort study. *Multiple Sclerosis Journal* 2018;**24**(2):502-3.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Naegelin 2019 *{published data only}*

* Naegelin Y, Naegelin P, von Felten S, Lorscheider J, Sonder J, Uitdehaag BM, et al. Association of rituximab treatment with disability progression among patients with secondary progressive multiple sclerosis. *JAMA Neurology* 2019;**76**(3):274-81.

Spelman 2018 *{published data only}*

* Spelman T, Frisell T, Piehl F, Hillert J. Comparative effectiveness of rituximab relative to IFN-β or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry. *Multiple Sclerosis* 2018;**24**(8):1087-95.

Vollmer 2020a *{published data only}*

Vollmer B, Nair K, Sillau S, Corboy J, Vollmer T, Alvarez E. Comparison of rituximab vs fingolimod, dimethyl fumarate and natalizumab in the treatment of multiple sclerosis: two year experience. *Neurology* 2018;**90**:15.

* Vollmer BL, Nair K, Sillau S, Corboy JR, Vollmer T, Alvarez E. Rituximab versus natalizumab, fingolimod, and dimethyl fumarate in multiple sclerosis treatment. *Annals of Clinical and Translational Neurology* 2020;**7**(9):1466-76.

References to studies excluded from this review

Airas 2020 *{published data only}*

Airas L, Nylund M, Mannonen I, Matilainen M, Sucksdorff M, Rissanen E. Rituximab in the treatment of multiple sclerosis in the Hospital District of Southwest Finland. *Multiple Sclerosis and Related Disorders* 2020;**40**:101980.

Alcalá 2018 *{published data only}*

Alcalá C, Gascón F, Pérez-Miralles F, Islam-Jakobsson P, Salzer J, Björck A, et al. Efficacy and safety of rituximab in relapsing and progressive multiple sclerosis: a hospital-based study. *Journal of Neurology* 2018;**265**:1690-7.

Perez Miralles FC, Alcala Vicente C, Gascon Gimenez F, Escutia Roig M, Bernad Felices A, Casanova Estruch B. Real-life experience with rituximab for the treatment of multiple sclerosis: report from two MS referral centres. *Multiple Sclerosis Journal* 2017;**23**(3):343.

Alldredge 2018 *{published data only}*

Alldredge B, Jordan A, Imitola J, Racke MK. Safety and efficacy of rituximab: experience of a single multiple sclerosis center. *Clinical Neuropharmacology* 2018;**41**(2):56-9.

Alvarez 2015 *{published data only}*

Alvarez E, Piccio L, Mikesell RJ, Trinkaus K, Parks BJ, Naismith RT, et al. Predicting optimal response to B-cell depletion with rituximab in multiple sclerosis using CXCL13 index, magnetic resonance imaging and clinical measures. *Multiple Sclerosis Journal – Experimental, Translational and Clinical* 2015;**1**:2055217315623800.

Alvarez E, Seibert J, Vollmer B, Blackburn J, Strobel M, Freeman J, et al. Assessing the efficacy, tolerability, and safety of rituximab for the treatment of multiple sclerosis: experience in 313 patients at a large academic center. *Multiple Sclerosis Journal* 2015;**23**(11):544.

Barmettler 2018 *{published data only}*

Barmettler S, Ong MS, Farmer JR, Choi H, Walter J. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. *JAMA Network Open* 2018;**1**(7):e184169.

Bar-Or 2008 *{published data only}*

Bar-Or A, Calabresi PA, Arnold D, Markowitz C, Shafer S, Kasper LH, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. *Annals of Neurology* 2008;**63**(6):803.

Barra 2016 *{published data only}*

Barra ME, Soni D, Vo KH, Chitnis T, Stankiewicz JM. Experience with long-term rituximab use in a multiple sclerosis clinic. *Multiple Sclerosis Journal Experimental, Translational and Clinical* 2016;**2**:2055217316672100.

Bellinvia 2020 *{published data only}*

Bellinvia A, Prestipino E, Portaccio E, Razzolini L, Fonderico M, Fratangelo R, et al. Experience with rituximab therapy in a real-life sample of multiple sclerosis patients. Neurological Sciences 2020;**41**(10):2939-45. [DOI: 10.1007/s10072-020-04434-1]

Bergman 2018 *{published data only}*

Bergman J, Burman J, Gilthorpe JD, Zetterberg H, Jiltsova E, Bergenheim T, et al. Intrathecal treatment trial of rituximab in progressive MS: an open-label phase 1b study. *Neurology* 2018;**91**(20):e1893-e1901.

Berntsson 2018 *{published data only}*

Berntsson SG, Kristoffersson A, Boström I, Feresiadou A, Burman J, Landtblom AM. Rapidly increasing off- label use of rituximab in multiple sclerosis in Sweden – outlier or predecessor? *Acta Neurologica Scandinavica* 2018;**138**:327-31.

Bhargava 2019 *{published data only}*

Bhargava P, Wicken C, Smith MD, Strowd RE, Cortese I, Reich DS, et al. Trial of intrathecal rituximab in progressive multiple sclerosis patients with evidence of leptomeningeal contrast enhancement. *Multiple Sclerosis and Related Disorders* 2019;**30**:136-40.

Boremalm 2021 *{published data only}*

Boremalm M, Sundström P, Salzer J. Discontinuation and dose reduction of rituximab in patients with relapsing remitting multiple sclerosis. *Multiple Sclerosis Journal* 2020;**26**(Suppl 3):528-9.

Boremalm M, Sundström P, Salzer J. Discontinuation and dose reduction of rituximab in relapsing-remitting multiple sclerosis. Journal of Neurology 2021;**268**(6):2161-8. [DOI: 10.1007/s00415-021-10399-8]

Boström 2016 *{published data only}*

Boström I, Burman J, Landtblom AM. Adverse events of rituximab in a Swedish MS population sample. *Multiple Sclerosis Journal* 2016;**22**:871.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Brown 2011 *{published data only}*

Brown BA, Torabi M. Incidence of infusion-associated reactions with rituximab for treating multiple sclerosis: a retrospective analysis of patients treated at a US centre. *Drug Safety* 2011;**34**(2):117-23.

Caldito 2021 *{published data only}*

* Caldito NG, Shirani A, Salter A, Stuve O. Adverse event profile differences between rituximab and ocrelizumab: findings from the FDA Adverse Event Reporting Database. Multiple Sclerosis 2021;**27**(7):1066-76.

Ciplea 2020 *{published data only}*

Ciplea AI, Langer-Gould A, de Vries A, Schaap T, Thiel S, Ringelstein M, et al. Monoclonal antibody treatment during pregnancy and/or lactation in women with MS or neuromyelitis optica spectrum disorder. *Neurology, Neuroimmunology & Neuroinflammation* 2020;**7**(4):e723.

Cross 2012 *{published data only}*

Cross AH, Klein RS, Piccio L. Rituximab combination therapy in relapsing multiple sclerosis. *Therapeutic Advances in Neurological Disorders* 2012;**5**(6):311-9.

D'Amico 2019 *{published data only}*

D'Amico E, Zanghì A, Chisari CG, Fermo SL, Toscano S, Arena S, et al. Effectiveness and safety of rituximab in demyelinating diseases spectrum: an Italian experience. *Multiple Sclerosis and Related Disorders* 2019;**27**:324-6.

Das 2018 *{published data only}*

Das G, Damotte V, Gelfand JM, Bevan C, Cree BA, Do L, et al. Rituximab before and during pregnancy: a systematic review, and a case series in MS and NMOSD. *Neurology, Neuroimmunology & Neuroinflammation* 2018;**5**(3):e453.

de Flon 2016 *{published data only}*

* de Flon P, Gunnarsson M, Laurell K, Söderström L, Birgander R, Lindqvist T, et al. Reduced inflammation in relapsing-remitting multiple sclerosis after therapy switch to rituximab. *Neurology* 2016;**87**(2):141-7.

de Flon P, Laurell K, Söderström L, Gunnarsson M, Svenningsson A. Improved treatment satisfaction after switching therapy to rituximab in relapsing-remitting MS. *Multiple Sclerosis Journal* 2017;**23**(9):1249-57.

de Flon P. Treatment with the monoclonal antibody rituximab in multiple sclerosis [Dissertation for PhD]. Umeå (Sweden): The Dean of the Medical Faculty, 2018.

EUCTR2010-023021-38-SE. Switch To RItuXimab in MS. A phase 2 open label study of Rituximab in MS patients previously treated with self-injectables using a target based therapy approach – STRIX-MS. www.clinicaltrialsregister.eu (first received 26 November 2010).

Disanto 2021 *{published data only}*

Disanto G, Ripellino P, Riccitelli GC, Sacco R, Scotti B, Fucili A, et al. De-escalating rituximab dose results in stability of clinical, radiological, and serum neurofilament levels in multiple sclerosis. Multiple Sclerosis 2021;**27**(8):1230-9. [DOI: 10.1177/1352458520952036]

Dunn 2018 *{published data only}*

Dunn N, Juto A, Ryner M, Manouchehrinia A, Piccoli L, Fink K, et al. Rituximab in multiple sclerosis: frequency and clinical relevance of anti-drug antibodies. *Multiple Sclerosis Journal* 2018;**24**(9):1224-33.

Durozard 2019 *{published data only}*

Durozard P, Maarouf A, Boutiere C, Ruet A, Brochet B, Vukusic S, et al. Efficacy of rituximab in refractory RRMS. *Multiple Sclerosis Journal* 2019;**25**(6):828-36.

Ellrichmann 2019 *{published data only}*

Ellrichmann G, Bolz J, Peschke M, Duscha A, Hellwig K, Lee De-H, et al. Peripheral CD19+ B-cell counts and infusion intervals as a surrogate for long-term B-cell depleting therapy in multiple sclerosis and neuromyelitis optica/neuromyelitis optica spectrum disorders. *Journal of Neurology* 2019;**266**(1):57-67.

EUCTR2013-002378-26 *{published data only}*

EUCTR2013-002378-26. Switch To RItuXimab in MS extension. An extension study of STRIX-MS – a phase 2 open label study of Rituximab in MS patients previously treated with self-injectables using a target based therapy approach. www.clinicaltrialsregister.eu/ctr-search/trial/2013-002378-26/results (first received 7 October 2018).

Gottesman 2017 *{published data only}*

Gottesman MH, Farley S, Friedman-Urevich S, Ye J, Grueneberg D, Martone L. JC titers in multiple sclerosis (MS) patients treated with rituximab, fingolimod and dimethyl fumarate at an American MS center. *Multiple Sclerosis Journal* 2017;**23**:96-7.

Hallberg 2019 *{published data only}*

Hallberg S, Boremalm M, Evertsson B, Lillvall E, Johansson F, Lycke J, et al. Risk of hypogammaglobulinemia in long-term treatment with rituximab in multiple sclerosis. *Multiple Sclerosis Journal* 2019;**25**(Suppl 2):20.

He 2020 *{published data only}*

He A, Merkel B, Brown JW, Zhovits Ryerson L, Kister I, Malpas CB, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurology* 2020;**19**(4):307-16.

Hellgren 2020 *{published data only}*

Hellgren J, Risedal A, Källén K. Rituximab in multiple sclerosis at general hospital level. *Acta Neurologica Scandinavica* 2020;**141**(6):491-9.

Honce 2019 *{published data only}*

* Honce JM, Nair KV, Sillau S, Valdez B, Miravalle A, Alvarez E, et al. Rituximab vs placebo induction prior to glatiramer acetate monotherapy in multiple sclerosis. *Neurology* 2019;**92**(7):e723-e732.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

NCT01569451. Comparison of rituximab induction therapy followed by glatiramer acetate (GATEWAYII). clinicaltrials.gov/show/NCT01569451 (first received 3 April 2012).

Juto 2020 *{published data only}*

Juto A, Fink K, Al Nimer F, Piehl F. Interrupting rituximab treatment in relapsing-remitting multiple sclerosis; no evidence of rebound disease activity. *Multiple Sclerosis and Related Disorders* 2020;**37**:101468.

Kuempfel 2019 *{published data only}*

Kuempfel T, Thiel S, Meinl I, Bayas A, Ciplea A, Hoffmann F, et al. Anti CD20 therapies and pregnancy in neuroimmunological disorders – a case series from Germany. *Neurology* 2019;**92**:Suppl 15.

Langer-Gould 2018 *{published data only}*

Langer-Gould A, Piehl F, Smith J, Frisell T. Mortality rates in large US and Swedish rituximab-treated multiple sclerosis cohorts. *Multiple Sclerosis Journal* 2018;**24**:231830.

Langer-Gould 2019 *{published data only}*

Langer-Gould A, Alping P, Smith J, Li B, Piehl F, Frisell T. Rituximab does not increase the risk of malignancy or breast cancer in two large US and Swedish rituximab-treated multiple sclerosis cohorts. *Multiple Sclerosis Journal* 2019;**25**(S2):570.

Langer-Gould 2020 *{published data only}*

Langer-Gould A, Smith JB, Albers KB, Xiang AH, Wu J, Kerezsi EH, et al. Pregnancy-related relapses and breastfeeding in a contemporary multiple sclerosis cohort. *Neurology* 2020;**94**(18):e1939-e1949.

Leonidou 2019 *{published data only}*

Leonidou E, Pantzaris M, Kleopa KA, Loizidou MA, Kyriakides T, Christou YP. A retrospective observational study of rituximab treatment in multiple sclerosis patients in Cyprus. *Postgraduate Medicine* 2019;**131**(7):486-9.

Maarouf 2020 *{published data only}*

Maarouf A, Rico A, Boutiere C, Perriguey M, Demortiere S, Pelletier J, et al. Extending rituximab dosing intervals in patients with MS during the COVID-19 pandemic and beyond? *Neurology Neuroimmunology & Neuroinflammation* 2020;**7**(5):e825.

Malucchi 2016 *{published data only}*

Lo Re M, Capobianco M, Ragonese P, Realmuto S, Malucchi S, Berchialla P, et al. Natalizumab discontinuation and treatment strategies in patients with multiple sclerosis (MS): a retrospective study from two Italian MS centers. *Neurology and Therapy* 2015;**4**(2):147-57.

* Malucchi S, Capobianco M, Di Sapio A, Lo Re M, Sperli F, Malentacchi M, et al. Rituximab as an effective treatment option after natalizumab withdrawal. *Multiple Sclerosis Journal* 2016;**22**(Suppl 3):653-4.

Mathew 2020 *{published data only}*

Mathew T, Baptist AA, Kamath V, Murgod U, Therambil M, Shaji A, et al. Rituximab in multiple sclerosis: real world experience from three tertiary care MS centers from southern India. *Multiple Sclerosis Journal* 2019;**25**:751.

Mathew T, John SK, Kamath V, Murgod U, Thomas K, Angela Baptista A, et al. Efficacy and safety of rituximab in multiple sclerosis: experience from a developing country. *Multiple Sclerosis and Related Disorders* 2020;**43**:102210.

Mazdeh 2020 *{published data only}*

Mazdeh M, Khamseh M, Taheri M, Ghafouri-Fard S. Effect of rituximab on Expanded Disability Status Scale and relapse rate in multiple sclerosis patients. *Journal of Molecular Neuroscience* 2020;**70**(8):1165-8.

Midaglia 2020 *{published data only}*

Midaglia L, Alvarez Bravo G, Robles Cedeño R, Zabalza A, Quibus L, Carbonell-Mirabent P, et al. Rituximab treatment for MS: an observational multicentric dose comparison. Strategies for disease modification. *Multiple Sclerosis Journal* 2020;**26**(Suppl 3):14-5.

Naismith 2010 *{published data only}*

Cross AH, Klein RS, Piccio L. Rituximab combination therapy in relapsing multiple sclerosis. *Therapeutic Advances in Neurological Disorders* 2012;**5**(6):311-9.

* Naismith RT, Piccio L, Lyons JA, Lauber J, Tutlam NT, Parks BJ, et al. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. *Neurology* 2010;**74**(23):1860-7.

Piccio L, Naismith RT, Trinkaus K, Klein RS, Parks BJ, Lyons JA, et al. Changes in B- and T-lymphocyte and chemokine levels with rituximab treatment in multiple sclerosis. *Archives of Neurology* 2010;**67**(6):707-14.

Naser Moghadasi 2019 *{published data only}*

Naser Moghadasi A, Darki A, Masoumi P, Hashemi SN, Ghadiri F. Evaluating the efficacy and safety of ZytuxTM (Rituximab, AryoGen pharmed) in Iranian multiple sclerosis patients: an observational study. *Multiple Sclerosis and Related Disorders* 2019;**36**:101419.

NCT02980042 *{published data only}*

Alvarez E, Nair K, Shelton I, Zanganeh N, Sillau S, Corboy J, et al. Tolerability and safety of switching from rituximab to ocrelizumab: evaluating factors associated with infusion related reactions. *Multiple Sclerosis Journal* 2019;**25**(S2):775.

* NCT02980042. Tolerability and safety of switching from rituximab to ocrelizumab in patients with relapsing forms of multiple sclerosis. clinicaltrials.gov/show/NCT03979456 (first received 14 January 2020).

NCT03979456 *{published data only}*

NCT03979456. RItuximab long-term DOSE trial in Multiple Sclerosis – RIDOSE-MS. clinicaltrials.gov/show/NCT03979456 (first received 7 June 2019).

Nielsen 2012 *{published data only}*

Nielsen AS, Miravalle A, Langer-Gould A, Cooper J, Edwards KR, Kinkel RP. Maximally tolerated versus minimally effective dose:

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

the case of rituximab in multiple sclerosis. *Multiple Sclerosis Journal* 2012;**18**(3):377-8.

Persson 2020 *{published data only}*

Persson R, Lee S, Ulcickas Yood M, Wagner Usn Mc CM, Minton N, Niemcryk S, et al. Infections in patients diagnosed with multiple sclerosis: a multi-database study. *Multiple Sclerosis and Related Disorders* 2020;**41**:101982.

Razaz 2020 *{published data only}*

* Razaz N, Piehl F, Frisell T, Langer-Gould AM, McKay KA, Fink K. Disease activity in pregnancy and postpartum in women with MS who suspended rituximab and natalizumab. *Neurology (R) Neuroimmunology & Neuroinflammation* 2020;**7**(6):e903.

Sahraian 2020 *{published data only}*

Sahraian MA, Azimi A, Navardi S, Ala S, Naser Moghadasi A. Evaluation of the rate of COVID-19 infection, hospitalization and death among Iranian patients with multiple sclerosis. *Multiple Sclerosis and Related Disorders* 2020;**46**:102472.

Salzer 2016 *{published data only}*

Salzer J, Svenningsson R, Alping P, Novakova L, Björck A, Fink K, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. *Neurology* 2016;**87**(20):2074-81.

Schwake 2020 *{published data only}*

Schwake C, Gold R. Severe pneumonia with formation of a pulmonary cavity associated with long-term rituximab therapy in multiple sclerosis. Neurological Research and Practice 2020;**2**:30. [DOI: 10.1186/s42466-020-00074-0]

Scotti 2018 *{published data only}*

Scotti B, Disanto G, Sacco R, Guigli M, Zecca C, Gobbi C. Effectiveness and safety of rituximab in multiple sclerosis: an observational study from Southern Switzerland. *Plos One* 2018;**13**(5):e0197415.

Shima 2020 *{published data only}*

Shima A, Hamaguchi T, Tada Y, Yamada M. Treatment with rituximab in the acute phase of relapsing remitting multiple sclerosis. *Internal Medicine (Tokyo, Japan)* 2020;**59**(1):121-4.

Smith 2020 *{published data only}*

Smith JB, Hellwig K, Fink K, Lyell DJ, Piehl F, Langer-Gould A. Rituximab, MS, and pregnancy. *Neurology Neuroimmunology & Neuroinflammation* 2020;**7**(4):e734.

Topping 2016 *{published data only}*

Topping J, Dobson R, Lapin S, Maslyanskiy A, Kropshofer H, Leppert D, et al. The effects of intrathecal rituximab on biomarkers in multiple sclerosis. *Multiple Sclerosis & Related Disorders* 2016;**6**:49-53.

Torgauten 2021 *{published data only}*

Torgauten HM, Myhr KM, Wergeland S, Bø L, Aarseth JH, Torkildsen Ø. Safety and efficacy of rituximab as first- and second line treatment in multiple sclerosis – a cohort study. Multiple Sclerosis Journal – Experimental, Translational and Clinical 2021;**7**(1):2055217320973049. [DOI: 10.1177/2055217320973049]

Tsao 2019 *{published data only}*

Tsao L, Otani IM, Bove L. Hypogammaglobulinemia in multiple sclerosis patients receiving disease-modifying immunomodulatory agents. *Journal of Allergy and Clinical Immunology* 2019;**143**(2 Suppl):AB16.

Vollmer 2020b *{published data only}*

Alvarez E, Nair K, Shelton I, Selva S, Voge N, Zanganeh N, et al. Evaluating the tolerability and safety of switching from rituximab to ocrelizumab: infusion related reactions in relapsing forms of multiple sclerosis. *Neurology* 2019;**92 (15 Suppl)**:P4.2-015.

* Vollmer BL, Wallach AI, Corboy JR, Dubovskaya K, Alvarez E, Kister I. Serious safety events in rituximab-treated multiple sclerosis and related disorders. Annals of Clinical and Translational Neurology 2020;**7**(9):1477-87. [DOI: 10.1002/acn3.51136]

Wijnands 2018 *{published data only}*

Wijnands JM, Zhu F, Kingwell E, Fisk JD, Evans C, Marrie RA, et al. Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study. *Journal of Neurology, Neurosurgery and Psychiatry* 2018;**89**(10):1050-6.

Wolf 2019 *{published data only}*

Wolf AB, Ryerson LZ, Pandey K, McGettigan BM, Vollmer T, Corboy JR, et al. Rituximab-induced serum sickness in multiple sclerosis patients. *Multiple Sclerosis and Related Disorders* 2019;**36**:101402.

Yamout 2018 *{published data only}*

Yamout BI, El-Ayoubi NK, Nicolas J, El Kouzi Y, Khoury SJ, Zeineddine MM. Safety and efficacy of rituximab in multiple sclerosis: a retrospective observational study. *Journal of Immunology Research* 2018;**2018**:9084759.

Zecca 2020 *{published data only}*

Zecca C, Bovis F, Novi G, Capobianco M, Lanzillo R, Frau J, et al. Treatment of multiple sclerosis with rituximab: a multicentric Italian-Swiss experience. *Multiple Sclerosis Journal* 2020;**26**(12):1519-31.

Zhovtis Ryerson 2018 *{published data only}*

Zhovtis Ryerson L. Serious adverse events related to Rituximab in multiple sclerosis and neuromyelitis optica spectrum disorder patients. *Multiple Sclerosis Journal* 2018;**24**(2):935-6.

References to studies awaiting assessment

Berrios Morales 2016 *{published data only}*

Berrios Morales I, Eleftheriou E, Maranda L, Ionete C. The safety and efficacy of rituximab use in secondary progressive multiple sclerosis (SPMS) at UMMHC: five years follow up data. *Multiple Sclerosis Journal* 2016;**22**:805.

Morales IB, Eleftheriou E, Maranda L, Politi L, Ionete C. The safety and efficacy of rituximab use in secondary-progressive

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multiple sclerosis (SPMS) at UMMHC: five years follow up data. *Neurology* 2017;**88**(Suppl 1):16.

Frisell 2019 *{published data only}*

Frisell T, Cuijpers M, Piehl F. Rate of cardiovascular disease among Swedish multiple sclerosis patients treated with rituximab, natalizumab, fingolimod, and dimethyl fumarate: a nationwide cohort study. *Multiple Sclerosis Journal* 2019;**25**:314.

Kalincik 2019 *{published data only}*

Kalincik T, Malpas CB, Sharmin S, Roos I, Patti F, Butzkueven H, et al. Comparison of the effectiveness of rituximab versus alemtuzumab and natalizumab in active relapsing-remitting MS. *Multiple Sclerosis Journal* 2019;**25**:912-4.

References to ongoing studies

EUCTR2017-000426-35-AT *{published data only}*

EUCTR2017-000426-35-AT. Efficacy of rituximab at low doses in multiple sclerosis – a prospective, randomized, double-blind, active controlled, pilot trial. www.clinicaltrialsregister.eu/ctr-search/trial/2017-000426-35/AT (first received 12 March 2018).

EUCTR2017-002634-24-SE *{published data only}*

EUCTR2017-002634-24-SE. MultipleMS – Multiple-omics approach to accelerate personalised medicine in a prospective cohort of newly diagnosed MS and CIS patients. www.clinicaltrialsregister.eu/ctr-search/trial/2017-002634-24/SE (first received 6 July 2017).

EUCTR2020-002981-15-DK *{published data only}*

Danish non-inferiority study of ocrelizumab and rituximab in MS (DanNORMS): a randomized study comparing the efficacy of ocrelizumab and rituximab in active multiple sclerosis. www.clinicaltrialsregister.eu/ctr-search/trial/2020-002981-15/DK (first received 13 July 2020.

NCT04688788. Non-inferiority study of ocrelizumab and rituximab in active multiple sclerosis (DanNORMS). clinicaltrials.gov/ct2/show/NCT04688788 (first received 30 December 2020).

IRCT20130812014333N125 *{published data only}*

IRCT20130812014333N125. Comparison of effectiveness and complication of rituximab and fingolimod in improvement disability motion. en.irct.ir/trial/38158 (first received 7 June 2019).

NCT02545959 *{published data only}*

EUCTR2014-005493-11. Intrathecal rituximab in progressive multiple sclerosis (EFFRITE). www.clinicaltrialsregister.eu/ctr-search/trial/2014-005493-11/FR (first received 15 March 2018).

NCT02545959. Intrathecal rituximab in progressive multiple sclerosis (EFFRITE). clinicaltrials.gov/show/NCT02545959 (first received 10 September 2015).

NCT02746744 *{published data only}*

EUCTR2015-004116-38. RItuximab versus FUmarate in Newly Diagnosed Multiple Sclerosis – RIFUND-MS. www.clinicaltrialsregister.eu/ctr-search/trial/2015-004116-38/SE (first received 20 October 2015).

EUCTR2018-000721-31. RItuximab Long-Term DOSE Trial in Multiple Sclerosis – RIDOSE-MS. www.clinicaltrialsregister.eu/ctr-search/trial/2018-000721-31/SE (first received 24 April 2018).

NCT02746744. RItuximab versus FUmarate in Newly Diagnosed Multiple Sclerosis (RIFUND-MS). clinicaltrials.gov/show/NCT02746744 (first received 21 April 2016).

NCT03979456. RItuximab Long-Term DOSE Trial in Multiple Sclerosis – RIDOSE-MS. clinicaltrials.gov/ct2/show/NCT03979456 (first received 7 June 2019).

NCT03193866 *{published data only}*

EUCTR2016-003587-39. COMBAT-MS (COMparison Between All immunoTherapies for Multiple Sclerosis). www.clinicaltrialsregister.eu/ctr-search/trial/2016-003587-39/SE (first received 23 March 2017).

NCT03193866. COMparison Between All immunoTherapies for Multiple Sclerosis (COMBAT-MS). clinicaltrials.gov/show/NCT03193866 (first received 21 June 2017).

NCT03315923 *{published data only}*

NCT03315923. Comparison of clinical effects of rituximab and glatiramer acetate in secondary progressive multiple sclerosis patients. clinicaltrials.gov/show/NCT03315923 (first received 20 October 2017).

NCT03500328 *{published data only}*

NCT03500328. Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial (TREAT-MS). clinicaltrials.gov/show/NCT03500328 (first received 18 April 2018).

NCT03535298 *{published data only}*

NCT03535298. Determining the Effectiveness of earLy Intensive Versus Escalation approaches for RRMS (DELIVER-MS). clinicaltrials.gov/show/NCT03535298 (first received 24 May 2018).

NCT04047628 *{published data only}*

NCT04047628. Best available therapy versus autologous hematopoetic stem cell transplant for multiple sclerosis (BEAT-MS). clinicaltrials.gov/show/NCT04047628 (first received 7 August 2019).

NCT04121403 *{published data only}*

EUCTR2019-001505-24. Norwegian study of Oral cladribine versus Rituximab in Multiple Sclerosis (NOR-MS). A prospective randomized open-label blinded endpoint (PROBE) multicenter non-inferiority study. www.clinicaltrialsregister.eu/ctr-search/trial/2019-001505-24/NO (first received 28 May 2019.

NCT04121403. Norwegian study of oral cladribine and rituximab in multiple sclerosis (NOR-MS). clinicaltrials.gov/show/NCT04121403 (first received 9 October 2019).

Nygaard G, Lorentzen A, Hognestad T, Simonsen C, Kampman M, Flemmen H, et al. A prospective randomized open-label blinded endpoint multicenter non-inferiority study

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

of oral cladribine and rituximab in multiple sclerosis (NOR-MS). *Multiple Sclerosis Journal* 2020;**26**(Suppl 3):207-8.

NCT04283747 *{published data only}*

NCT04283747. Rituximab-induced hypogammaglobulinemia in multiple sclerosis. clinicaltrials.gov/show/NCT04283747 (first received 25 February 2020).

NCT04578639 *{published data only}*

NCT04578639. Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease (OVERLORD-MS). clinicaltrials.gov/ct2/show/NCT04578639 (first received 8 October 2020).

Additional references

Alping 2019

Alping P, Piehl F, Langer-Gould A, Frisell T, COMBAT-MS Study Group. Validation of the Swedish Multiple Sclerosis Register: further improving a resource for pharmacoepidemiologic evaluations. *Epidemiology* 2019;**30**:230-3.

Banerjee 2018

Banerjee S, Adcock L. Rituximab for the Treatment of Myasthenia Gravis: a Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2018.

Bar-Or 2010

Bar-Or A, Fawaz L, Fan B, Darlington PJ, Rieger A, Ghorayeb C, et al. Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? *Annals of Neurology* 2010;**67**(4):452-61.

Batista 2009

Batista FD, Harwood NE. The who, how and where of antigen presentation to B cells. *Nature Reviews. Immunology* 2009;**9**(1):15-27.

Benedict 2020

Benedict RH, Amato MP, DeLuca J, Geurts JJ. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *Lancet Neurology* 2020;**19**(10):860-71.

Berger 2018

Berger JR, Malik V, Lacey S, Brunetta P, Lehane PB. Progressive multifocal leucoencephalopathy in rituximab-treated rheumatic diseases: a rare event. *Journal of Neurovirology* 2018;**24**(3):323-31.

Berntsson 2018

Berntsson SG, Kristoffersson A, Boström I, Feresiadou A, Burman J, Landtblom AM. Rapidly increasing off-label use of rituximab in multiple sclerosis in Sweden – outlier or predecessor? *Acta Neurologica Scandinavica* 2018;**138**:327-31.

Castillo-Trivino 2013

Castillo-Trivino T, Braithwaite D, Bacchetti P, Waubant E. Rituximab in relapsing and progressive forms of multiple sclerosis: a systematic review. *PloS One* 2013;**8**(7):e66308.

Comi 2021

Comi G, Bar-Or A, Lassmann H, Uccelli A, Hartung HP, Montalban X, et al. Expert Panel of the 27th Annual Meeting of the European Charcot Foundation. Role of B Cells in Multiple Sclerosis and Related Disorders. *Annals of Neurology* 2021;**89**(1):13-23.

Damato 2016

Damato V, Evoli A, Iorio R. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. *JAMA Neurology* 2016;**73**(11):1342-8.

Deeks 2019

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Delate 2020

Delate T, Hansen ML, Gutierrez AC, Le KN. Indications for rituximab use in an integrated health care delivery system. *Journal of managed care & speciality pharmacy* 2020;**26**(7):832-8.

Duddy 2007

Duddy M, Niino M, Adatia F, Hebert S, Freedman M, Atkins H, et al. Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis. *Journal of Immunology* 2007;**178**(10):6092-9.

EMA 2015

European Medicines Agency (EMA). Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. EMA/CHMP/771815/2011, Rev. 2. www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-multiple-sclerosis_en-0.pdf 2015.

European Commission 2017

European Commission. Study on off-label use of medicinal products in the European Union. ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf 2017.

Evens 2011

Evens AM, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Annals of Oncology* 2011;**22**(5):1170-80.

Fasano 2017

Fasano S, Gordon P, Hajji R, Loyo E, Isenberg DA. Rituximab in the treatment of inflammatory myopathies: a review. *Rheumatology (Oxford)* 2017;**56**(1):26-36.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

FDA 2019a

US Food and Drug Administration. New Drug Application (NDA): 209884. www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 15 September 2020).

FDA 2019b

FDA. New Drug Application (NDA): 022561. www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022561 (accessed 15 September 2020).

FDA 2020a

US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. www.accessdata.fda.gov/drugsatfda_docs/label/2020/103705s5460lbl.pdf (accessed 28 March 2020).

FDA 2020b

US Food and Drug Administration. New Drug Application (NDA): 209899. www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209899 (accessed 13 September 2020).

Filippini 2021a

Filippini G. Outcomes for relapsing and progressive multiple sclerosis [personal communication]. Email to: O Stuve 2 March 2021.

Filippini 2021b

Filippini G. Outcomes for relapsing and progressive multiple sclerosis [personal communication]. Email to: E Alvarez 2 March 2021.

Filippini 2021c

Filippini G. Outcome for relapsing and progressive multiple sclerosis [personal communication]. Email to: P Alping 2 March 2021.

Filippini 2021d

Filippini G. Total number of patients treated with fingolimod and those treated with glatiramer. Email to: A Langer-Gould 2 April 2021.

Ghajarzadeh 2020

Ghajarzadeh M, Azimi A, Valizadeh Z, Sahraian MA, Mohammadifar M. Efficacy and safety of rituximab in treating patients with multiple sclerosis (MS): a systematic review and meta-analysis. *Autoimmunity Reviews* 2020;**19**(8):102585.

Giovannoni 2012

Giovannoni G, Southam E, Waubant E. Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2012;**18**(7):932-46.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed 12 October 2020. Available at gradepro.org.

Granqvist 2018

Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. *JAMA Neurology* 2018;**75**(3):320-7.

Greenfield 2018

Greenfield AL, Hauser SL. B cell therapy for multiple sclerosis: entering an era. *Annals of Neurology* 2018;**83**(1):13-26.

Hallberg 2019

Hallberg S, Boremalm M, Evertsson B, Lillvall E, Johansson F, Lycke J, et al. Risk of hypogammaglobulinemia in long-term treatment with rituximab in multiple sclerosis. ECTRIMS online library. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 2019 Sept 11-13; Stockholm (Sweden) 2019. [Abstract 64]

Hauser 2015

Hauser SL. The Charcot Lecture: beating MS: a story of B cells, with twists and turns. *Multiple Sclerosis* 2015;**21**:8-21.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2017

Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

Higgins 2019

Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook/archive/v6.

Hillert 2015

Hillert J, Stawiarz L. The Swedish MS Registry clinical support tool and scientific resource. *Acta Neurologica Scandinavica* 2015;**132**:11-9.

Hillert 2020

Neuroreg.Se: Swedish Multiple Sclerosis Register. neuroreg.se/ (accessed 1 July 2020).

Hu 2019

Hu Y, Nie H, Yu HH, Qin C, Wu LJ, Tang ZP, et al. Efficacy and safety of rituximab for relapsing-remitting multiple sclerosis: a systematic review and meta-analysis. *Autoimmunity Reviews* 2019;**18**(5):542-8.

Ineichen 2020

Ineichen BV, Moridi T, Granberg T, Piehl F. Rituximab treatment for multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2020;**26**(2):137-52.

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Jelcic 2018

Jelcic I, Al Nimer F, Wang J, Lentsch V, Planas R, Jelcic I, et al. Memory B cells activate brain-homing, autoreactive CD4+ T cells in multiple sclerosis. *Cell* 2018;**175**(1):85-100.e23.

Kurtzke 1983

Kurtzke JF. Rating neurological impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983;**33**:1444-52.

Lancet Neurology 2019

Lancet Neurology. Essential medicines for patients with multiple sclerosis. *Lancet Neurology* 2019;**18**(12):1067.

Langdon 2012

Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Multiple Sclerosis* 2012;**18**:891-8.

Laurson-Doube 2021

Laurson-Doube J, Rijke N, Helme A, Baneke P, Banwell B, Viswanathan S, et al. Ethical use of off-label disease-modifying therapies for multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2021;**27**(9):1403-10.

Lefebvre 2019

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook/archive/v6.

Lublin 1996

Lublin FD, Reingold SC, National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology* 1996;**46**:907-11.

Lublin 2014

Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014;**83**(3):278-86.

Maloney 1997

Maloney DG, Grillo-Lopez AJ, Bodkin DJ, White CA, Liles TM, Royston I, et al. IDECC2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *Journal of Clinical Oncology* 1997;**15**(10):3266-74.

Marques 2018

Marques VD, Passos GR, Mendes MF, Callegaro D, Lana-Peixoto MA, Comini-Frota ER, et al. Brazilian consensus for the treatment of multiple sclerosis: Brazilian Academy of Neurology and Brazilian Committee on Treatment and Research in Multiple Sclerosis. *Arquivos de Neuro-psiquiatria* 2018;**76**(8):539-54.

Mathew 2020

Mathew T, John SK, Kamath V, Murgod U, Thomas K, Baptist AA, et al. Efficacy and safety of rituximab in multiple sclerosis: experience from a developing country. *Multiple Sclerosis and Related Disorders* 2020;**43**:102210.

Mathias 2017

Mathias A, Perriard G, Canales M, Soneson C, Delorenzi M, Schluep M, et al. Increased ex vivo antigen presentation profile of B cells in multiple sclerosis. *Multiple Sclerosis* 2017;**23**(6):802-9.

McDonald 2001

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Annals of Neurology* 2001;**50**(1):121-7.

McKenzie 2019

McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV, Thomas J. Chapter 3: Defining the criteria for including studies and how they will be grouped for the synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook/archive/v6.

Meyer-Moock 2014

Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurology* 2014;**14**:58.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097.

Montalban 2018

Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Multiple Sclerosis Journal* 2018;**24**(2):96-120.

MSIF 2020

The Multiple Sclerosis International Federation (MSIF). Atlas of MS, 3rd Edition. www.atlasofms.org September 2020.

Nepal 2020

Nepal G, Shing YK, Yadav JK, Rehrig JH, Ojha R, Huang DY, et al. Efficacy and safety of rituximab in autoimmune encephalitis: a meta-analysis. *Acta Neurologica Scandinavica* 2020;**142**(5):449-59.

Nicholas 2020

Nicholas JA, Edwards NC, Edwards RA, Dellarole A, Grosso M, Phillips AL. Real-world adherence to, and persistence with, once- and twice-daily oral disease-modifying drugs in patients

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

with multiple sclerosis: a systematic review and meta-analysis. *BMC Neurology* 2020;**20**(1):281.

Page 2019

Page MJ, Higgins JP, Sterne JA. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019 Available from training.cochrane.org/handbook/archive/v6.

Polman 2005

Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Annals of Neurology* 2005;**58**(6):840-6.

Polman 2011

Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology* 2011;**69**(2):292-302.

Poser 1983

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology* 1983;**13**(3):227-31.

Pourcher 2020

Pourcher V. What are the infectious risks with disease-modifying drugs for multiple sclerosis and how to reduce them? A review of literature. *Revue Neurologique (Paris)* 2020;**176**(4):235-43.

Pust 2020

Pust GE, Untiedt B, Randerath J, Barabasch A, Köpke S, Rahn AC, et al. Exploring adherence to first-line and second-line immunotherapies in multiple sclerosis: an interview study. *International Journal of MS Care* 2020;**22**(5):219-25.

Rae-Grant 2018

Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BA, Gronseth GS, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;**90**(17):777-88.

Reeves 2019

Reeves BC, Deeks JJ, Higgins JP, Shea B, Tugwell P, Wells GA. Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook/archive/v6.

Review Manager Web [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 2.2.1. The Cochrane Collaboration, 2021. Available from revman.cochrane.org.

Roll 2006

Roll P, Palanichamy A, Kneitz C, Dorner T, Tony HP. Regeneration of B cell subsets after transient B cell depletion using anti-CD20 antibodies in rheumatoid arthritis. *Arthritis and Rheumatism* 2006;**54**(8):2377-86.

Sabatino 2019

Sabatino JJ, Pröbstel A-K, Zamvil SS. B cells in autoimmune and neurodegenerative central nervous system diseases. *Nature Reviews. Neuroscience* 2019;**20**(12):728-45.

Salzer 2016

Salzer J, Svenningsson R, Alping P, Novakova L, Björck A, Fink K, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. *Neurology* 2016;**87**(20):2074-81.

Santesso 2020

Santesso N, Glenton C, Dahm P, Garner P, Akl A, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *Journal of Clinical Epidemiology* 2020;**119**:126-35.

Sarsour 2020

Sarsour K, Beckley-Kartey S, Melega S, Odueyungbo A, Kirchner P, Khalife N, et al. Rituximab utilization for approved and off-label nononcology indications and patients' experiences with the Patient Alert Card. *Pharmacology Research & Perspectives* 2020;**8**(1):e00555.

Schünemann 2019

Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *Journal of Clinical Epidemiology* 2019;**111**:105-14.

Schünemann 2020

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook/archive/v6.1.

Serafini 2004

Serafini B, Rosicarelli B, Magliozzi R, Stigliano E, Aloisi F. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. *Brain Pathology* 2004;**14**(2):164-74.

Siddiqui 2020

Siddiqui MK, Singh B, Attri S, Veraart C, Harty G, Wong SL. Use of rituximab in adults with relapsing-remitting multiple sclerosis: a systematic literature review. *Current Medical Research and Opinion* 2020;**36**(5):809-26.

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Skoetz 2020

Skoetz N, Goldkuhle M, van Dalen EC, Akl EA, Trivella M, Mustafa RA, et al. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and evidence profiles. *Journal of Clinical Epidemiology* 2020;**118**:124-31.

St Clair 2010

St Clair EW. Good and bad memories following rituximab therapy. *Arthritis and Rheumatism* 2010;**62**(1):1-5.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Thompson 2018

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurology* 2018;**17**(2):162-73.

Tian 2020

Tian X, Chen C, Ma L, Wei R, Li M, Wang X, et al. Efficacy and safety of rituximab in relapsing-remitting multiple sclerosis: a systematic review and meta-analysis. *Journal of Neuroimmunology* 2020;**347**:577317.

Trojano 2017

Trojano M, Tintore M, Montalban X, Hillert J, Kalincik T, Iaffaldano P, et al. Treatment decisions in multiple sclerosis – insights from real-world observational studies. *Nature Reviews. Neurology* 2017;**13**:105-18.

Tsao 2019

Tsao L, Otani IM, Bove R. Hypogammaglobulinemia in multiple sclerosis patients receiving disease-modifying immunomodulatory agents. *Journal of Allergy and Clinical Immunology* 2019;**143**(Suppl 2):AB16.

US Department of Health and Human Services 2017

US Department of Health and Human Services. Criteria for Adverse Events (CTCAE) v5.0. ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf 2017.

van Vollenhoven 2015

van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Long-term safety of rituximab: final report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 years. *Journal of Rheumatology* 2015;**42**(10):1761-6.

Vickrey 1995

Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Quality of Life Research* 1995;**4**(3):187-206.

Wadstrom 2017

Wadstrom H, Frisell T, Askling J. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, tocilizumab, abatacept, or rituximab in clinical practice: a nationwide cohort study from Sweden. *JAMA Internal Medicine* 2017;**177**(11):1605-12.

Wongseelashote 2018

Wongseelashote S, Tayal V, Bourke PF. Off-label use of rituximab in autoimmune disease in the Top End of the Northern Territory, 2008–2016. *Internal Medicine Journal* 2018;**48**(2):165-72.

Yamout 2020

Yamout B, Sahraian M, Bohlega S, Al-Jumah M, Goueider R, Dahdaleh M, et al. Consensus recommendations for the diagnosis and treatment of multiple sclerosis: 2019 revisions to the MENACTRIMS guidelines. *Multiple Sclerosis and Related Disorders* 2020;**37**:101459.

Yukitake 2018

Yukitake M. Drug-induced progressive multifocal leukoencephalopathy in multiple sclerosis: a comprehensive review. *Clinical and Experimental Neuroimmunology* 2018;**9**(Suppl 1):37-47.

Zhong 2020

Zhong M, van der Walt A, Campagna MP, Stankovich J, Butzkueven H, Jokubaitis V. The pharmacogenetics of rituximab: potential implications for anti-CD20 therapies in multiple sclerosis. Neurotherapeutics 2020;**17**(4):1768-84. [DOI: 10.1007/s13311-020-00950-2]

References to other published versions of this review

Filippini 2021

Filippini G, Kruja J, He D, Del Giovane C. Rituximab for people with multiple sclerosis. *Cochrane Database of Systematic Reviews* 2021, Issue 2. Art. No: CD013874. [DOI: 10.1002/14651858.CD013874]

He 2013

He D, Guo R, Zhang F, Zhang C, Dong S, Zhou H. Rituximab for relapsing-remitting multiple sclerosis. *Cochrane Database of Systematic Reviews* 2013, Issue 12. Art. No.: CD009130. Art. No: CD009130. [DOI: 10.1002/14651858.CD009130.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

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Alcalá 2019

Study characteristics	
Methods	Retrospective multicentre cohort study Location: Spain Study period: ? to April 2018 Aim of study: to analyse the effectiveness and safety of alemtuzumab compared with rituximab in relapsing MS participants who switched from fingolimod therapy due to treatment failure. Data collection: data collected from the GITEM Register. Follow-up information obtained from the medical records at 2 University hospital MS Units in Valencia: the Hospital Universitari i Politècnic La Fe and the Hospital Clínic Universitari. No further details provided. Setting: outpatient facilities Analysis: Kaplan–Meier survival analysis for the median time to a relapse and to disability worsening
Participants	**Active relapsing MS** ***Switching from fingolimod to alemtuzumab vs rituximab*** **Inclusion criteria** • MS diagnosis according to the 2010 revisions to the McDonald criteria (Polman 2011). • Reasons for switching: failure to fingolimod treatment or having adverse effects with previously aggressive disease. Failure defined as the presence of 2 relapses in 1 year, or 1 no-disabling relapse and presence of ≥ 1 GEL in an MRI acquired ≥ 3 months after the beginning of the clinical relapse, or 1 disabling relapse. • Minimum follow-up from fingolimod discontinuation of 6 months. In most of the participants, natalizumab had been previously withdrawn due to progressive multifocal leukoencephalopathy risk. **Intervention group (alemtuzumab):** n = 28; % women: 75.0; age: mean 34.1 (SD 7.2) years; baseline EDSS score: mean 2.8 (SD 1.0); disease duration from the first relapse to alemtuzumab: mean 7.8 (SD 5.5) years; ARR the year before: mean 1.25 (SD 0.9); % of participants with GEL at baseline: 77.8; previous treatments before fingolimod: median 2 (IQR 1–3); washout period: median 42 (IQR 21.3–59.5) days; follow-up time: median 18.1 (IQR 11.8–31.4) months. **Comparator (rituximab):** n = 27; % women: 77.8; age: mean 34.6 (SD 8.3) years; baseline EDSS score: mean 3.1 (SD 1.3); disease duration from the first relapse to rituximab: mean 11.4 (SD 6.2) years; ARR the year before: mean 1.15 (SD 0.8); % of participants with GEL at baseline: 66.7; previous treatments before fingolimod: median 3 (IQR 1–4); washout period: median 34 (IQR 17.3–61.3) days; follow-up time: median 32.0 (IQR 10.6–48.6) months.
Interventions	**Alemtuzumab:** dose not reported. Administered daily intravenously on 5 consecutive days at month 0, and on 3 consecutive days at month 12. Premedication with intravenous methylprednisolone 1 g/day, paracetamol 1 g, and dexchlorpheniramine 5 mg throughout all 5 days of alemtuzumab treatment. Prophylactic acyclovir (200 mg/12 hours) during the 1st month of treatment. **Rituximab:** 1000 mg intravenous on day 1 and day 15. For maintenance, an isolated dose of 1000 mg was administrated when the percentage of total CD19+ cells was ≥ 2%. Premedication with prednisolone 100 mg, paracetamol 1 g. and dexchlorpheniramine 5 mg.
Outcomes	Outcome timing: 12 months • ARR. Data: baseline mean and post-treatment mean at 1 year with the P value in each group. SD not reported. • Disability measured by the EDSS. Data: baseline median (IGR) and post-treatment median (IQR) at 1 year with the P value in each group.

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Alcalá 2019 *(Continued)*

- Number of participants free from disability worsening.
- Number of participants free from relapses.
- Number of participants free from radiological activity defined as the presence of new T2 or gadolinium-enhancing lesions, or both on a brain MRI scan.
- Number of participants with no evidence of disease activity defined as the absence of relapses or sustained progression of disability or both and the absence of radiological activity.
- Number of participants withdrawn from treatment.
- Number of participants with AEs.
- Number of participants with SAEs.

Notes

- After alemtuzumab administration, scheduled clinical visits were planned every month for the first 3 months and every 3 months later. A blood and urine test was done every month, with thyroid function and lymphocyte subpopulations counts every 3 months. An MRI scan was performed 6 and 12 months from the first administration of alemtuzumab and then annually.
- After rituximab, scheduled clinical visits and complete blood test, including lymphocyte subpopulations counts, were planned every 3 months and an MRI scan annually.

Authors' conclusions: quote: "Treating relapsing MS patients with alemtuzumab or rituximab after fingolimod withdrawal is effective and safe, without significant differences between both groups in our series".

Funding not reported.

Alping 2016

Study characteristics

Methods

Retrospective multicentre cohort study

Location: Sweden

Study period: 2009–2015

Aim of study: to compare the effectiveness, tolerability, and safety of rituximab and fingolimod in relapsing MS participants who switched from natalizumab due to JC virus antibody positivity.

Data collection: data collected from the Swedish MS Register and from the medical records at 3 University hospitals: Karolinska (Stockholm, 1 January to 24 February 2015), Sahlgrenska (Gothenburg, 1 January 2010 to 18 April 2015), and Norland's (Umeå, 1 January 2009 to 12 April 2015). Medical records were examined regarding detailed descriptions of MRI results, clinical relapse symptoms, and AEs (scored according to CTCAE). Data collection done manually at the respective centres using a common data collection form.

Setting: inpatient facilities

Analysis: for the MRI outcomes, the number of participants with positive scans per participant with valid scans was calculated, and the differences in these proportions were tested in logistic regression models. For the outcomes clinical relapses, AEs, and drug survival, person-years and yearly incidence were calculated, and Kaplan–Meier curves and Cox proportional hazards models were used, with time from the first administration of rituximab or fingolimod as timescale. To explore potential confounding factors, sex, age, time receiving natalizumab, washout time, baseline EDSS, follow-up time (only in logistic models), and study centre were included in sequential regression models. HRs and ORs were first calculated with none of the factors, with age and sex, and by sequentially adding baseline EDSS, time receiving natalizumab, washout time, follow-up time (for OR only), and study centre. This was done using a complete-case strategy, discarding participants with incomplete data for any of these parameters.

Participants

Relapsing MS

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Alping 2016 *(Continued)*

	Switching from natalizumab, due to JC virus antibody positivity to rituximab or fingolimod **Inclusion criteria:** participants ending treatment with natalizumab due to JC virus antibody positivity and switching to either rituximab or fingolimod. **Exclusion criteria:** natalizumab treatment for < 6 months, switch for reasons other than only JC virus status, a washout period > 6 months, and participants who had registered a wish not to be included in studies. **Treatment group (rituximab):** n = 114; % women: 64.0; age: median 40.17 (IQR 33.74–50.44) years; baseline EDSS score: median 2.00 (IQR 1.00–3.50); duration of MS since diagnosis: median 8.00 (IQR 4.53–11.84) years; time receiving natalizumab before switch: median 3.49 (IQR 2.07–5.37) years; washout period: median 1.45 (IQR 1.13–2.03) months; follow-up time: median 1.24 (IQR 0.75–2.02) years. **Treatment group (fingolimod):** n = 142; % women: 61.0; age: median 40.79 (IQR 33.73–47.73) years; baseline EDSS score: median 2.50 (IQR 1.50–3.50); duration of MS since diagnosis: median 7.88 (IQR 5.20–11.22) years; time receiving natalizumab before switch: median 3.16 (IQR 1.79–4.58) years; washout period: median 2.12 (IQR 1.88–3.01) months; follow-up time: median 1.82 (IQR 1.40–2.36) years.
Interventions	**Rituximab:** intravenous infusions of 500 mg or 1000 mg every 6 months; however, in some cases the first infusion was repeated after 2 weeks. **Fingolimod:** oral administration once daily of 0.5 mg. Co-interventions not reported.
Outcomes	Outcome timing: 18 months • Clinical relapse. Data: incidence of participants with clinical relapse per year. • Time to first relapse. Data: crude and adjusted HR with 95% CI. Variables used to adjust HR: age, sex, EDSS, time receiving natalizumab, washout time, and study centre. • Number of participants with new gadolinium-enhancing positive T1-weighted lesions on brain MRI. Data: crude and adjusted OR with 95% CI. Variables used to adjust OR: age, sex, EDSS, time receiving natalizumab, washout time, follow-up time, and study centre. • Number of participants with new gadolinium-enhancing positive T1-weighted lesions or new T2-weighted lesions or both on brain MRI. Data: crude and adjusted OR with 95% CI. Variables used to adjust OR: age, sex, EDSS, time receiving natalizumab, washout time, follow-up time, and study centre. • AEs. Severity grade 1–5 according to CTCAE (National Cancer Institute 2010). Data: incidence of participants with AEs per year. • Time to AEs. Data: crude and adjusted HR with 95% CI. Variables used to adjust HR: age, sex, EDSS, time receiving natalizumab, washout time, and study centre. • Treatment discontinuation. Data: incidence of participants with discontinuation per year. • Time to treatment discontinuation. Data: crude and adjusted HR with 95% CI. Variables used to adjust HR: age, sex, EDSS, time receiving natalizumab, washout time, and study centre.
Notes	Authors' conclusions: quote: "Our findings suggest an improved effectiveness and tolerability of rituximab compared with fingolimod in stable relapsing MS patients who switch from natalizumab due to JC virus antibody positivity. Although residual confounding factors cannot be ruled out, the shared reason for switching from natalizumab and the preferential use of either rituximab or fingolimod in two of the centres mitigates these concerns". Funding: the Swedish Medical Research Council (grant 2014-3077) and Stockholm County. The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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Alping 2020

Study characteristics

Methods	Retrospective nationwide cohort study Location: Sweden Study period: 1 January 2011 to 31 December 2017 Aim of study: to compare the risk of cancer in a large population of people with MS treated with rituximab, fingolimod, or natalizumab. Data collection: data were collected from the Swedish MS Register (www.neuroreg.se/) linked to the Swedish Cancer Register and the national patient register with data on all inpatient and outpatient visits and the associated diagnosis codes. Other databases used for the study included the national prescribed drug register with complete data on all medications collected from pharmacies, national demographic registers with data on age, sex, education, and birth region for all residents, and national registers with data on sick leave and disability pension. Analysis: investigators performed Poisson and Cox regression based on propensity scores. Propensity scores were calculated using multinomial logistic regression as the inverse of the model-predicted probability of receiving the treatment that the participant had in fact received and stabilised by multiplication with the marginal population proportion receiving the same therapy. Clinically important terms were included in the model that generated the probability that a participant would receive each treatment. The investigators used stabilised inverse probability of treatment weighting in the Poisson and Cox regressions to adjust for any imbalances.
Participants	**All types of MS** ***Switching from other DMTs to rituximab, fingolimod, or natalizumab*** **Inclusion criteria:** diagnosis of MS; who first initiated rituximab, fingolimod, or natalizumab between 1 January 2011, and 31 December 2017; matched for age, sex, and location to 37,801 people from a general population without MS. Participants included in > 1 treatment group as they progressed in treatment over time. **Exclusion criteria:** therapy episodes started > 60 days prior to inclusion in the Swedish MS register to avoid potential immortal-time bias. **Rituximab group:** n = 4187 therapy initiation; % women: 71.0; mean age: 40.6 (SD 11.2) years; mean EDSS: 2.6 (SD 1.8); mean duration of MS: 9.2 (SD 8.0) years; % MS type: relapsing-remitting MS 84.1; secondary progressive MS 12.2; primary progressive MS 2.4; progressive-relapsing MS 1.3; % participants who used DMTs before rituximab: 76.4%; % participants with any invasive cancer < 5 years: 1.0; mean follow-up 2.30 years. **Fingolimod group:** n = 1620 therapy initiation; % women: 72.5; mean age: 40.7 (SD 11.1) years; mean EDSS: 2.6 (SD 1.8); mean duration of MS: 9.4 (SD 7.9) years; % MS type: relapsing-remitting MS 83.1; secondary progressive MS 13.7; primary progressive MS 1.9; progressive-relapsing MS 1.3; % participants who used DMTs before fingolimod: 79.2%; % participants with any invasive cancer < 5 years: 1.2; mean follow-up 3.96 years. **Natalizumab group:** n = 1670 therapy initiation; % women: 71.9; mean age: 40.5 (SD 11.4) years; mean EDSS: 2.5 (SD 1.8); mean duration of MS: 9.1 (SD 8.0) years; % MS type: relapsing-remitting MS 83.8; secondary progressive MS 13.8; primary progressive MS 1.3; progressive-relapsing MS 1.0; % participants who used DMTs before natalizumab: 77.2%; % participants with any invasive cancer < 5 years: 1.1; mean follow-up = 3.94 years. MS participants matched to 37,801 people without MS from general population (mean follow-up 3.03 years).
Interventions	7477 treatment initiations were included from 6136 participants. **Rituximab:** 4187 initiations (mean follow-up 2.30 years).

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Alping 2020 *(Continued)*

	Fingolimod: 1620 initiations (mean follow-up 3.96 years). **Natalizumab:** 1670 initiations (mean follow-up 3.94 years).
Outcomes	• Time to first invasive cancer, basal-cell carcinoma, cervical intraepithelial neoplasia grade 3, breast cancer, prostate cancer, melanoma, non-melanoma skin cancer (not including basal-cell carcinoma), and lymphoma. Data: HR with 95% CI.
Notes	Potential confounders included in the multiple imputation and propensity score models were: age; sex; birth region (Nordic/non-Nordic); highest achieved education level; use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, immunosuppressive agents, and systemic hormonal contraceptives (women only) in the previous 5 years; arrhythmia and major acute cardiovascular event diagnoses in the previous 5 years; parity (women only); history of any invasive cancer and the specified outcome cancer (if applicable) during and before the previous 5 years; number of hospital days in the previous 5 years; presence of sick leave and disability pension the previous year; and MS type, disease duration, number of previous therapies, previous interferon, previous glatiramer acetate, EDSS, SDMT, and MSIS-29 for people in the MS register (all times relative to start of therapy). Authors' conclusions: quoted: "In this first large comparative study of three highly effective MS disease-modifying therapies, no increased risk of invasive cancer was seen with rituximab and natalizumab, compared to the general population. However, there was a borderline-significant increased risk with fingolimod, compared to both the general population and rituximab. It was not possible to attribute this increased risk to any specific type of cancer, and further studies are warranted to validate these findings". This study was funded through a Patient-Centered Outcomes Research Institute Award (MS-1511–33196) and supported by the Swedish Foundation for MS Research.

Boremalm 2019

Study characteristics	
Methods	Retrospective multicentre cohort study Location: Sweden Study period: 1 January 2011 to 31 December 2015 Aim of study: to compare the efficacy, safety, and medication persistence of natalizumab, rituximab, and fingolimod as escalation therapy in relapsing MS. Data collection: data were collected from the Swedish MS register (Hillert 2015; www.neuroreg.se/) and from the medical records at 4 centres: Umeå University Hospital; Karolinska University Hospital and Danderyd Hospital, Stockholm (10 January 2017); Sahlgrenska University Hospital, Gothenburg (24 March 2017). Setting: inpatient facilities Analysis: multivariate Cox proportional hazard models were used to adjust for several potential confounding factors in baseline characteristics, i.e. sex, age at inclusion, duration since debut, EDSS score at baseline, time receiving last DMT before switch and time from disease activity to switch, and centre.
Participants	**Active relapsing MS** ***Switching from interferon beta or glatiramer acetate to rituximab or natalizumab or fingolimod*** **Inclusion criteria:** diagnosis according to Polman 2011. Participants ending treatment with interferons or glatiramer acetate due to treatment failure (defined as relapse or GEL on MRI or both) and switching to natalizumab, rituximab, or fingolimod between 1 January 2011 and 31 December 2015.

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Boremalm 2019 *(Continued)*

	Exclusion criteria: reason for switch not relapse or CEL; missing or incomplete patient data on inclusion criteria; uncertainty regarding compliance to treatment; participation in clinical trial with unknown treatment allocation; untreated before switch deduced from baseline high titres of neutralising antibodies. **Rituximab group:** n = 48; % women: 72.9; age: median 39.1 (IQR 31.7–46.7) years; baseline EDSS score: median 2.0 (IQR 1.0–3.0); duration of MS: median 6.7 (IQR 3.6–13.0) years; time receiving interferon or glatiramer acetate before switch: median 2.4 (IQR 1.0–4.9) years; % of participants with CEL on baseline MRI within 6 months before switch: 39.0; washout period: median 107 (IQR 55–162) days; follow-up time: median 33.6 (IQR 25.2–43.2) months. **Natalizumab group:** n = 105; % women: 75.2; age: median 34.9 (IQR 28.9–42.0) years; baseline EDSS score: median 2.5 (IQR 1.5–3.1); duration of MS: median 5.6 (IQR 2.1–10.6) years; time receiving interferon or glatiramer acetate before switch: median 1.4 (IQR 0.8–5.0) years; % of participants with CEL on baseline MRI within 6 months before switch: 56.8; washout period: median 77 (IQR 43–129) days; follow-up time: median 33.6 (IQR 22.8–54.0) months. **Fingolimod group:** n = 88; % women: 65.9; age: median 37.1 (IQR 30.9–44.7) years; baseline EDSS score: median 2.0 (IQR 1.0–3.0); duration of MS: median 6.6 (IQR 2.9–13.5) years; time receiving interferon or glatiramer acetate before switch: median 2.9 (IQR 1.3–6.1) years; % of participants with CEL on baseline MRI within 6 months before switch: 64.9; washout period: median 117 (IQR 77–171) days; follow-up time: median 31.2 (IQR 20.4–45.6) months.
Interventions	**Escalation therapy after interferons or glatiramer acetate failure** **Natalizumab:** intravenous infusions of 300 mg every 4 weeks. **Rituximab:** intravenous infusions of 500 or 1000 mg every 6 months. **Fingolimod:** oral administration of 0.5 mg once daily. Co-interventions not reported.
Outcomes	Outcome timing: 24 months • Clinical relapse. Data: incidence of participants with clinical relapse per year. • Time to first relapse. Data: crude and adjusted HR with 95% CI. Variables used to adjust HR: sex, age at inclusion, duration since debut, EDSS at baseline, time receiving last DMT before switch, time from disease activity to switch and centre. • Number of participants with new gadolinium-enhancing positive T1-weighted lesions on brain MRI. • AEs grade 1–5 according to CTCAE (National Cancer Institute 2010). Data: incidence of participants with AEs per year. • Time to AEs. Data: crude and adjusted HR with 95% CI. Variables used to adjust HR: sex, age at inclusion, MS duration since debut, EDSS score at baseline, time receiving last DMT before switch, time from disease activity to switch and centre. • Treatment discontinuation. Data: incidence of participants with discontinuation per year. • Time to treatment discontinuation. Data: crude and adjusted HR with 95% CI. Variables used to adjust HR: sex, age at inclusion, MS duration since debut, EDSS score at baseline, time receiving last DMT before switch, time from disease activity to switch.
Notes	Authors' conclusions: quote: "In patients with relapsing MS on interferon or glatiramer acetate with breakthrough disease, switching to natalizumab or rituximab was associated with less disease activity compared with fingolimod. Rituximab displayed superior medication persistence compared with both natalizumab and fingolimod". Funding: the Foundation of Swedish MS Research, Neuro Sweden and the Research Fund for Clinical Neuroscience at Umeå University Hospital.

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Cheshmavar 2021

Study characteristics	
Methods	Parallel RCT. Single centre Location: Iran; MS Clinic of Kashani Hospital, Isfahan Recruitment period: December 2017 to March 2019 Aim of study: to assess the efficacy of rituximab compared to glatiramer acetate regarding deceleration of disease progression in people with secondary progressive MS with active relapses. Analyses were described as intention-to-treat and per-protocol.
Participants	**Active secondary progressive MS** ***Switching from another DMT*** **Inclusion criteria:** diagnosis according to Polman 2011; diagnosis of secondary progressive MS for ≥ 1 year; aged 18–55 years; baseline EDSS 0–5 points; ARR ≥ 1; 1 month drug-free washout period prior to starting the study treatment. **Exclusion criteria:** history of other demyelinating diseases of the CNS, autoimmune diseases, cardiac diseases (e.g. arrhythmia, angina pectoris), immunodeficiency syndromes, uncontrolled respiratory, renal, hepatic, endocrine, or gastrointestinal diseases, encephalopathy (infectious or metabolic), bone marrow transplant, whole body radiotherapy, or other treatments leading to reduction of lymphocytes, and brain and spinal cord malignancies; relapse within 30 days prior to intervention; systemic corticosteroid therapy, plasmapheresis or intravenous Ig during the last 30 days; active, chronic, or recurrent infections; pregnancy or lactation; receiving live attenuated viral vaccines during the last 4 weeks; history of severe allergic reactions or anaphylaxis to monoclonal antibodies; history of alcohol or drug abuse during the last 2 years; unable to undergo MRI; white blood cell count < 2500 cells/µL or lymphocyte count < 400 cells/µL, creatinine > 1.4 mg/dL in women and >1.6 mg/dL in men, aspartate transaminase and alanine transaminase > 2.5 the normal amount, platelet count < 100,000 cells/µL, or haemoglobin < 8.5 g/dL. **Treatment group (rituximab):** n = 43; % women: 79.1; mean age: 40.95 (SD 8.30) years; mean ARR 1.30 (SD 0.52); mean EDSS: 3.09 (SD 0.95); disease duration: 12.0 (SD 6.62) years; % participants with active lesions on brain MRI: 18.6; % participants with active lesions on cervical spinal MRI: 11.6. **Treatment group (glatiramer):** n = 41; % women: 63.4; mean age: 44.85 (SD 7.95) years; mean ARR 1.17 (SD 0.38); mean EDSS: 3.27 (SD 1.27); disease duration: 15.51 (SD 8.71) years; % participants with active lesions on brain MRI: 34.1; % participants with active lesions on cervical spinal MRI: 14.6.
Interventions	**Rituximab:** 3 courses of intravenous infusion of 1000 mg each, 6 months apart. **Glatiramer:** 40 mg 3 times per week through subcutaneous injection. Co-interventions: methylprednisolone 100 mg, chlorpheniramine 10 mg, and paracetamol 500 mg intravenously during each cycle of rituximab.
Outcomes	Outcome timing: 12 months **Primary** • Disability measured by 12-month mean EDSS score and compared between the 2 groups using 1-way analysis of covariance adjusting for age, disease duration, and baseline EDSS. **Secondary** • ARR measured by 12-month mean ARR and compared between the 2 groups using 1-way analysis of covariance adjusting for age, disease duration, and baseline ARR. • Number of participants with total and active lesions in the brain MRI and in the cervical spine, presence of longitudinal extensive transverse myelitis and multiple patchy lesions.

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Cheshmavar 2021 *(Continued)*

	Number of participants with SAEs or AEs.
Notes	Authors' conclusions: quote: "Neither rituximab nor glatiramer affects EDSS in secondary progressive MS patients. They are equally effective in the relapse control of these patients". Clinicaltrials.gov ID: NCT03315923. This study was funded by vice-chancellor for research and technology of Isfahan University of Medical Sciences (grant number: 396514).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We assigned a random number to each participant using Microsoft Excel function to generate random numbers".
Allocation concealment (selection bias)	High risk	Quote: "We allocated even and odd numbers to rituximab and glatiramer group, respectively".
Blinding of participants (performance bias) All outcomes	High risk	Open-label study.
Blinding of personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A neurologist who was blinded to treatment assignment, evaluated patients for disease clinical course, ARR, and EDSS at the baseline and at the end of the study and interpreted neuroimaging findings" (appendix File S1).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rituximab: completed n = 37 (86%); not completed n = 6 (14%). Reason not completed: lost to follow-up n = 6 (2 participants excluded due to AEs and 4 decided to withdraw). Glatiramer: completed n = 36 (88%); not completed n = 5 (12%). Reason not completed: lost to follow-up n = 5 (2 participants excluded due to adverse events, 1 moved to another city, and 2 decided to withdraw). Quote: "For ITT analysis, we assumed that EDSS, ARR and MRI lesions have remained unchanged throughout the study". The numbers of participants with SAEs and further AEs were available for 39 (91%) participants in the rituximab group and 38 (93%) in the glatiramer group.
Selective reporting (reporting bias)	Low risk	Outcomes are those reported in the protocol (ClinicalTrials.gov: NCT03315923).
Other bias	Low risk	The outcome data were skewed and the study was small. Previous therapy for MS before study entry not reported. Quote: "Patients in the glatiramer group had longer disease duration and were older compared to the rituximab group". Comment: this result may have occurred by chance (small sample size).

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Etemadifar 2019

Study characteristics	
Methods	Pragmatic multicentre parallel RCT Location: Iran. MS clinics affiliated to Isfahan MS Society Recruitment period: October 2015 to April 2017 Aim of study: to compare the efficacy of rituximab and cyclophosphamide on active secondary progressive MS. Analysis is described as per protocol.
Participants	**Active secondary progressive MS** ***Switching from another DMT*** **Inclusion criteria:** MS diagnosis according to Polman 2011 and active secondary progressive MS defined according to Lublin 2014; aged < 60 years; ≥ 2 attacks during the last year; > 3 GELs in brain MRI or > 1 score progression in EDSS within the last year; EDSS < 6 points. **Exclusion criteria:** any other types of MS; neuromyelitis optica; history of myelopathy or neurodegenerative disorders; history of other autoimmune disorders; recent or recurrent infections and presence of any haematological, immunological, or metabolic laboratory abnormalities. **Rituximab group:** n = 40 (baseline data reported for 39 participants). % women: 89.7; age: mean 31.9 (SD 7.7) years; EDSS score: not reported; follow-up time: not reported. **Cyclophosphamide group:** n = 40 (baseline data reported for 30 participants). % women: 73.3; age: mean 37.9 (SD 7.5) years; EDSS score: not reported; follow-up time: not reported.
Interventions	**Rituximab:** 1000 mg intravenous infusion repeated after 2 weeks, and then every 6 months with the same dosage if there was an increase in CD19 and CD20 levels. **Cyclophosphamide:** 1000 mg intravenous pulse plus intravenous methylprednisolone 1 g every month until 2 years. Treatments with DMTs before rituximab or cyclophosphamide not reported.
Outcomes	Outcome timing: 24 months • Disability measured by the EDSS. Data: baseline mean (SD) and post-treatment mean (SD) at 6, 12, 18, and 24 months with the P value of the trend in each group and the P value between the 2 groups in each time. • Relapse. Data: baseline mean (SD) and post-treatment mean (SD) at 6, 12, 18, and 24 months with the P value of the trend in each group and the P value between the 2 groups in each time. • New T2 lesion in MRI. Data: baseline mean (SD) and post-treatment mean (SD) at 6, 12, 18, and 24 months with the P value of the trend in each group and the P value between the 2 groups in each time. • GELs. Data: baseline mean (SD) and post-treatment mean (SD) at 6, 12, 18, and 24 months with the P value of the trend in each group and the P value between the 2 groups in each time. • Number of participants with AEs. Severity grades not reported.
Notes	Authors' conclusions: quote: "Rituximab and cyclophosphamide were well-tolerated by patients with active secondary progressive MS. The EDSS was increased in the rituximab group but the disability score did not worsen in the cyclophosphamide group. Both therapies were associated with a reduction in disease attacks and improvement in radiologic findings in a two-year period of follow-up". Funding: not reported
Risk of bias	

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Etemadifar 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using random allocation software, and each patient was given a number in a concealed envelope".
Allocation concealment (selection bias)	High risk	The enrolling investigator likely had knowledge of the forthcoming allocation. Quote: "Odds and even numbers were considered to receive rituximab and cyclophosphamide, respectively. The envelope was opened by the neurologist who was not blind about the drug, prescribed the medication and provided educational supports regarding the medication and appropriate dosage".
Blinding of participants (performance bias) All outcomes	High risk	Rituximab or cyclophosphamide were administered at different times. Quote: "Rituximab was administered every 6 months. Cyclophosphamide was administered every month". Comment: participants knew the adverse effects of each treatment.
Blinding of personnel (performance bias) All outcomes	High risk	Quote: "A non-blinded neurologist prescribed the medication and educated possible side effects and alarm signs about the specific administered drug".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The second neurologist was the same for all patients and checked possible medication side effects during each session regardless of the consumed drug". Comment: rituximab and cyclophosphamide groups differed in the frequencies of administration and clinical examinations, every 6 months for rituximab and monthly for cyclophosphamide.
Incomplete outcome data (attrition bias) All outcomes	High risk	Rituximab: 39/40 (97.5%) participants completed and included in analysis. Cyclophosphamide 30/40 (75.0%) participants completed and included in analysis. Reasons for withdrawals not reported. Quote: "Adverse effects were reported in 20 of patients in both groups (33.3% in the rituximab group versus 23.3% in cyclophosphamide group)".
Selective reporting (reporting bias)	Unclear risk	Study protocol not available.
Other bias	Low risk	Study appeared free of other sources of bias.

Evertsson 2020

Study characteristics	
Methods	Retrospective multicentre cohort study. The Swedish MS Register and the database at the Rocky Mountain MS Clinic, Utah, US Location: Sweden and US Aims of study: to compare a real-world cohort of people initiating treatment with rituximab or ocrelizumab to determine effects on Ig levels, B cell depletion measured in blood, and treatment outcomes over the first year.

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Evertsson 2020 *(Continued)*

	Data collection: data were collected from the Swedish MS Register for the Karolinska University Hospital (2010 to 28 May 2018) and from a database search of electronic medical records at the Rocky Mountain Multiple Sclerosis Clinic, Utah, US (1 May 2017 to 30 November 2018). Setting: inpatients and outpatient facilities Analysis: a linear mixed effect model and Generalised Estimating Equations were used.
Participants	**Relapsing MS** ***Switching from another DMT*** **Inclusion criteria:** MS diagnosis according to Thompson 2018, relapsing MS defined according to Lublin 2014; treatment initiated due to MS and infusions given in intervals of 5–7 months. **Exclusion criteria:** not reported. **Intervention group (rituximab):** n = 311; % women: 71.3; age: mean 44.0 (SD 11.7) years; % relapsing-remitting MS: 72; % secondary progressive MS: 28; baseline EDSS score: median 2.5 (IQR 2.125; range 0 to 8.5); disease duration: mean 11.3 (SD 8.87) years; % naive: 25.7; initiating intervention between 2010 and 28 May 2018; follow-up time: not reported. **Intervention group** (o**crelizumab):** n = 161; % women: 59.0; age: mean 49.8 (SD 11.9) years; % relapsing-remitting MS: 100; baseline EDSS score: not reported; disease duration: mean 12.5 (SD 8.32) years; % naive: 4.34; initiating intervention between 1 May 2017 and 30 November 2018; follow-up time: not reported.
Interventions	**Rituximab:** 1 infusion 500 mg or 1000 mg followed by a single infusion of 500 mg every 5–7 months. **Ocrelizumab:** 2 × 300 mg infusions 2 weeks apart followed by a single infusion of 600 mg every 5–7 months. Co-interventions not reported.
Outcomes	Outcome timing: 12 months • IgG, IgM, and Ig A levels. • Total lymphocyte numbers and number of $CD3^+$ $CD4^+$ or $CD3^+$ $CD8^+$ in blood. • Number of B cells $CD19^+$ $CD3^-$ in blood. • Treatment discontinuation with reasons. • AEs.
Notes	Authors' conclusions: quoted: "Differences between rituximab and ocrelizumab were small. Although the study design precludes robust conclusions regarding the risk–benefit with the studied therapies, our findings indicate that the tolerability and safety with rituximab is not inferior to ocrelizumab". Funding: no financial support.

Granqvist 2018

Study characteristics	
Methods	Retrospective multicentre cohort study. The Swedish MS Register Location: Sweden Study period: 1 January 2012 to 31 October 2015 Aim of study: to compare outcomes for people with relapsing MS receiving their first DMT in a region using a traditional escalating strategy (Stockholm) with a region using a sustained induction strategy, ini-

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Granqvist 2018 *(Continued)*

tiating, and maintaining treatment with highly efficient therapies (Västerbotten, where rituximab was predominately used). Furthermore, the investigators compared outcomes for rituximab with all other frequent DMTs in the combined cohort.

Data collection: data were collected from the Swedish MS Register (www.neuroreg.se) with manual cross-referring and additional data retrieval from medical records at 3 centres. Stockholm County: Karolinska University Hospital (11 April 2016), Danderyds Hospital (3 May 2016), and Västerbotten County: University Hospital of Umeå (18 October 2015).

Analysis: sequential regression models were used to calculate a propensity score for each treatment group in comparison with rituximab based on age, sex, baseline EDSS score, MS duration after debut and diagnosis, relapse in the year before treatment initiation, region, and follow-up time (OR only). Propensity scores were separately adjusted for as stratified quintiles in the regression models. Multivariate logistic regression was used to assess the relative odds of experiencing new gadolinium-enhancing positive lesions on brain MRI. Cox proportional hazards regression was used to compare drug survival and relapse rates using time from first day of drug administration to outcome of interest used as timescale.

Participants	**Active relapsing MS** ***First choice treatment*** **Inclusion criteria:** participants with newly diagnosed MS according to the McDonald criteria (Polman 2011) and first treatment with a DMD from 1 January 2012 to 31 October 2015. Participants who had a diagnosis of clinically isolated syndrome or radiologically isolated syndrome were included if their symptoms instead fulfilled the diagnostic criteria of relapsing MS within the follow-up period and otherwise fulfilled inclusion and exclusion criteria. Participants receiving their first DMT in a region using a traditional escalating strategy (i.e. Karolinska and Danderyds hospitals) with a region using a sustained induction strategy, initiating, and maintaining treatment with highly efficient therapies (i.e. Umeå hospital where rituximab was predominately used). **Exclusion criteria:** people who received a diagnosis before study period, or who received diagnosis or treatment initiation outside of Stockholm or Västerbotten Counties; participation in randomised clinical trials with unknown treatment allocation; lack of follow-up data; and migration to another county or country. **Treatment group (rituximab):** n = 120; % women: 65.8; age: median 37.8 (IQR 28.7–48.8) years; EDSS score: median 2.0 (IQR 1.0–2.5); duration of MS since diagnosis: median 1.0 (IQR 0.3–1.9) months; participants with relapse 12 months before treatment: 93 (77.5%); follow-up time: median 18.8 (IQR 12.3–28.0) months. **Treatment group (interferon beta + glatiramer acetate):** n = 215; % women: 67.0; age: median 35.1 (IQR 28.6–43.5) years; EDSS score: median 1.5 (IQR 1.0–2.0); duration of MS since diagnosis: median 1.2 (IQR 0.5–2.8) months; participants with relapse 12 months before treatment: 161 (74.9%); follow-up time: median 15.3 (IQR 8.6–26.3) months. **Treatment group (dimethyl fumarate):** n = 86; % women: 72.1; age: median 33.1 (IQR 28.2–39.1) years; EDSS score: median 1.5 (IQR 1.0–2.0); duration of MS since diagnosis: median 0.9 (IQR 0.5–1.5) months; participants with relapse 12 months before treatment: 64 (74.4%); follow-up time: median 14.2 (IQR 8.6–18.9) months. **Treatment group (fingolimod):** n = 17; % women: 64.7; age: median 31.7 (IQR 23.6–39.6) years; EDSS score: median 1.8 (IQR 1.0–2.5); duration of MS since diagnosis: median 1.2 (IQR 0.6–2.5) months; participants with relapse 12 months before treatment: 16 (94.0%); follow-up time: median 12.1 (IQR 7.9–22.3) months. **Treatment group (natalizumab):** n = 50; % women: 68.0; age: median 29.4 (IQR 22.6–35.6) years; EDSS score: median 1.5 (IQR 1.0–2.5); duration of MS since diagnosis: median 1.0 (IQR 0.5–1.9) months; participants with relapse 12 months before treatment: 47 (94.0%); follow-up time: median 19.0 (IQR 11.4–27.5) months.

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Granqvist 2018 *(Continued)*

Interventions	**Rituximab:** intravenous infusions of 500 mg or 1000 mg every 6 months; however, in some cases the first infusion had been repeated after 2 weeks. **Interferon beta or glatiramer acetate:** interferon beta 1b subcutaneous injection of 0.25 mg every other day; interferon beta 1a intramuscular injection of 0.03 mg once per week; interferon beta 1a subcutaneous injection of 0.022 mg or 0.044 mg once per week; glatiramer acetate subcutaneous injection of 20 mg daily. **Dimethyl fumarate:** oral administration of 120 mg once daily for 7 days tapered upwards to 240 mg twice a day. **Fingolimod:** oral administration of 0.5 mg once daily. **Natalizumab:** intravenous infusions of 300 mg every 4 weeks. Previously treated with DMT: 0 in all the comparison groups. Co-interventions not reported.
Outcomes	**Outcome timing:** 24 months **Primary** • Treatment discontinuation. Data: incidence of participants with discontinuation per year. • Time to treatment discontinuation due to any reason. Data: crude and adjusted HR propensity score with 95% CI. Variables used to adjust HR: age, sex, baseline EDSS score, MS duration after debut and diagnosis, relapse in the year before treatment initiation, and region. **Secondary** • Clinical relapse. Data: incidence of participants with clinical relapse per year. • Time to first relapse. Data: crude and adjusted HR propensity score with 95% CI. Variables used to adjust HR: age, sex, baseline EDSS score, MS duration after debut and diagnosis, relapse in the year before treatment initiation, and region. • New gadolinium-enhancing positive T1-weighted lesions on brain MRI. Data: number of participants with positive scan. Crude and adjusted OR propensity score with 95% CI. Variables used to adjust OR: age, sex, baseline EDSS score, MS duration after debut and diagnosis, relapse in the year before treatment initiation, region, and follow-up time. • AEs grade 1–5 according to CTCAE (National Cancer Institute 2010). Data: incidence of participants with AEs per year.
Notes	Propensity scores were estimated for each treatment group in comparison with rituximab and were separately adjusted for as stratified quintiles in the regression models. Authors' conclusions: quote: "Rituximab was superior to all other DMT in terms of drug discontinuation and displayed better clinical efficacy compared with injectable DMTs and dimethyl fumarate with borderline significance compared with natalizumab and fingolimod. The county where rituximab constituted the main initial treatment choice displayed better outcomes in most measured variables. Collectively, our findings suggest that rituximab performs better than other commonly used DMTs in patients with newly diagnosed relapsing MS". This study was funded by grant 2014-3077 from the Swedish Medical Research Council, and by the Stockholm County, Karolinska Institutet, the Foundation for Clinical Neuroscience at Umeå University Hospital, and Neuroförbundet.

Hauser 2008

Study characteristics

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Hauser 2008 *(Continued)*

Methods	Parallel multicentre RCT Location: 32 centres in the US and Canada Recruitment period: December 2004 to December 2006 Aim of study: to assess the efficacy of rituximab compared to placebo in patients with relapsing MS. Analysis is described as intention-to-treat
Participants	**Relapsing MS** ***Switching from other DMTs to rituximab vs placebo*** **Inclusion criteria:** diagnosis according to McDonald 2001; aged 18–55 years; ≥ 1 relapse during the preceding year; baseline EDSS 0–5 points. **Exclusion criteria:** secondary progressive, primary progressive, or progressive relapsing MS; relapse within 30 days; cyclophosphamide or mitoxantrone treatment within 12 months; systemic corticosteroid therapy within 30 days; treatment with interferon beta, glatiramer acetate, natalizumab, plasmapheresis, or intravenous Ig within 60 days; non-lymphocyte-depleting immunosuppressive therapies within 90 days. **Rituximab group:** n = 69; % women: 75.4; mean age: 39.6 (SD 8.7) years; median EDSS: 2.5 (range 0–5); mean duration of MS since diagnosis: 6.2 (SD 5.2) years; median relapse in past year: 1.0 (range 0–4); % participants with baseline gadolinium-enhancing lesions: 36.2; % participants with any therapy for MS before study entry: 78.3. **Placebo group:** n = 35; % women: 82.9; mean age: 41.5 (SD 8.5) years; median EDSS: 2.5 (range 0–5); mean duration of MS since diagnosis: 6.9 (SD 6.2) years; median relapse in past year: 1.0 (range 0–5); % participants with baseline gadolinium-enhancing lesions: 14.3; % participants with any therapy for MS before study entry: 77.1.
Interventions	**Rituximab:** a single course of intravenous rituximab 1000 mg on days 1 and 15. **Placebo:** a single course of intravenous infusion 1000 mg on days 1 and 15. Placebo not described. Co-interventions: on days 1 and 15, paracetamol 1 g and diphenhydramine hydrochloride 50 mg were administered orally 30–60 minutes before each infusion. Infusion-related reactions were to be treated with paracetamol plus intramuscular or slow intravenous administration of an antihistamine (diphenhydramine hydrochloride), or both, if indicated. If a severe infusion-related reaction occurred, the infusion was to be immediately interrupted, and symptomatic treatment initiated. Proportion of participants receiving rituximab after previous DMT for MS was 78% and placebo was 77%.
Outcomes	Timing: relapse outcome 24 and 48 weeks; MRI outcome 12 weeks, 24 weeks, 36 weeks; AE outcomes 48 weeks. **Primary** • Total number of GELs on serial T1-weighted MRI brain scans at weeks 12, 16, 20, and 24. Lesions that persisted for > 4 weeks were counted more than once. Data: number of participants with lesions (0, > 0–1, > 1–2, > 2–3, > 3). Mean (SD) number of lesions. Median (range) number of lesions. **Secondary** • Clinical relapse. Data: number of participants with relapse at weeks 24 and 48 with relative risk (90% CI). Mean (SD, range) number of relapses. • ARR from week 0 to weeks 24 and 48. ARR defined as the number of relapses for each participant divided by the total number of years of follow-up. Data: unadjusted and adjusted rates (90% CI), mean (SD) and median. • New GELs observed on serial T1-weighted MRI brain scans at weeks 12, 16, 20, and 24. Lesions persisting for > 4 weeks were counted only once. Because a reference scan was needed to determine whether

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Hauser 2008 *(Continued)*

a lesion was new, there was no count of new GELs for the baseline scan. Data: number of participants with new lesions (0, > 0–1, > 1–2, > 2–3, > 3). Mean number (SD) of new lesions. Median number (range) of new lesions.

- Changes in volume of lesions on T2-weighted MRI from baseline to week 24 and from baseline to week 36. Data: mean (SD) and median.
- Treatment discontinuation. Data: number of participants who discontinued treatment with reasons within 48 weeks.
- Number of participants with SAEs defined as life-threatening, resulting in death, requiring prolonged inpatient hospitalisation, disabling, resulting in a congenital anomaly or malignant condition, or requiring surgical intervention to prevent one of these outcomes.
- Number of participants with AEs. Severity grade 1–5 according to CTCAE (version 3.0).

Notes	The study was originally designed to enrol 280 participants but before the primary endpoint at week 24, the sample-size target was reduced to 99 participants while the investigators were still unaware of the data. Authors' conclusions: quote: "A single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. This trial was not designed to assess long-term safety or to detect uncommon adverse events. The data provide evidence of B-cell involvement in the pathophysiology of relapsing MS". Funding: the study was supported by Genentech, Inc. and Biogen Idec, Inc. Data were collected by the investigators and held and analysed by Genentech. Dr Waubant received a fellowship grant from Genentech; Dr Langer-Gould was an employee of Genentech while the study was being carried out, and received consulting fees from and holding stock options in Genentech. Drs Smith, Sarkar, and Agarwal were stockholders and employees of Genentech. ClinicalTrials.gov Identifier: NCT00097188.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported but likely computer generated. Quote: "Patients were randomly assigned in a 2:1 ratio to receive rituximab or placebo, and they were hierarchically stratified according to study site, status with respect to previous treatment with interferon beta or glatiramer acetate and baseline disease severity according to the EDSS score ≤2.5 versus >2.5".
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants (performance bias) All outcomes	Unclear risk	Participants received rituximab or placebo infusions at 0 and 2 weeks. However, there was no information to determine if placebo infusion was indistinguishable from rituximab infusion in terms of taste, appearance, and duration of infusion.
Blinding of personnel (performance bias) All outcomes	High risk	Quote: "The treating investigator was the safety assessor and made all treatment decisions based on the patient's clinical response and laboratory findings".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The outcome assessor (distinct from the treating investigator) administered the EDSS with access only to those data. Staff members from a central MRI reading centre (NeuroRx, Montreal), who were unaware of the data, evaluated all scans".
Incomplete outcome data (attrition bias) All outcomes	High risk	Completed 24 weeks: rituximab: 66 (95.7%); placebo: 30 (85.7%). Completed 48 weeks: rituximab: 58 (84.1%); placebo: 21 (60.0%). Discontinued before 48 weeks: rituximab: 11 (15.9%); placebo: 14 (40%).

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Hauser 2008 *(Continued)*

		Quote: "Patients who discontinued treatment early without having a relapse were considered to be relapse-free". "Missing values for MRI gadolinium-enhancing lesions were replaced by the average number of lesions detected on available scans obtained during the first 24 weeks. Similar analyses were performed for other lesion-count end points". Comment: a risk of attrition bias could have resulted for relapse due to the imputation method including 15.9% of the participants in the rituximab group and 40% in the placebo group. Completed safety follow-up at week 48. Rituximab: 7 (10%); placebo: 5 (14%).
Selective reporting (reporting bias)	Low risk	Outcomes were those reported in the protocol (ClinicalTrials.gov: NCT00097188).
Other bias	Low risk	Study appeared free of other sources of bias.

Hawker 2009

Study characteristics	
Methods	Parallel multicentre RCT Location: 60 centres in the US and Canada Recruitment period: start not reported, end October 2007 Aim of study: to assess the efficacy of rituximab relative to placebo over a 96-week treatment period, and to evaluate the safety and tolerability of rituximab in people with primary progressive MS. Analysis described as intention-to-treat.
Participants	**Primary progressive MS** ***First choice treatment*** (65% of participants having no prior MS therapies) **Inclusion criteria:** diagnosis according to McDonald 2001; aged 18–65 years; disease duration ≥ 1 year; baseline EDSS 2.0–6.5 points; presence of IgG oligoclonal bands or elevated CSF IgG index, or both. **Exclusion criteria:** history of MS exacerbation, neuromyelitis optica, myelopathy or neurodegenerative CNS conditions; systemic autoimmune disorders; recurrent or chronic infections; recent treatment with immunomodulating or immunosuppressant therapies; and metabolic, haematological, or immunological laboratory abnormalities. **Treatment group (rituximab):** n = 292; % women: 47.9; mean age: 50.1 (SD 9.0) years; mean EDSS: 4.8 (SD 1.4); mean duration of MS since diagnosis: 4.1 (SD 4.2) years; % no prior interferon beta or glatiramer acetate therapies: 64.7. **Placebo group:** n = 147; % women: 55.1; mean age: 49.6 (SD 8.7) years; mean EDSS: 4.7 (SD 1.4); mean duration of MS since diagnosis: 3.8 (SD 4.2) years; % no prior interferon beta or glatiramer acetate therapies: 65.3.
Interventions	**Rituximab:** 4 courses of 2 intravenous infusion of 1000 mg each, 2 weeks apart. **Placebo:** 4 courses of 2 intravenous infusion of 1000 mg each, 2 weeks apart. Placebo not described. Co-interventions not reported. Proportion of participants receiving rituximab or placebo after previous DMT for MS were 35% in both groups.

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Hawker 2009 *(Continued)*

Outcomes	Outcome timing: 96 weeks. SAEs and AEs: 122 weeks. **Primary** • Time to confirmed disability progression and sustained ≥ 12 weeks after initial progression. Progression defined as a sustained EDSS increase of 1.0 point from baseline EDSS if the baseline EDSS was 2.0–5.5 points (inclusive), or an EDSS increase of 0.5 point if the baseline EDSS was 5.5 points, for which change was not attributable to another aetiology. Data: HR (95% CI). • Number of participants with confirmed disease progression at week 96. **Secondary** • Total volume of MRI T2-weighted lesions. Data: mean (SD) and median change from baseline to week 96. • Brain volume. Data: mean (SD) and median change from baseline to week 96. • Number of participants with SAEs measured through 122 weeks. • Number of participants with AEs measured through 122 weeks. AEs graded according to the National Cancer Institute CTCAE, Version 3.0.
Notes	Authors' conclusions: quote: "Although time to confirmed disease progression between groups was not significant, overall subgroup analyses suggest selective B-cell depletion may affect disease progression in younger patients, particularly those with inflammatory lesions". The study was designed jointly by Genentech and the investigators and supported by Genentech, Inc. and Biogen Idec, Inc. Data collected by the investigators was held and analysed by Genentech. Members of the publication committee had full access to data, and all authors vouch for the veracity and completeness of the data and data analysis. ClinicalTrials.gov Identifier: NCT00087529.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported but likely computer generated. Quote: "Patients were randomly assigned in a 2:1 ratio and hierarchically stratified according to study site, previous MS therapies with interferon-beta or glatiramer acetate and baseline disease severity according to the EDSS score (≤4.0 vs >4.0)".
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants (performance bias) All outcomes	Unclear risk	Participants received 4 courses of rituximab or placebo infusions. However, there was no information to determine if placebo infusion was indistinguishable from rituximab infusion in terms of taste, appearance, and duration of infusion.
Blinding of personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Disability was assessed by EDSS scores at least quarterly by a neurologist blinded to treatment and other patient data including imaging and laboratory results. MRI scans were blindly evaluated at the University of Colorado Brain Imaging Research Laboratory, an independent MRI reading facility.
Incomplete outcome data (attrition bias)	Low risk	NCT00087529. Rituximab: completed: 224 (77%); not completed: 68 (23%). Reason not completed: lost to follow-up: 3 (1%); withdraw treatment: 65

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Hawker 2009 *(Continued)*

All outcomes		(22%). Placebo: completed: 116 (79%); not completed: 31 (21%). Reason not completed: lost to follow-up: 2 (1%); withdraw treatment: 29 (20%). Quote: "Time to CDP was the time from randomisation to initial disability progression, estimated using Kaplan-Meier analysis. Patients with an initial disease progression who subsequently discontinued the study treatment before a subsequent confirmatory assessment could be obtained were considered to have disease progression. Data from patients who discontinued the study early or were lost to follow-up and had not shown an initial disease progression were censored at time of their last visit. Patients who demonstrated an initial disease progression at the end of the treatment period (week 96) were censored at that time and were not considered to have progression. For MRI measures related to change from baseline, the last-observed value before the treatment period discontinuation was used to impute the missing values". Quote: "Completed safety follow-up at week 122. Rituximab: n. 224 (93%) of 241 participants who completed 96 weeks of treatment. Placebo: n. 116 (93.5%) of 124 participants who completed 96 weeks of treatment".
Selective reporting (reporting bias)	Low risk	Outcomes were those reported in the protocol (ClinicalTrials.gov: NCT00087529).
Other bias	Low risk	Study appeared free of other sources of bias.

Komori 2016

Study characteristics	
Methods	Single centre, parallel RCT Location: US. National Institutes of Health Recruitment period: September 2010 to December 2015 Aim of study: to investigate whether intrathecal and intravenous administration of rituximab can effectively deplete B cells and inhibit activation of T cells in the CNS compartment of secondary progressive MS. Analysis described in the interim analysis as per protocol and descriptive statistics.
Participants	**Secondary progressive MS** ***Switching from another DMT*** **Inclusion criteria:** diagnosis according to the McDonald's criteria (Polman 2005); aged 18–65 years; disease duration ≥ 1 year; baseline EDSS 3.0–7.0 points; no relapse in the preceding 1 year and sustained progression of disability over 3 months; no DMTs for ≥ 1 month prior to enrolment; informed consent; commitment to the use of an accepted method of contraception. **Exclusion criteria:** primary progressive MS; history or signs of immunodeficiency or chronic infections; any serious medical disorder; clinically relevant abnormal blood tests (including IgM and IgG abnormalities); positive pregnancy test; positive CSF or serum JC virus. **Treatment group (rituximab):** n = 18; % women: 50.0; median age: 55.2 (range 42.0–66.0) years; median EDSS: 6.5 (range 2.5–7.0); median duration of MS: 24.4 (range 16.5–38.5) years; % participants with GELs (month −12/month 0): 14.3/0; duration of follow-up: median 24.0 (range 13.5–36.0) months.

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Komori 2016 *(Continued)*

	Placebo group: n = 9; % women: 77.8; median age: 60.1 (range 39.3–64.8) years; median EDSS: 6.5 (range 5.0–6.5); median duration of MS: 26.0 (range 10.4–43.6) years; % participants with GELs (month −12/month 0): 25.0/11.1; duration of follow-up: median 30.0 (range 18.0–36.0) months.
Interventions	**Rituximab:** 25 mg (1:1 dilution in normal saline) intrathecal injection followed by 200 mg intravenous infusion at day 0 and 15, and 25 mg of intrathecal rituximab at months 1.5 and 12. **Placebo:** intrathecal and intravenous normal saline at month 0, followed by additional normal saline intravenously at month 0.5 and another dose of intrathecal normal saline at months 1.5 and 12. Premedication with intravenous methylprednisolone 100 mg, diphenhydramine 50 mg, paracetamol 650 mg, and lorazepam 1 mg. Co-interventions: not reported. Treatments with DMTs before rituximab or placebo not reported.
Outcomes	Outcome timing: 24 months. **Primary** • Changes from baseline in CSF of chemokine CXCL13. This outcome was for interim analysis of the efficacy of B-cell depletion from the CSF 3 months after rituximab or placebo into the CSF. The protocol-stipulated threshold for trial continuation was at least 25% decrease in CSF CXCL13 induced by active treatment with significance level P=0.025 (NCT01212094). • Changes from baseline in CSF of B-cell activating factor. This outcome was for interim analysis of the efficacy of B-cell depletion from the CSF 3 months after rituximab or placebo into the CSF. The protocol-stipulated threshold for trial continuation was ≥ 50% increase in CSF B-cell activating factor induced by active treatment with significance level P = 0.025 (NCT01212094). **Secondary** • Changes from baseline in CSF B-cell numbers between rituximab and placebo. This outcome was for interim analysis of the efficacy of B-cell depletion from the CSF 3 months after giving rituximab or placebo into the CSF. • EDSS, Scripps Neurological Rating Scale, and MS Functional Composite Scale. Data available: median (range) values at 6, 12, 18, and 24 months. • Mean cumulative CEL counts on brain MRI. • Number of participants with SAEs at 24 months. • Number of participants with AEs at 24 months.
Notes	5 participants per group terminated 24 months' follow-up. The study was stopped early, because the treatment efficacy on CSF biomarkers failed to reach criteria for continuation of the trial. Authors' conclusions: quote: "Biomarker studies reliably quantified complementary pharmacodynamic effects of rituximab in the CNS, exposed causes for poor efficacy and determined that RIVITALISE trial- would be underpowered to measure efficacy on clinical outcomes. Identified mechanisms for poor efficacy are applicable to all CNS-inflammation targeting monoclonal antibodies". Funding: Intramural Research program of the National Institute of Neurological Disorders and Stroke of the National Institutes of Health. ClinicalTrials.gov Identifier: NCT01212094.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done by the pharmacy of the National Institutes of Health using a table of random numbers".

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Komori 2016 *(Continued)*

		Comment: stratified by age.
Allocation concealment (selection bias)	High risk	Likely predictable sequence due to deducing last allocation in fixed small size blocks. Quote: "Using a block size of 3: within a block of three the highest two numbers were assigned to rituximab and the lowest number to placebo".
Blinding of participants (performance bias) All outcomes	Unclear risk	Quote: "double-blind" only.
Blinding of personnel (performance bias) All outcomes	Unclear risk	No information available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Completed all study visits: rituximab: 5/18 (28%) participants; placebo: 5/9 (55%) participants.
Selective reporting (reporting bias)	Low risk	Outcomes were those reported in the protocol (ClinicalTrials.gov: NCT01212094).
Other bias	High risk	The investigators terminated the study prematurely based on an interim analysis on CSF biomarkers. Participants were not followed up to measure clinical outcomes.

Luna 2020

Study characteristics	
Methods	Retrospective nationwide cohort study Location: Sweden Study period: 1 January 2011 to 31 December 2017 Aim of study: to estimate and compare the infection risks among contemporary Swedish people with MS who were treated with rituximab, natalizumab, fingolimod, and interferon beta and glatiramer acetate. Data collection: data were collected from the Swedish MS Register (www.neuroreg.se/) linked to national healthcare and census registries using the national personal identity number. Analysis: 5 comparator participants were matched for each person with MS from the general population by age, sex, and region. Used Cox proportional hazard models. As participants could contribute data to multiple treatment cohorts, robust 95% CIs were calculated. Potential confounding variables adjusted for in the models were age, sex, country of birth, educational level, number of days hospitalised during the last 5 years, and other general health variables, year of treatment start, disease duration, EDSS score, MSIS-29 score, SDMT score, and EQ-5D scale score. Multiple imputation was applied to account for missing data. The comparison between high-efficacy DMTs was adjusted for number of previous DMTs.
Participants	**Relapsing MS**

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Luna 2020 *(Continued)*

	Switching from another DMT **Inclusion criteria:** participants whose data were recorded in the Swedish MS Register and who started treatment with interferon beta and glatiramer acetate, fingolimod, natalizumab, or rituximab between 1 January 2011 and 31 December 2017, matched for age, sex, and location to 42,645 people without MS from general population. Participants with MS contributed to multiple treatment cohorts, entering each at their first start of each drug. **Treatment episodes (rituximab):** n = 3260; start year: median 2016 (IQR 2014–2017); % women:72.3; age: mean 40.4 (SD 10.6) years; EDSS score: mean 2.1 (SD 1.5); duration of MS: mean 8.7 (SD 7.6) years; time receiving interferon or glatiramer acetate before switch: median 2.4 (IQR 1.0–4.9) years; treatment duration: mean 2.0 years; % of participants with no previous use of DMTs: 23.7; % of participants with any relapse last year: 27.9. **Treatment episodes (interferon beta or glatiramer acetate):** n = 2217; start year: median 2013 (IQR 2012–2014); % women: 73.6; age: mean 40.1 (SD 11.3) years; EDSS score: mean 1.6 (SD 1.3); duration of MS: mean 6.2 (SD 7.4) years; treatment duration: mean 2.1 years; % of participants with no previous use of DMTs: 94.3; % of participants with any relapse last year: 35.6. **Treatment episodes (fingolimod):** n = 1535; start year: median 2013 (IQR 2012–2015); % women: 68.1; age: mean 38.8 (SD 9.6) years; EDSS score: mean 2.1 (SD 1.5); duration of MS: mean 8.8 (SD 6.6) years; time receiving interferon or glatiramer acetate before switch: median 2.9 (IQR 1.3–6.1) years; treatment duration: mean 2.7 years; % of participants with no previous use of DMTs: 12.6; % of participants with any relapse last year: 27.9. **Treatment episodes (natalizumab):** n = 1588; start year: median 2014 (IQR 2012–2015); % women: 72.5; age: mean 35.0 (SD 10.1) years; EDSS score: mean 2.3 (SD 1.5); duration of MS: mean 5.8 (SD 6.2) years; time receiving interferon or glatiramer acetate before switch: median 1.4 (IQR 0.8–5.0) years; treatment duration: mean 2.5 years; % of participants with no previous use of DMTs: 31.5; % of participants with any relapse last year: 49.0. **General population:** n = 42,645; start year: median 2014 (IQR 2012–2016); % women: 72.0; age: mean 39.0 (SD 10.7) years.
Interventions	Included 8600 treatment initiations from 6421 participants. **Interferon beta and glatiramer acetate:** 2217 initiations. Mean total treatment duration: 2.1 years. **Rituximab:** 3260 initiations. Mean total treatment duration: 2.0 years. **Fingolimod:** 1535 initiations. Mean total treatment duration: 2.7 years. **Natalizumab:** 1588 initiations. Mean total treatment duration: 2.5 years.
Outcomes	**Outcome timing:** 72 months. • Time until the first serious infection, defined as any infection recorded as the main reason for a hospitalisation. Participants could contribute data to multiple treatment cohorts. Data: HR (95% CI). • Less serious infections identified through the Prescribed Drug register according to filled prescriptions of any systemic antibiotic and antiviral medication for herpetic infections.
Notes	Authors' conclusions: quote: "Patients with MS are at a generally increased risk of infections, and this differs by treatment. The rate of infections was lowest with interferon beta and glatiramer acetate; among newer treatments, off-label use of rituximab was associated with the highest rate of serious infections. The different risk profiles should inform the risk-benefit assessments of these treatments". Funding: a Patient-Centered Outcomes Research Institute Award (grant MS-1511–33196) and funds from the Swedish Foundation for MS Research.

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Naegelin 2019

Study characteristics	
Methods	Case-control study Location: the MS centres in Basel and Lugano, Switzerland and the MS centre in Amsterdam (University medical centre Amsterdam, the Netherlands) Study period: 2004–2017 Aim of study: to compare disease progression between people treated with rituximab and people who had never been treated with rituximab. Data collection: data of participants treated with rituximab were collected from the 2 MS centres in Switzerland. Participants never treated with rituximab (control group) were recruited from 2 cohorts, 1 at the MS centre in Basel and 1 at the MS centre in Amsterdam. Follow-up time: up to 10 years Analysis: the rituximab-treated and the control groups were matched 1:1 using propensity scores. The matching variables were sex, age, EDSS score, and disease duration at baseline. To estimate effect sizes for disability worsening, the investigators used a linear mixed-effects model that included propensity score-based matching and covariate adjustment. Covariates included age, sex, disease duration, baseline EDSS score, treatment (rituximab vs control), time after baseline, and the interaction between treatment and time after baseline.
Participants	**Secondary progressive MS** ***Switching from another DMT*** **Inclusion criteria:** diagnosis according to the criteria of Lublin 1996; ≥ 1 dose of rituximab and 1 clinical follow-up visit; informed consent. **Exclusion criteria:** not reported. *Baseline characteristics after propensity score matching.* **Rituximab group:** n = 44; % women: 59; age: mean 49.7 (SD 10.0) years; baseline EDSS score: mean 5.93 (SD 1.40); duration of MS: mean 18.2 (SD 9.4) years; % of participants with previous use of DMTs in the year before baseline: 59.0; follow-up: mean 41.8 (SD 32.2) months. **Never treated with rituximab:** n = 44; % women: 61; age: mean 51.3 (SD 7.4) years; baseline EDSS score: mean 5.70 (SD 1.29); duration of MS: mean 19.4 (SD 8.7) years; % of participants with previous use of DMTs in the year before baseline: 52.0; follow-up: mean 457.7 (26.5) months.
Interventions	**Rituximab:** doses, timing, and frequency not reported. **Control:** never treated: 23 (52%) participants; interferon beta 1b: 12 (27%) participants; other DMTs: 9 (21%) participants. Doses, timing, and frequency of control treatments not reported. 7 (16%) participants in the control group and 0 in the rituximab group switched during follow-up to another treatment. Co-interventions: not reported. Treatment with DMTs 1 year before baseline: rituximab: 26 (59%); control: 23 (52%).
Outcomes	Outcome timing: 36 months **Primary** • Change from baseline in disability measured by yearly EDSS score. Mean difference (95% CI). **Secondary**

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Naegelin 2019 *(Continued)*

- Time to confirmed disability worsening defined as an increase in the EDSS score ≥ 12 months after baseline and confirmed by a second examination 12 months later. Data: HR (95% CI).
- Number of participants with AEs reported only in the rituximab group.

Notes	Before matching, participants from the rituximab group were significantly younger and had a higher grade of disability. A higher proportion (59%) of the rituximab-treated participants had been treated with DMTs in the year before baseline compared with the control participants (48%). Propensity score-based matching in combination with covariate adjustment was used in the statistical models. Authors' conclusions: quote: "In this study, patients with secondary progressive MS treated with rituximab had a significantly lower EDSS score for up to 10 years of follow-up and a significantly delayed-confirmed progression compared with matched controls, suggesting that B-cell depletion by rituximab may be therapeutically beneficial in these patients. A prospective randomized clinical trial with a better level of evidence is needed to confirm the efficacy of rituximab in such patients". Funding: not reported.

Spelman 2018

Study characteristics	
Methods	Retrospective cohort nationwide study. The Swedish MS register The dataset included all patients from the SMSreg with baseline dates from April 2005 to November 2015 Aim of study: to compare benefit and treatment persistence in people with relapsing MS who initiated rituximab relative to a contemporaneous, propensity-matched cohort of people treated with interferon beta or glatiramer acetate.
Participants	**Relapsing MS** ***Switching from another DMT*** **Inclusion criteria:** aged ≥ 18 years at baseline defined as the start date of interventions. A minimum of 3-month persistence on the index intervention required. *Baseline characteristics after propensity score matching* **Rituximab:** n = 461; % women: 74.4; age: median 41.5 (IQR 34.5–48.5) years; EDSS score: median 2 (IQR 1.5–3); duration of MS: median 10.6 (IQR 7.4–15.0) years; proportion of disease duration on treatment: median 0.6 (IQR 0.3–0.7); number of DMT starts: median 2 (IQR 1–3); number of DMT starts/disease duration: median 0.2 (IQR 0.1–0.3); relapse last 12 months: mean 0.07 (SD 0.29); relapse last 24 months: mean 0.10 (SD 0.39); on-treatment follow-up: mean 2.14 (SD 1.42) years. **Interferon or glatiramer acetate:** n = 922; % women: 75.8; age: median 40.0 (IQR 33.1–45.7) years; EDSS score: median 2 (IQR 1.5–3); duration of MS: median 9.9 (IQR 6.4–12.8) years; proportion of disease duration on treatment: median 0.6 (IQR 0.2–0.7); number of DMT starts: median 2 (IQR 1–3); number of DMT starts/disease duration: median 0.2 (IQR 0.1–0.3); relapse last 12 months: mean 0.15 (SD 0.47); relapse last 24 months: mean 0.10 (SD 0.38); on-treatment follow-up: mean 2.80 (SD 2.05) years.
Interventions	**Rituximab:** intravenous infusions of 500 or 1000 mg every 6 months. **Interferon or glatiramer acetate:** interferon beta 1b subcutaneous injection0.25 mg every other day; interferon beta 1a intramuscular injection 0.03 mg once per week; interferon beta 1a subcutaneous injection of 0.022 or 0.044 mg once per week; glatiramer acetate subcutaneous injection 20 mg daily. Co-interventions not reported.
Outcomes	Outcome timing: 24 months.

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Spelman 2018 *(Continued)*

Primary

- ARR.
- Time to first relapse on therapy.
- Time to treatment discontinuation.

Secondary

- Time to confirmed disability progression. 3-month confirmed disability progression was defined as ≥ 3-month confirmed increases of ≥ 0.5 points for participants with a baseline EDSS score > 5.5, ≥ 1.0 point for those with a baseline EDSS score 1.0–5.5, inclusive, and ≥ 1.5 points for those with a baseline EDSS score of 0. EDSS scores recorded within 30 days after the onset of a relapse were excluded. A minimum of 3 visits(including baseline) at which an EDSS was formally recorded were, by definition, required to first observe and then confirm the disability progression event.
- EDSS change from baseline at 1–4 years of treatment.

AEs not reported.

Notes	Quote: "The Swedish MS register is currently used in all neurology departments across Sweden, capturing approximately 80% of the prevalent Swedish MS population". Authors' conclusions: quote: "Rituximab appears to be superior to first-generation DMTs with respect to relapse control and tolerability, whereas superiority on disability outcomes is less clear". Study supported by the Swedish Research Council, the Swedish Brain Foundation, and the Karolinska University Hospital.

Vollmer 2020a

Study characteristics	
Methods	Single centre, retrospective cohort study Setting: the Rocky Mountain MS Center at the University of Colorado, US Recruitment: January 2010 to October 2013 Aim of study: to investigate the comparative effectiveness and discontinuation patterns of people treated with rituximab compared to those treated with natalizumab, fingolimod, or dimethyl fumarate. Follow-up time: 2 years
Participants	**All types of MS** ***Shifting to rituximab vs other DMTs*** **Inclusion criteria:** participants who initiated rituximab, natalizumab, fingolimod, or dimethyl fumarate between January 2010 and October 2013; negative JC virus serology test at baseline for participants treated with natalizumab. **Rituximab:** n = 182; % women: 65.9; age: mean 43.9 (SD 11.8) years; % relapsing MS 62.1; % progressive MS 37.9; EDSS: not reported; duration of MS: mean 12.7 (SD 8.4) years; % no DMT within 6 months prebaseline: 28.0; % with baseline MRI CELs: 28.4. **Fingolimod:** n = 271; % women: 72.0; age: mean 42.5 (SD 11.4) years; % relapsing MS 90.0; % progressive MS 10.0; EDSS: not reported; duration of MS: mean 11.5 (SD 7.5) years; % no DMT within 6 months prebaseline: 24.4; % with baseline MRI CELs: 24.6.

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Vollmer 2020a *(Continued)*

	Dimethyl fumarate: n = 342; % women: 69.6; age: mean 45.8 (SD 12.2) years; % relapsing MS 77.5; % progressive MS 22.5; EDSS: not reported; duration of MS: mean 11.1 (SD 7.4) years; % no DMT within 6 months prebaseline: 24.6; % with baseline MRI CELs: 14.6. **Natalizumab:** n = 451; % women: 76.7; age: mean 39.8 (SD 12.1) years; % relapsing MS 84.7; % progressive MS 15.3; EDSS: not reported; duration of MS: mean 11.4 (SD 7.5) years; % no DMT within 6 months prebaseline: 37.7; % with baseline MRI CEL: 33.1.
Interventions	**Rituximab:** induction dose 2000 mg (1000 mg at day 1 and day 14) and 500 mg every 6 months thereafter in most (77.4%) participants. **Natalizumab, fingolimod,** and **dimethyl fumarate:** doses, timing, and frequency not reported. Co-interventions not reported.
Outcomes	Outcome timing: 24 months. **Primary** • Disease activity: a composite outcome defined as the participant experiencing a clinical relapse, CELs or new T2 lesion on follow-up MRI. **Secondary** • Relapse defined as clinician-reported per participant chart notes as new or worsening neurological symptoms lasting > 24 hours in the absence of fever or infection. • CELs and new T2 lesion on MRI data obtained from neuroradiology reports and clinical reports. • Discontinuation of therapy, defined as no longer on drug at 24 months after start date, or initiation of any other MS DMT during the 24-month follow-up period. • Primary reason for discontinuation of therapy. • Number of participants with AEs. SAEs not reported.
Notes	Quote: "Propensity scores generated through logistic regression on sample group 1:2 nearest neighbour matched by propensity scores with replacement. Preselected covariates: age, sex, disease duration, diagnosis, and contrast-enhancing lesions on baseline MRI". Authors' conclusions: quote: "Rituximab demonstrated superior effectiveness and discontinuation outcomes compared to fingolimod and dimethyl fumarate. Although rituximab demonstrated similar effectiveness and discontinuation compared to natalizumab, rituximab had superior effectiveness during months 6–24 and fewer discontinuations when excluding discontinuations due to insurance issues. Results suggest superiority of rituximab in reducing disease activity and maintaining long-term treatment in a real-world MS cohort". Study received no funding.

AE: adverse event; ARR: annualised relapse rate; CEL: contrast-enhancing lesion; CI: confidence interval; CNS: central nervous system; CSF: cerebrospinal fluid; CTCAE: Common Terminology Criteria for Adverse Events; DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; GEL: gadolinium-enhancing lesion; GITEM: Grup d'Investigació i Tractament de l'Esclerosi Múltiple; HR: hazard ratio; IG: immunoglobulin; IQR: interquartile range; JC: John Cunningham; MRI: magnetic resonance imaging; MS: multiple sclerosis; n: number of participants; MSIS-29: MS Impact Scale-29; OR: odds ratio; RCT: randomised controlled trial; SAE: serious adverse event; SD: standard deviation; SDMT: Symbol Digit Modalities Test.

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

Study	Reason for exclusion
Airas 2020	Before-after (pre–post) study with no control group.

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Study	Reason for exclusion
Alcalá 2018	Before-after (pre–post) study with no control group.
Alldredge 2018	Before-after (pre–post) study with no control group.
Alvarez 2015	Case series with no control group.
Barmettler 2018	Retrospective cohort study with no control group.
Bar-Or 2008	Before-after (pre–post) study with no control group.
Barra 2016	Retrospective cohort study with no control group.
Bellinvia 2020	Before-after (pre–post) study with no control group.
Bergman 2018	Before-after (pre–post) study with no control group.
Berntsson 2018	Retrospective cohort study with no control group.
Bhargava 2019	Before-after (pre–post) study with no control group.
Boremalm 2021	Before-after (pre–post) study with no control group.
Boström 2016	Retrospective cohort study with no control group.
Brown 2011	Retrospective cohort study with no control group.
Caldito 2021	Ineligible design. The study investigated the adverse event profile of rituximab and ocrelizumab reported to the Food and Drug Administration Adverse Event Reporting System (FAERS) database.
Ciplea 2020	Retrospective cohort study. Data source: the German Multiple Sclerosis and Pregnancy Registry. The study aimed to assess possible adverse effects on breastfed infants of mothers receiving monoclonal antibodies during pregnancy or lactation, or both. Of 23 women who breastfed under monoclonal antibodies, only 3 women were treated with rituximab.
Cross 2012	Before-after (pre–post) study with no control group.
D'Amico 2019	Before-after (pre–post) study with no control group.
Das 2018	Case series in MS and neuromyelitis optica spectrum disorders.
de Flon 2016	Before-after (pre–post) study with no control group.
Disanto 2021	Before-after (pre–post) study with no control group.
Dunn 2018	Cross-sectional study to evaluate antibodies to rituximab with no control group.
Durozard 2019	Before-after (pre–post) study with no control group.
Ellrichmann 2019	Before-after (pre–post) study with no control group.
EUCTR2013-002378-26	A before-after (pre–post) study with no control group.
Gottesman 2017	Study recorded no relevant outcomes. Only recorded the John Cunningham antibody titres.
Hallberg 2019	Abstract. No comparison of rituximab with other disease-modifying treatments.

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Study	Reason for exclusion
He 2020	Retrospective international observational study comparing long-term disability outcomes between people who started high-efficacy therapies within 2 years of disease onset with those who started 4–6 years after disease onset. No comparison of rituximab with other included treatments (ocrelizumab, mitoxantrone, alemtuzumab, natalizumab).
Hellgren 2020	Before-after (pre–post) study with no control group.
Honce 2019	The comparison of rituximab vs placebo was confounded by treatment with glatiramer acetate. 55 participants with clinically isolated syndrome or relapsing MS were included. The rituximab group received a single course of intravenous infusion of rituximab 1000 mg on days 1 and 15, and the control group received a single course of intravenous infusion of placebo 1000 mg on days 1 and 15. On study day 28, all participants received glatiramer acetate 20 mg injected subcutaneously daily up to a maximum of 33 months. Outcome assessed at a median 24 months' follow-up.
Juto 2020	Retrospective cohort study to evaluate possible rebound activity after rituximab discontinuation, with no control group.
Kuempfel 2019	Case series.
Langer-Gould 2018	Abstract. No comparison of rituximab with other disease-modifying treatments.
Langer-Gould 2019	Abstract only available. We wrote to authors asking for the total number of participants in the comparison groups (fingolimod and glatiramer), but received no reply (Filippini 2021d). This was a retrospective multicentre cohort study conducted in the USA (Kaiser Permanent Southern California) and Sweden. 1175 people with MS treated with rituximab with 2467 person-years of follow-up in the Kaiser Permanent Southern California cohort, and 3165 people treated with rituximab with 6003 person-years of follow-up in the Swedish cohort. Rituximab compared to glatiramer acetate in the Kaiser Permanent Southern California cohort. Rituximab compared to fingolimod in the Swedish cohort. Only hazard ratios (95% confidence intervals) were available for cancer risk.
Langer-Gould 2020	Retrospective cohort study that aimed to assess whether risk of postpartum relapses is modified by breastfeeding or MS disease-modifying treatments. Comparison among disease-modifying treatments was not drawn.
Leonidou 2019	Before-after (pre–post) study with no control group.
Maarouf 2020	Before-after (pre–post) study with no control group.
Malucchi 2016	Case series.
Mathew 2020	Before-after (pre–post) study with no control group.
Mazdeh 2020	Before-after (pre–post) study with no control group.
Midaglia 2020	Before-after (pre–post) study comparing 2 doses of rituximab with no control group.
Naismith 2010	Before-after (pre–post) study with no control group.
Naser Moghadasi 2019	Before-after (pre–post) study with no control group.
NCT02980042	Type of intervention outside inclusion criteria (switching from rituximab to ocrelizumab).
NCT03979456	Randomised controlled trial comparing rituximab 500 mg every 6 months with rituximab 500 mg every 12 months with no control group.

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Study	Reason for exclusion
Nielsen 2012	A before-after (pre–post) study with no control group.
Persson 2020	Retrospective cohort study based on 2 databases, the United States Department of Defense health-care system and the United Kingdom's Clinical Practice Research Datalink GOLD. This study was unable to give data on the risk of infection with individual disease-modifying treatments due to lack of available data.
Razaz 2020	Type of intervention outside inclusion criteria (women with MS who suspended rituximab and natalizumab within 6 months before conception and women who were not treated with any disease-modifying treatment within 1 year of conception).
Sahraian 2020	Case series.
Salzer 2016	Before-after (pre–post) study with no control group.
Schwake 2020	Case report.
Scotti 2018	No relevant outcomes were recorded in the study. Only recorded the outcome 'evidence of disease activity'.
Shima 2020	Case report.
Smith 2020	Retrospective cohort study that aimed to describe the safety and efficacy of rituximab in MS and pregnancy. Comparison among disease-modifying treatments was not drawn.
Topping 2016	Before-after (pre–post) study with no control group.
Torgauten 2021	Retrospective cohort study with no control group.
Tsao 2019	Case series.
Vollmer 2020b	Retrospective cohort study with no control group.
Wijnands 2018	Study included interferon beta, glatiramer acetate, natalizumab, fingolimod, and dimethyl fumarate. No participants received rituximab.
Wolf 2019	Case series.
Yamout 2018	Before-after (pre–post) study with no control group.
Zecca 2020	Before-after (pre–post) study with no control group.
Zhovtis Ryerson 2018	Case series.

MS: multiple sclerosis.

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

Berrios Morales 2016

Methods	Observational open-label, controlled study involving 1 centre in the US comparing people with secondary progressive MS treated with rituximab vs controls (people with secondary progressive MS treated with other DMTs) regarding safety, tolerability, and progression of disease. Safety and tolerability were assessed by monitoring the adverse effects to rituximab. Efficacy in delaying progression of disease was measured by a multivariate survival modelling.

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Berrios Morales 2016 *(Continued)*

Participants	People with secondary progressive MS
Interventions	• Rituximab group: n = 40 • Control group: n = 20
Outcomes	• Disability worsening measured by EDSS • Adverse events
Notes	Study characteristics extracted from the study abstract. Sufficient information not available on study design, characteristics of participants, interventions, and outcomes. We contacted study investigators to request missing data.

Frisell 2019

Methods	Retrospective cohort study including people with MS initiating treatment with rituximab, dimethyl fumarate, natalizumab, or fingolimod in Sweden 2011–2017. Treatment episodes and clinical data were extracted from the Swedish MS register; linkage to national healthcare and census registers provided data on potential confounders and diagnosed cardiovascular disease (in hospital or non-primary outpatient care). Individuals were followed from treatment start until recorded outcome, drug discontinuation, death, emigration, or 31 December 2017. Baseline differences were adjusted for with inverse probability of treatment weights, and group difference in incidence rate tested with Cox regression.
Participants	People with MS
Interventions	• Rituximab: n = 3260 • Dimethyl fumarate: n = 2046 • Natalizumab: n = 1588 • Fingolimod: n =1535
Outcomes	• Major adverse cardiovascular events • Conduction disorders • Cerebrovascular events • Thrombotic events • Fatal cardiac events Mean 2.1 years of follow-up
Notes	Study characteristics extracted from the abstract. Sufficient information not available on study design, characteristics of participants, interventions, and outcomes. We contacted study investigators to request missing data.

Kalincik 2019

Methods	Retrospective cohort study based on MSBase registry
Participants	People with relapsing MS followed for > 3 months after commencing rituximab, natalizumab, or alemtuzumab and with a minimum data set.
Interventions	• Rituximab • Natalizumab • Alemtuzumab

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Kalincik 2019 *(Continued)*

Outcomes	• Annualised relapse rate • Cumulative hazard of relapses • 3-month confirmed disability worsening or improvement
Notes	Study characteristics extracted from the abstract. Sufficient information not available on study design, characteristics of participants, interventions, and outcomes. We contacted study investigators to request missing data.

DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; n: number of participants.

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

EUCTR2017-000426-35-AT

Study name	Efficacy of rituximab at low doses in multiple sclerosis – a prospective, randomized, double-blind, active controlled, pilot trial
Methods	Randomised controlled trial Sample size: 70 Country: Austria Number of centres: 2
Participants	Relapsing MS
Interventions	• Rituximab 100 mg every 10–12 weeks • Other, currently used dosing regimens
Outcomes	• Primary: annualised relapse rate at 48 weeks
Starting date	2018
Contact information	Medical University of Vienna, Department of Neurology (neurologie-sekretariat@meduni-wien.ac.at)
Notes	Recruitment status: recruiting Prospective completion date: not reported Sponsor/funding: Medical University of Vienna, Department of Neurology

EUCTR2017-002634-24-SE

Study name	MultipleMS – Multiple-omics approach to accelerate personalised medicine in a prospective cohort of newly diagnosed MS and CIS patients
Methods	Prospective controlled cohort study Sample size: 150 Country: Sweden Number of centres: 1

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EUCTR2017-002634-24-SE *(Continued)*

Participants	Newly diagnosed people with CIS and MS – both relapsing remitting and primary progressive
Interventions	Number of treatment arms in the trial: 8 • Rituximab • Natalizumab • Dimethyl fumarate • Fingolimod • Glatiramer acetate • Interferon beta • Alemtuzumab • Teriflunomide
Outcomes	• Primary: new and enlarging MRI T2 lesions in brain and spinal cord at baseline and after 24 months of treatment
Starting date	29 September 2017
Contact information	Neurology Clinic Karolinska University Hospital (fredrik.piehl@ki.se)
Notes	Recruitment status: recruiting Prospective completion date: not reported Sponsor/funding: Karolinska Institutet Sweden

EUCTR2020-002981-15-DK

Study name	Danish non-inferiority study of ocrelizumab and rituximab in MS (DanNORMS): a randomized study comparing the efficacy of ocrelizumab and rituximab in active multiple sclerosis
Methods	Randomised controlled non-inferiority trial Sample size: 594 Country: Denmark Number of centres: 12
Participants	All active forms of MS according to the diagnostic criteria of Thompson 2018
Interventions	• Rituximab • Ocrelizumab
Outcomes	• Percentage of participants with no new or enlarging MRI T2 white matter lesions from month 6 to month 24
Starting date	15 December 2020
Contact information	Danish Multiple Sclerosis Center, Rigshospitalet (telephone number 45 3863 3045)
Notes	Recruitment status: recruiting Prospective completion date: 30 January 2028 Sponsor/funding: Danish Multiple Sclerosis Center, Rigshospitalet, Denmark

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IRCT20130812014333N125

Study name	One year comparison of effectiveness and complication of rituximab and fingolimod in multiple sclerosis (MS) patients
Methods	Randomised controlled trial Sample size: 36 Country: Iran Number of centres: 1; Imam Reza hospital Kermanshah, Iran
Participants	Active MS defined as ≥ 1 relapse in the past year or 2 relapses in the past 2 years. A new T2 or gadolinium-enhancing lesion lesions on brain MRI in the past year despite treatment with di-methyltryptamine
Interventions	• Rituximab 1000 mg at week 0, week 2, and every 6 months for 1 year • Fingolimod 0.5 mg oral daily for 1 year
Outcomes	• Disability motion • Relapse • Medicine complications
Starting date	10 May 2018
Contact information	Nazanin Razazian (nrazazian@gmail.com)
Notes	Recruitment status: complete Sponsor/funding: Kermanshah University of Medical Sciences

NCT02545959

Study name	Intrathecal rituximab in progressive multiple sclerosis (EFFRITE)
Methods	Randomised control parallel trial Sample size: 12 Country: France Number of centres: 1
Participants	Secondary or primary progressive MS, in progressive phase for > 2 years
Interventions	• Single intrathecal infusion of rituximab 20 mg (with intravenous methylprednisolone 120 mg to avoid adverse effects) and rituximab intravenous 375 mg/m^2 the same day • Single blood infusion of methylprednisolone intravenous 120 mg
Outcomes	Primary • Change in osteopontin level in cerebrospinal fluid at day 4, day 21, day 180 Secondary measured at day 4, day 21, day 180 • Change in tumour necrosis factor alpha level in cerebrospinal fluid

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NCT02545959 *(Continued)*

	• Change in immunoglobulin G synthesis in cerebrospinal fluid • Change in neurofilament level in cerebrospinal fluid Other outcome measures • Change in clinical parameters at day 4, day 21, day 180, day 365. Subjective appreciation and multiple clinical scales (walking time, 9 hole peg test, Expanded Disability Status Scale Symbol Digit Modalities Test, SDMT, Fatigue Intensity Scale) • Brain volume atrophy at day 180, day 365. Percent change in total brain volume
Starting date	30 November 2015
Contact information	Mickael Bonnan, Centre Hospitalier de PAU University Hospital, Bordeaux France
Notes	Recruitment status: completed (2 September 2019) Sponsor/funding: Centre Hospitalier de PAU Bordeaux France

NCT02746744

Study name	RItuximab versus FUmarate in Newly Diagnosed Multiple Sclerosis (RIFUND-MS)
Methods	Parallel randomised clinical trial Sample size: 200 Country: Sweden Number of centres: 17
Participants	Relapsing remitting MS according to the 2017 revised McDonald criteria or 1 demyelinating episode in conjunction with ≥ 1 asymptomatic high-intensity T2 lesion with size and location compatible with MS
Interventions	• Rituximab every 6 months • Dimethyl fumarate daily according to clinical practice
Outcomes	• Primary: freedom of relapse within 2 years
Starting date	May 2016
Contact information	Anders Svenningsson, Karolinska Institutet, Stockholm, Sweden (anders.svenningsson@ki.se)
Notes	Recruitment status: active, not recruiting Prospective completion date: August 2021 Sponsor: Anders Svenningsson

NCT03193866

Study name	COMparison Between All immunoTherapies for Multiple Sclerosis (COMBAT-MS)
Methods	Observational prospective cohort study Sample size: 3526

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NCT03193866 *(Continued)*

	Country: Sweden Number of centres: 2 (Karolinska Institutet, Stockholm, Sweden; Kaiser Permanent Southern California, Los Angeles, USA)
Participants	Participants with CIS or relapsing remitting MS who initiate a first MS DMT, or initiate a second-ever DMT, of a different drug class than the first, regardless of time between drugs or reason for discontinuation from 1 January 2011 to 30 June 2018.
Interventions	• Rituximab • Natalizumab, fingolimod, alemtuzumab, interferon beta, glatiramer acetate, or dimethyl fumarate
Outcomes	Primary • Confirmed disease progression in participants with EDSS ≤ 2.5 at baseline over 3 years of follow-up • Confirmed disease progression in participants with EDSS ≥ 2.5 at baseline over 3 years of follow-up • Disease-related impact on daily life over 3 years of follow-up
Starting date	1 February 2017
Contact information	Fredrik Piehl, Karolinska Institutet, Stockholm, Sweden
Notes	Recruitment status: active, not recruiting Prospective completion date: 31 December 2022 Sponsor/funding: Karolinska Institute Sweden

NCT03315923

Study name	Comparison of clinical effects of rituximab and glatiramer acetate in secondary progressive multiple sclerosis patients
Methods	Parallel randomised controlled trial Sample size: 84 Country: Iran Number of centres: 1
Participants	People with secondary progressive MS
Interventions	• Rituximab 1000 mg intravenous infusion repeated every 6 months. In addition, participants will receive methylprednisolone 100 mg, chlorpheniramine 10 mg, and paracetamol 500 mg • Glatiramer acetate 40 mg 3 times per week through subcutaneous injection
Outcomes	Primary • Disability measured by EDSS at 1 year Secondary • Adverse drug reactions at 1 year • Number of gadolinium-enhanced brain lesions and neuroimaging findings at 1 year • Annualised relapse rate at 1 year

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NCT03315923 *(Continued)*

Starting date	1 December 2017
Contact information	Vahid Shaygannejad, Isfahan University of Medical Sciences, Isfahan, Iran
Notes	Recruitment status: completed Completion date: 1 March 2019 Sponsor/funding: Isfahan University of Medical Sciences, Iran

NCT03500328

Study name	TRaditional versus Early Aggressive Therapy for multiple sclerosis trial (TREAT-MS)
Methods	Randomised pragmatic controlled multicentre trial Sample size: 900 Country: USA Number of centres: 49
Participants	Relapsing-remitting MS according to 2017 McDonald criteria. Excluded people with CIS.
Interventions	Experimental: higher-efficacy DMT • Natalizumab 300 mg intravenously every 4 weeks • Alemtuzumab 12 mg intravenously daily for 5 days; 1 year later: 12 mg intravenously daily for 3 days • Ocrelizumab 300 mg intravenously every 2 weeks (for 2 doses) at initiation; subsequently, 600 mg intravenously every 6 months • Rituximab 1000 mg intravenously every 2 weeks (for 2 doses); may repeat every 16–24 weeks Comparator: traditional, first-line DMT • Glatiramer acetate 20 mg subcutaneously daily, or 40 mg subcutaneously 3 times a week • Interferon (Avonex) 30 µg intramuscularly weekly • Interferon 0.25 mg subcutaneously every other day (Betaseron, Extavia); 44 µg subcutaneously 3 times per week (Rebif) • Pegylated interferon 125 µg subcutaneously every 14 days • Teriflunomide 14 mg orally daily • Dimethyl fumarate 240 mg orally twice per day • Fingolimod 0.5 mg orally daily
Outcomes	• Primary: time to sustained disability progression up to 48 months
Starting date	2 May 2018
Contact information	Sandra Cassard (scassar1@jhmi.edu); Susan Emrich (semrich1@jhmi.edu)
Notes	Recruitment status: recruiting Prospective completion date: 1 August 2023 Sponsor/funding: Johns Hopkins University

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NCT03535298

Study name	Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for RRMS (DELIVER-MS)
Methods	Randomised controlled multicentre trial Sample size: 800 Country: USA and UK Number of centres: 23
Participants	Active relapsing remitting MS defined as ≥ 1 relapses within the last 18 months prior to screening visit or radiological evidence of MS activity (≥ 2 new T2 lesions within the last 12 months from screening, compared to a previous recent MRI within 18 months of screening, or ≥ 1 gadolinium-enhancing lesion demonstrated on brain or spinal cord MRI performed within the last 12 months of screening)
Interventions	Experimental: highly effective MS therapy as initial treatment • Alemtuzumab • Ocrelizumab • Natalizumab • Rituximab Comparator: escalation with any other approved MS therapy as initial treatment • Interferon beta • Glatiramer acetate • Teriflunomide • Fingolimod • Dimethyl fumarate
Outcomes	• Primary: brain volume loss measured using MRI at month 36
Starting date	3 January 2019
Contact information	Sarah Planchon Pope (planchs@ccf.org)
Notes	Recruitment status: recruiting Prospective completion date: September 2023 Sponsor/funding: the Cleveland Clinic, USA

NCT04047628

Study name	Best Available Therapy Versus Autologous Hematopoetic Stem Cell Transplant for Multiple Sclerosis (BEAT-MS)
Methods	Randomised controlled parallel multicentre trial Sample size: 156 Country: USA and UK

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NCT04047628 *(Continued)*

	Number of centres: 21
Participants	Highly active treatment-resistant relapsing MS, defined as ≥ 2 episodes of treatment failure in the 24 months prior to the screening visit
Interventions	• Myeloablative and immunoablative therapy followed by autologous haematopoietic stem cell transplantation • Best available therapy selected by the site investigator from: natalizumab, alemtuzumab, ocrelizumab, or rituximab
Outcomes	• Primary: relapse-free survival up to 36 months
Starting date	19 December 2019
Contact information	Jeffrey A Cohen (Mellen Center for MS Treatment and Research, Cleveland Clinic); George E Georges (Fred Hutchinson Cancer Research Center); Paolo A Muraro (Department of Medicine, Imperial College London)
Notes	Recruitment status: recruiting Prospective completion date: October 2028 Sponsor/funding: National Institute of Allergy and Infectious Diseases

NCT04121403

Study name	Norwegian Study of Oral Cladribine and rituximab in Multiple Sclerosis (NOR-MS)
Methods	Randomised clinical trial, parallel, multicentre non-inferiority study Sample size: 264 Country: Norway Number of centres: 10
Participants	Active relapsing remitting MS
Interventions	• Rituximab intravenous infusion • Cladribine oral
Outcomes	• Primary: the number of new or enlarging cerebral MRI T2 lesions per participant from week 12 to week 96
Starting date	October 2019
Contact information	Gro Owren Nygaard (uxgryg@ous-hf.no)
Notes	Recruitment status: recruiting Prospective completion date: December 2023 Sponsor/funding: Oslo University Hospital, Norway

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NCT04283747

Study name	Hypogammaglobulinemia and immunization responses to measles in rituximab-treated multiple sclerosis
Methods	Non-randomised prospective study Sample size: 170 Country: Iran Single centre, MS clinic of Bu Ali Sina Hospital, Sari, Iran
Participants	Diagnosis of MS compatible with 2017 McDonald criteria
Interventions	• Rituximab for ≥ 18 months
Outcomes	• Primary: rate of hypogammaglobulinaemia
Starting date	28 February 2020
Contact information	Athena Sharifi Razavi (athena.sharifi@yahoo.com)
Notes	Recruitment status: recruiting Prospective completion date: December 2022 Sponsor/funding: Mazandaran University of Medical Sciences, Iran

NCT04578639

Study name	Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease (OVERLORD-MS)
Methods	Prospective, parallel, randomised, double-blind, multicentre, non-inferiority study Sample size: 211 Country: Norway Number of centres: 6
Participants	Active relapsing MS
Interventions	• Ocrelizumab • Rituximab
Outcomes	• Primary: proportion of participants with no new or enlarging T2-weighted brain MRI lesions from month 6 (re-baseline) to month 24
Starting date	2 November 2020
Contact information	Øivind Torkildsen (oivind.fredvik.grytten.torkildsen@helse-bergen.no) Kjell-Morten Myhr (kjell-morten.myhr@helse-bergen.no)
Notes	Recruitment status: recruiting Prospective completion date: 14 February 2025

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NCT04578639 *(Continued)*

Sponsor/funding: Haukeland University Hospital, Norway

CIS: clinically isolated syndrome; DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; MS: multiple sclerosis.

DATA AND ANALYSES

Comparison 1. Comparison: rituximab as 'first choice' versus other disease-modifying treatments (DMT) for relapsing multiple sclerosis – results from non-randomised studies of interventions (NRSIs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Time to relapse over 24 months	1		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Rituximab vs interferons beta or glatiramer acetate	1	335	Hazard Ratio (IV, Fixed, 95% CI)	0.14 [0.05, 0.39]
1.1.2 Rituximab vs dimethyl fumarate	1	206	Hazard Ratio (IV, Fixed, 95% CI)	0.29 [0.08, 1.00]
1.1.3 Rituximab vs natalizumab	1	170	Hazard Ratio (IV, Fixed, 95% CI)	0.24 [0.06, 1.00]
1.1.4 Rituximab vs fingolimod	1	137	Hazard Ratio (IV, Fixed, 95% CI)	0.26 [0.04, 1.69]
1.2 Gadolinium magnetic resonance imaging (MRI) lesions	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Rituximab vs interferons beta or glatiramer acetate	1	263	Odds Ratio (IV, Fixed, 95% CI)	0.10 [0.02, 0.43]
1.2.2 Rituximab vs dimethyl fumarate	1	177	Odds Ratio (IV, Fixed, 95% CI)	0.12 [0.02, 0.59]
1.2.3 Rituximab vs natalizumab	1	147	Odds Ratio (IV, Fixed, 95% CI)	0.12 [0.01, 1.11]
1.2.4 Rituximab vs fingolimod	1	119	Odds Ratio (IV, Fixed, 95% CI)	0.33 [0.01, 10.00]
1.3 Treatment discontinuation due to adverse events	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
1.3.1 Rituximab vs interferon beta or glatiramer acetate	1	335	Odds Ratio (IV, Fixed, 95% CI)	0.02 [0.00, 0.16]
1.3.2 Rituximab vs dimethyl fumarate	1	206	Odds Ratio (IV, Fixed, 95% CI)	0.05 [0.01, 0.41]
1.3.3 Rituximab vs natalizumab	1	170	Odds Ratio (IV, Fixed, 95% CI)	0.20 [0.02, 2.28]
1.3.4 Rituximab vs fingolimod	1	137	Odds Ratio (IV, Fixed, 95% CI)	0.04 [0.00, 0.40]
1.4 Grade 3–4 adverse events over 24 months	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only

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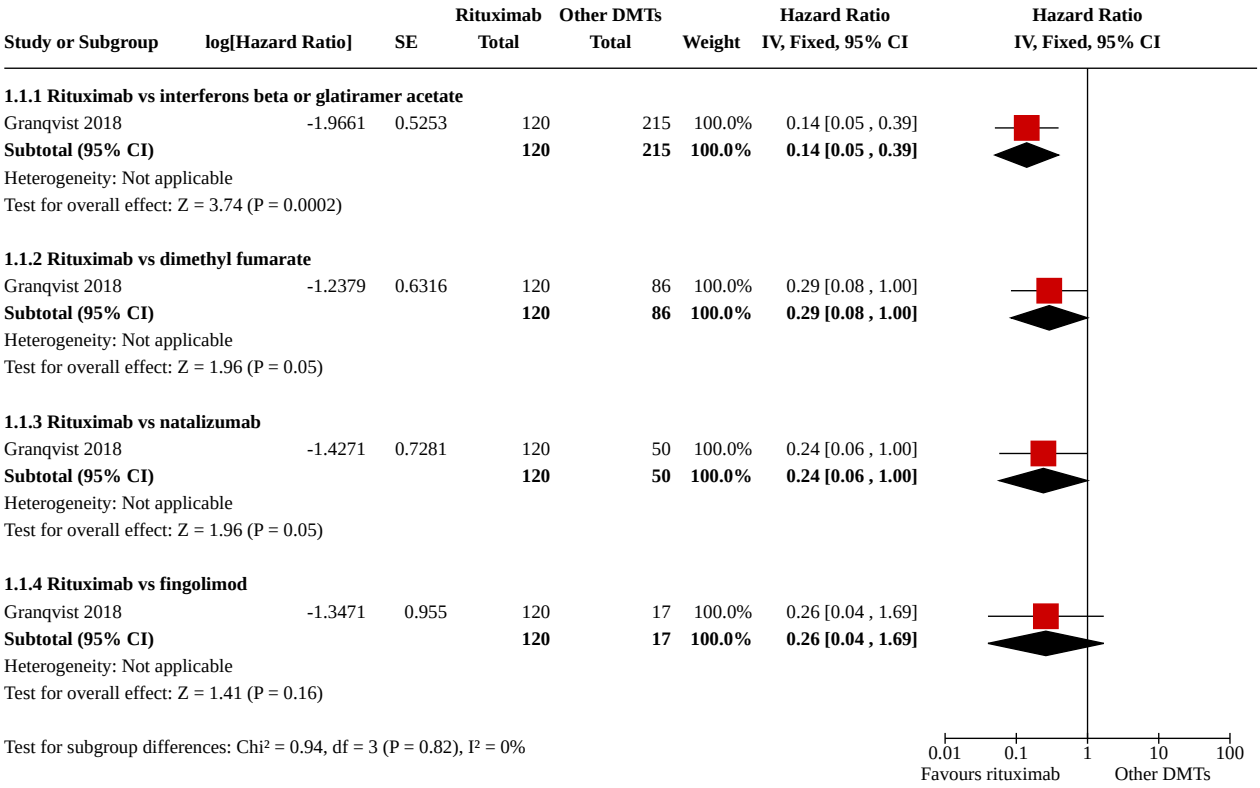
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.1 Rituximab vs interferon beta or glatiramer acetate	1	335	Odds Ratio (IV, Fixed, 95% CI)	0.89 [0.26, 3.03]
1.4.2 Rituximab vs dimethyl fumarate	1	206	Odds Ratio (IV, Fixed, 95% CI)	2.93 [0.32, 26.69]
1.4.3 Rituximab vs fingolimod	1	137	Odds Ratio (IV, Fixed, 95% CI)	1.35 [0.07, 26.21]
1.4.4 Rituximab vs natalizumab	1	170	Odds Ratio (IV, Fixed, 95% CI)	0.40 [0.10, 1.65]

Analysis 1.1. Comparison 1: Comparison: rituximab as 'first choice' versus other disease-modifying treatments (DMT) for relapsing multiple sclerosis – results from non-randomised studies of interventions (NRSIs), Outcome 1: Time to relapse over 24 months



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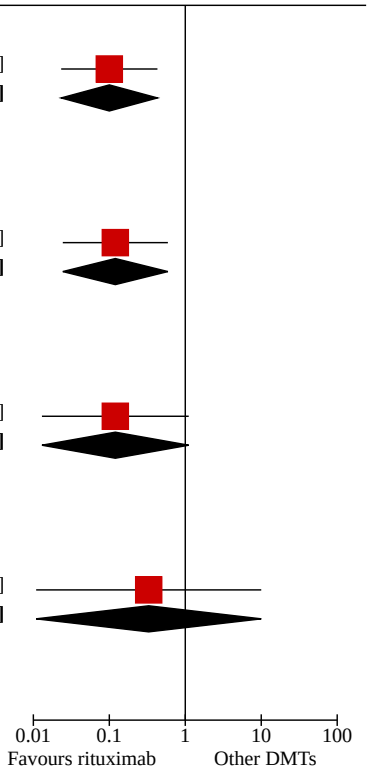
Analysis 1.2. Comparison 1: Comparison: rituximab as 'first choice' versus other disease-modifying treatments (DMT) for relapsing multiple sclerosis – results from non-randomised studies of interventions (NRSIs), Outcome 2: Gadolinium magnetic resonance imaging (MRI) lesions

Study or Subgroup	log[OR]	SE	Rituximab Total	Other DMTs Total	Weight	Odds Ratio IV, Fixed, 95% CI
1.2.1 Rituximab vs interferons beta or glatiramer acetate						
Granqvist 2018	-2.3026	0.7442	104	159	100.0%	0.10 [0.02 , 0.43]
Subtotal (95% CI)			**104**	**159**	**100.0%**	**0.10 [0.02 , 0.43]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
1.2.2 Rituximab vs dimethyl fumarate						
Granqvist 2018	-2.1203	0.8126	104	73	100.0%	0.12 [0.02 , 0.59]
Subtotal (95% CI)			**104**	**73**	**100.0%**	**0.12 [0.02 , 0.59]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.61 (P = 0.009)						
1.2.3 Rituximab vs natalizumab						
Granqvist 2018	-2.1203	1.135	104	43	100.0%	0.12 [0.01 , 1.11]
Subtotal (95% CI)			**104**	**43**	**100.0%**	**0.12 [0.01 , 1.11]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						
1.2.4 Rituximab vs fingolimod						
Granqvist 2018	-1.1087	1.7405	104	15	100.0%	0.33 [0.01 , 10.00]
Subtotal (95% CI)			**104**	**15**	**100.0%**	**0.33 [0.01 , 10.00]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi² = 0.40, df = 3 (P = 0.94), I² = 0%						



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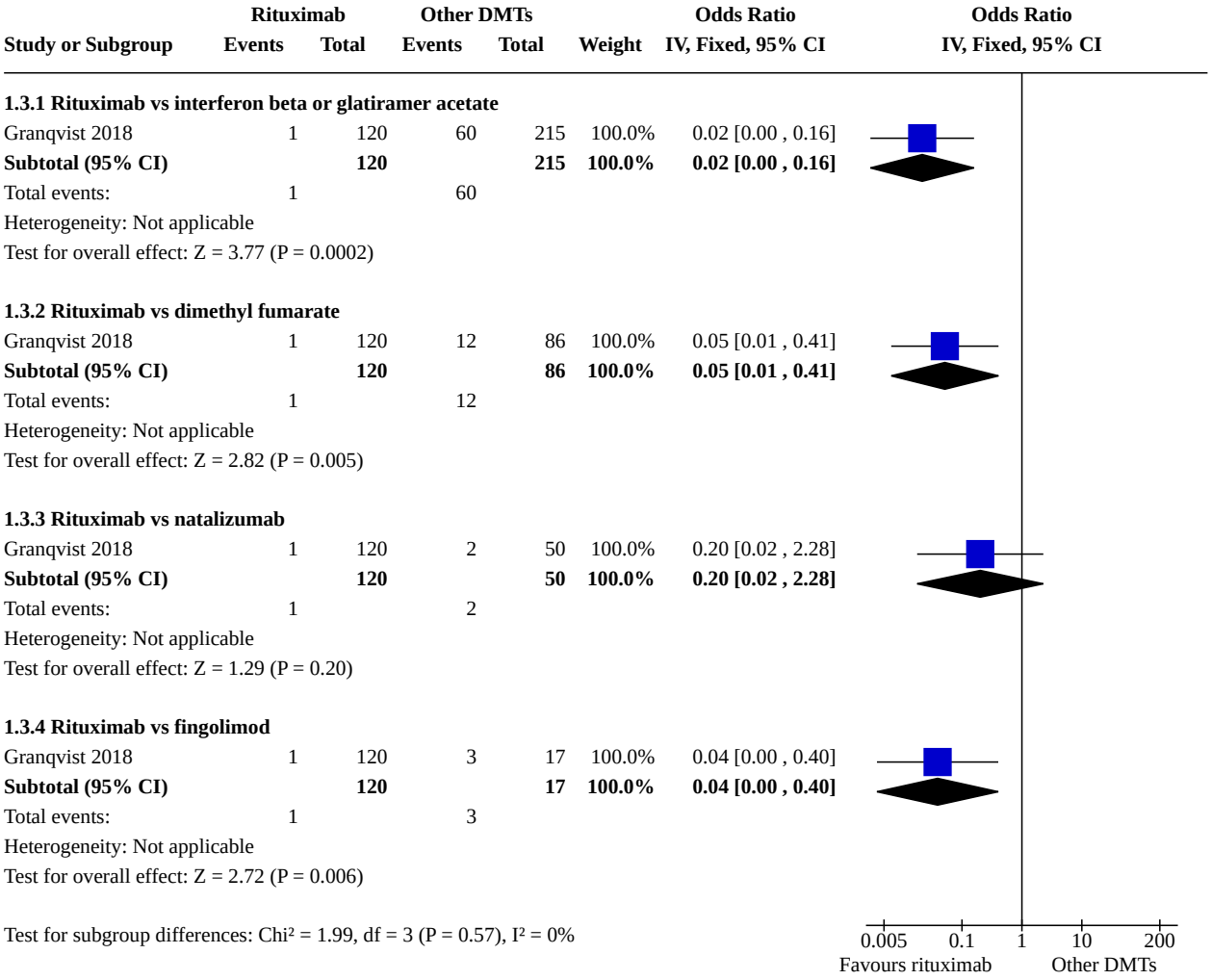
Analysis 1.3. Comparison 1: Comparison: rituximab as 'first choice' versus other disease-modifying treatments (DMT) for relapsing multiple sclerosis – results from non-randomised studies of interventions (NRSIs), Outcome 3: Treatment discontinuation due to adverse events



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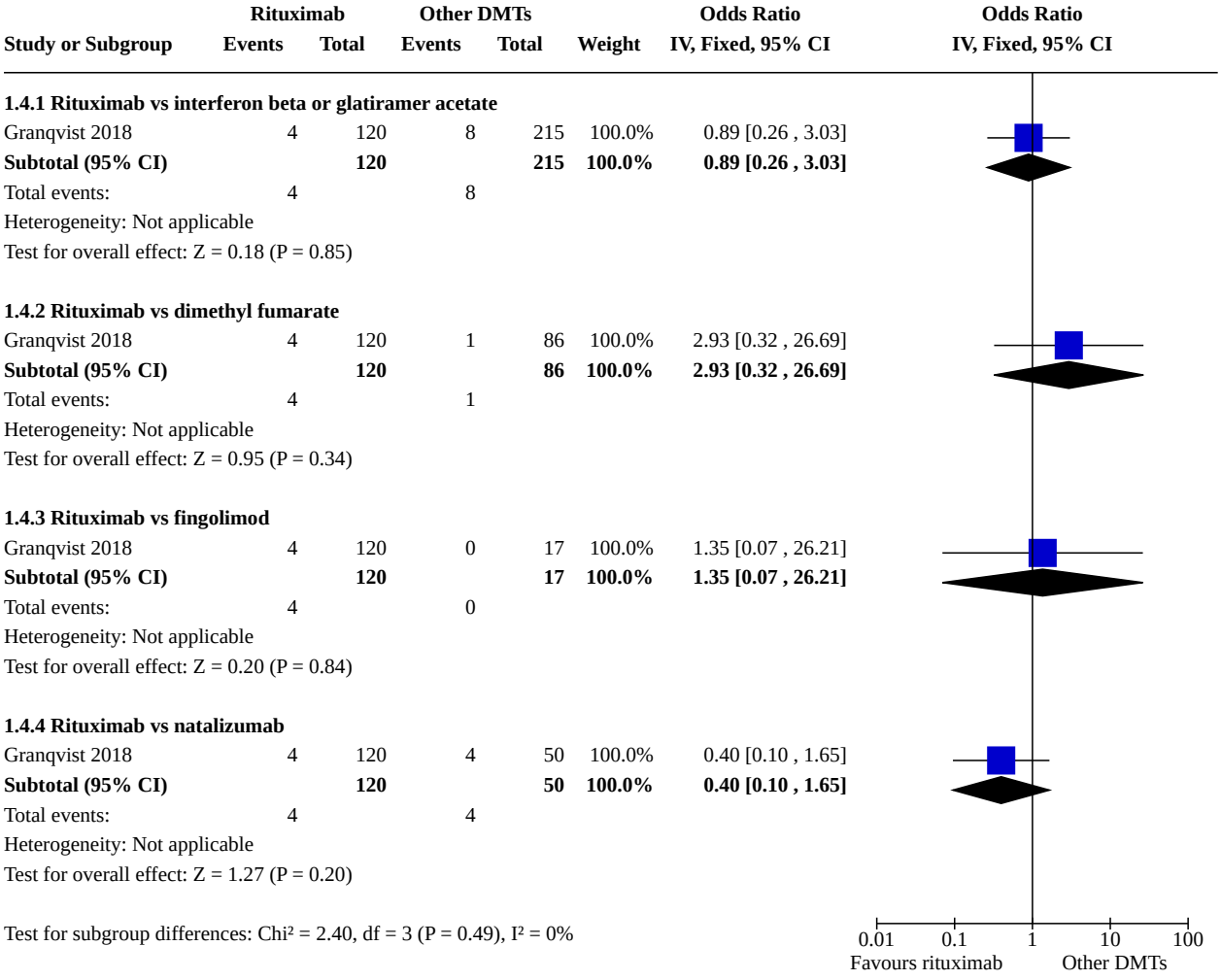
Analysis 1.4. Comparison 1: Comparison: rituximab as 'first choice' versus other disease-modifying treatments (DMT) for relapsing multiple sclerosis – results from non-randomised studies of interventions (NRSIs), Outcome 4: Grade 3–4 adverse events over 24 months



Comparison 2. Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Disability worsening over 24 months	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
2.2 Relapse over 24 months	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
2.3 Serious adverse events over 24 months	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
2.4 Common infections over 24 months	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
2.5 Cancer over 24 months	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only

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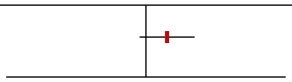
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6 Mortality over 24 months	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
2.7 Treatment discontinuation due to adverse events	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
2.8 Grade 3 or 4 adverse events	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
2.9 First infusion reactions	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
2.10 Second infusion reactions	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 1: Disability worsening over 24 months

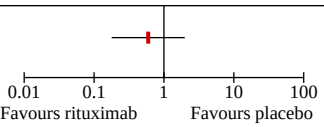
Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009	-0.3484	0.2315	292	147	0.71 [0.45 , 1.11]		+ ? ? ? + + + +



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.2. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 2: Relapse over 24 months

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009	-0.5178	0.6142	292	147	0.60 [0.18 , 1.99]		+ ? ? ? + + + +



Risk of bias legend
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(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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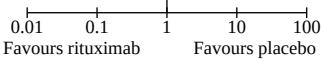
Analysis 2.3. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 3: Serious adverse events over 24 months

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009	0.2225	0.2878	292	147	1.25 [0.71 , 2.20]		+ ? ? ? + + + +



Risk of bias legend
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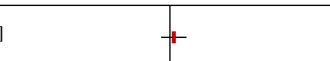
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.4. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 4: Common infections over 24 months

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009	0.1282	0.214	292	147	1.14 [0.75 , 1.73]		+ ? ? ? + + + +



Risk of bias legend
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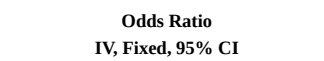
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.5. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 5: Cancer over 24 months

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009	-0.6931	1.0052	292	147	0.50 [0.07 , 3.59]		+ ? ? ? + + + +



Risk of bias legend
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(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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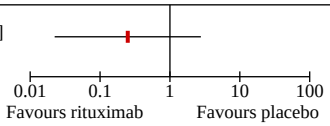
Analysis 2.6. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 6: Mortality over 24 months

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009	-1.3897	1.229	292	147	0.25 [0.02 , 2.77]		+ ? ? ? + + + +



Risk of bias legend
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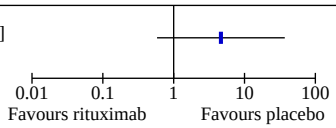
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.7. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 7: Treatment discontinuation due to adverse events

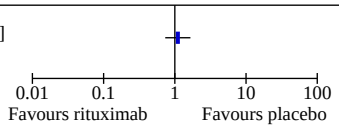
Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009	9	292	1	147	4.64 [0.58 , 37.00]		+ ? ? ? + + + +



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.8. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 8: Grade 3 or 4 adverse events

Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009	118	292	56	147	1.10 [0.73 , 1.66]		+ ? ? ? + + + +



Risk of bias legend
(A) Random sequence generation (selection bias)
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(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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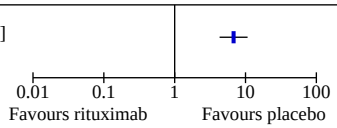
Analysis 2.9. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 9: First infusion reactions

Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009 (1)	196	292	34	147	6.79 [4.31 , 10.69]		+ ? ? ? + + + +

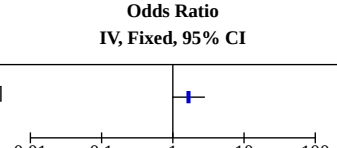


Footnotes
(1) Follow-up time point: 24 months

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.10. Comparison 2: Comparison: rituximab as 'first choice' versus placebo for primary progressive multiple sclerosis – results from randomised controlled trials (RCTs) , Outcome 10: Second infusion reactions

Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hawker 2009 (1)	66	292	22	147	1.66 [0.98 , 2.82]		+ ? ? ? + + + +



Footnotes
(1) Follow-up timepoint: 24 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 3. Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Relapse over 12 months in relapsing MS	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.2 Serious adverse events (SAEs)	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.2.1 SAEs over 12 months in relapsing MS	1	104	Odds Ratio (IV, Fixed, 95% CI)	0.90 [0.28, 2.92]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Common infections	2		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.3.1 Common infections over 12 months in relapsing MS	1	104	Odds Ratio (IV, Fixed, 95% CI)	0.91 [0.37, 2.24]
3.3.2 Common infections over 24 months in secondary progressive MS	1	27	Odds Ratio (IV, Fixed, 95% CI)	0.40 [0.08, 2.12]
3.4 Cancer	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.4.1 Relapsing MS over 12 months	1	104	Odds Ratio (IV, Fixed, 95% CI)	1.55 [0.06, 39.15]
3.5 Mortality	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.6 Annualised relapse rate	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.7 Gadolinium MRI lesions over 12 months	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.8 Treatment discontinuation due to adverse events	2		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.8.1 Rituximab when switching from another DMT in relapsing MS	1	104	Odds Ratio (IV, Fixed, 95% CI)	0.75 [0.12, 4.71]
3.8.2 Rituximab when switching from another DMT in secondary progressive MS	1	27	Odds Ratio (IV, Fixed, 95% CI)	1.63 [0.06, 44.01]
3.9 Grade 3–4 adverse events	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.10 Cardiovascular events	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.10.1 Rituximab when switching from another DMT in relapsing MS	1	104	Odds Ratio (IV, Fixed, 95% CI)	1.55 [0.06, 39.15]
3.11 First infusion reactions	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
3.12 Second infusion reactions	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only

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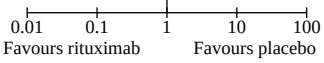
Analysis 3.1. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 1: Relapse over 12 months in relapsing MS

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hauser 2008	-0.9628	0.4568	69	35	0.38 [0.16 , 0.93]		+ ? ? - + - + +

Test for subgroup differences: Not applicable

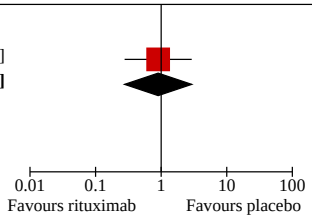


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.2. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 2: Serious adverse events (SAEs)

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
3.2.1 SAEs over 12 months in relapsing MS								
Hauser 2008	-0.1054	0.6009	69	35	100.0%	0.90 [0.28 , 2.92]		+ ? ? - + - + +
Subtotal (95% CI)			**69**	**35**	**100.0%**	**0.90 [0.28 , 2.92]**		
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.86)								

Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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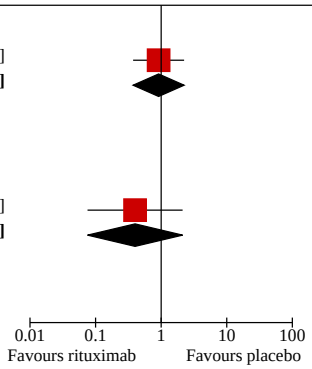
Analysis 3.3. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 3: Common infections

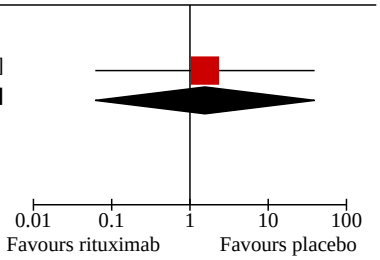
Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
3.3.1 Common infections over 12 months in relapsing MS								
Hauser 2008	-0.0896	0.4566	69	35	100.0%	0.91 [0.37 , 2.24]		+ ? ? - + - + +
Subtotal (95% CI)			**69**	**35**	**100.0%**	**0.91 [0.37 , 2.24]**		
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
3.3.2 Common infections over 24 months in secondary progressive MS								
Komori 2016	-0.9163	0.8515	18	9	100.0%	0.40 [0.08 , 2.12]		+ - ? ? ? - + -
Subtotal (95% CI)			**18**	**9**	**100.0%**	**0.40 [0.08 , 2.12]**		
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Test for subgroup differences: $Chi^2 = 0.73$, df = 1 (P = 0.39), $I^2 = 0\%$								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.4. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 4: Cancer

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
3.4.1 Relapsing MS over 12 months							
Hauser 2008	0.4413	1.646	69	35	100.0%	1.55 [0.06 , 39.15]	
Subtotal (95% CI)			**69**	**35**	**100.0%**	**1.55 [0.06 , 39.15]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.27 (P = 0.79)							
Test for subgroup differences: Not applicable							



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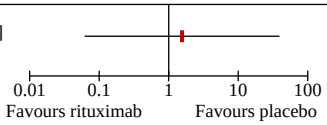
Analysis 3.5. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 5: Mortality

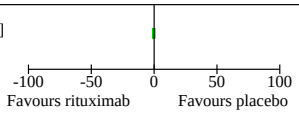
Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hauser 2008	0.4413	1.646	69	35	1.55 [0.06 , 39.15]		+ ? ? - + - + +



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.6. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 6: Annualised relapse rate

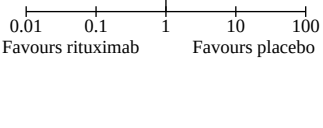
Study or Subgroup	Rituximab Mean	Rituximab SD	Rituximab Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hauser 2008	0.4	0.81	69	0.7	1.05	35	-0.30 [-0.70 , 0.10]		+ ? ? - + - + +



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.7. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 7: Gadolinium MRI lesions over 12 months

Study or Subgroup	log[OR]	SE	Rituximab Total	Placebo Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Hauser 2008	-1.5509	0.4827	66	35	0.21 [0.08 , 0.55]		+ ? ? - + - + +



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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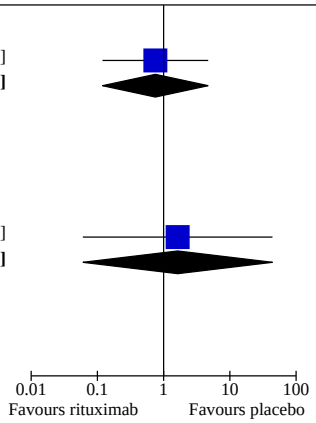
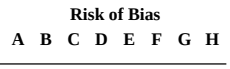
Analysis 3.8. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 8: Treatment discontinuation due to adverse events

Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.8.1 Rituximab when switching from another DMT in relapsing MS						
Hauser 2008 (1)	3	69	2	35	100.0%	0.75 [0.12 , 4.71]
Subtotal (95% CI)		**69**		**35**	**100.0%**	**0.75 [0.12 , 4.71]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
3.8.2 Rituximab when switching from another DMT in secondary progressive MS						
Komori 2016 (1)	1	18	0	9	100.0%	1.63 [0.06 , 44.01]
Subtotal (95% CI)		**18**		**9**	**100.0%**	**1.63 [0.06 , 44.01]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%						



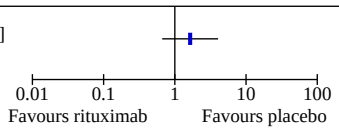


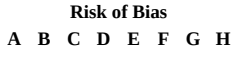
Footnotes
(1) 12 months' follow-up.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.9. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 9: Grade 3–4 adverse events

Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Odds Ratio IV, Fixed, 95% CI
Hauser 2008	25	69	9	35	1.64 [0.67 , 4.05]





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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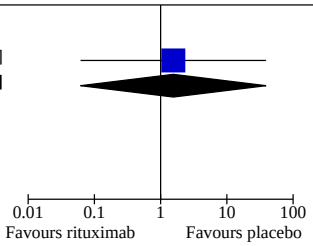
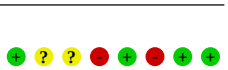
Analysis 3.10. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 10: Cardiovascular events

Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.10.1 Rituximab when switching from another DMT in relapsing MS						
Hauser 2008 (1)	1	69	0	35	100.0%	1.55 [0.06 , 39.15]
Subtotal (95% CI)		**69**		**35**	**100.0%**	**1.55 [0.06 , 39.15]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Test for subgroup differences: Not applicable						



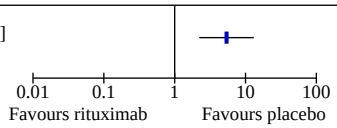


Footnotes
(1) Follow-up timepoint: over 12 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.11. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 11: First infusion reactions

Study or Subgroup	Rituximab Events	Rituximab Total	Placebo Events	Placebo Total	Odds Ratio IV, Fixed, 95% CI
Hauser 2008 (1)	54	69	14	35	5.40 [2.23 , 13.09]



Footnotes
(1) Follow-up timepoint: 12 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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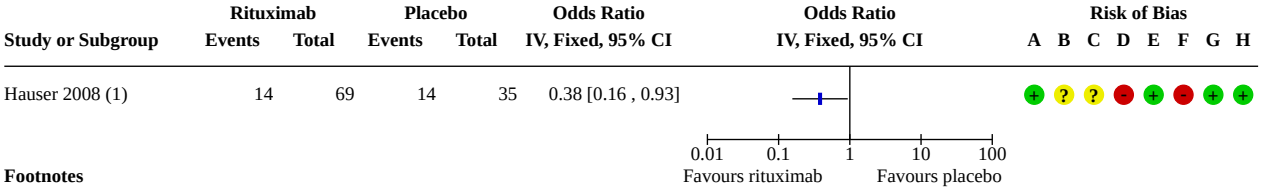
Analysis 3.12. Comparison 3: Comparison: rituximab as 'switching' versus placebo for relapsing multiple sclerosis (MS) – results from RCTs, Outcome 12: Second infusion reactions



Footnotes
(1) Follow-up timepoint: 12 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 4. Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Time to disability worsening over 24 months	1		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
4.1.1 Rituximab vs interferons or glatiramer	1	853	Hazard Ratio (IV, Fixed, 95% CI)	0.86 [0.52, 1.42]
4.2 Time to relapse over 24 months	3		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
4.2.1 Rituximab vs interferons beta or glatiramer acetate	1	1383	Hazard Ratio (IV, Fixed, 95% CI)	0.18 [0.07, 0.49]
4.2.2 Rituximab vs fingolimod	1	164	Hazard Ratio (IV, Fixed, 95% CI)	0.08 [0.02, 0.32]
4.2.3 Rituximab vs natalizumab	1	153	Hazard Ratio (IV, Fixed, 95% CI)	1.00 [0.20, 5.00]
4.3 Common infections	4		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
4.3.1 Rituximab vs interferons beta or glatiramer acetate	1	5477	Odds Ratio (IV, Fixed, 95% CI)	1.71 [1.11, 2.62]
4.3.2 Rituximab vs fingolimod	3	5187	Odds Ratio (IV, Fixed, 95% CI)	1.26 [0.90, 1.77]
4.3.3 Rituximab vs natalizumab	2	5001	Odds Ratio (IV, Fixed, 95% CI)	1.58 [1.08, 2.32]
4.3.4 Rituximab vs ocrelizumab	1	472	Odds Ratio (IV, Fixed, 95% CI)	0.02 [0.00, 0.40]
4.4 Mortality	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
4.4.1 Rituximab vs fingolimod	1	136	Odds Ratio (IV, Fixed, 95% CI)	5.59 [0.22, 139.89]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4.2 Rituximab vs natalizumab	1	153	Odds Ratio (IV, Fixed, 95% CI)	6.66 [0.27, 166.58]
4.5 Annualised relapse rate (change from baseline) – by type of DMT	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.5.1 Rituximab vs interferons beta or glatiramer acetate	1	1383	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.03, -0.01]
4.6 T2 MRI lesions	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
4.6.1 Rituximab vs fingolimod	1	182	Odds Ratio (IV, Fixed, 95% CI)	0.01 [0.00, 0.06]
4.7 Gadolinium MRI lesions	2		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
4.7.1 Rituximab vs fingolimod	2	288	Odds Ratio (IV, Fixed, 95% CI)	0.09 [0.03, 0.30]
4.7.2 Rituximab vs natalizumab	1	138	Odds Ratio (IV, Fixed, 95% CI)	1.00 [0.20, 5.00]
4.8 Treatment discontinuation due to adverse events – by type of DMT	2		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
4.8.1 Rituximab vs fingolimod	1	136	Odds Ratio (IV, Fixed, 95% CI)	0.13 [0.01, 2.37]
4.8.2 Rituximab vs natalizumab	1	153	Odds Ratio (IV, Fixed, 95% CI)	0.30 [0.02, 5.96]
4.8.3 Rituximab vs ocrelizumab	1	472	Odds Ratio (IV, Fixed, 95% CI)	0.26 [0.11, 0.62]
4.9 Grade 3–4 adverse events over 24 months	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.9.1 Rituximab vs fingolimod	2	392	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.06, 2.09]
4.9.2 Rituximab vs natalizumab	1	153	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.41]
4.10 Cardiovascular events – by type of DMT	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.10.1 Rituximab vs fingolimod	2	392	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.05, 1.85]
4.10.2 Rituximab vs natalizumab	1	153	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4.11 First infusion reactions	2		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
4.11.1 Rituximab vs fingolimod	1	256	Odds Ratio (IV, Fixed, 95% CI)	4.71 [2.19, 10.14]
4.11.2 Rituximab vs ocrelizumab	1	472	Odds Ratio (IV, Fixed, 95% CI)	0.51 [0.07, 3.69]

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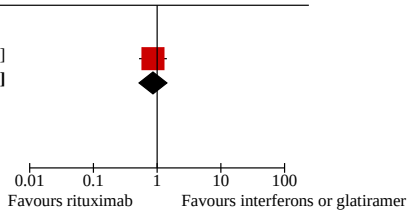
Analysis 4.1. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 1: Time to disability worsening over 24 months

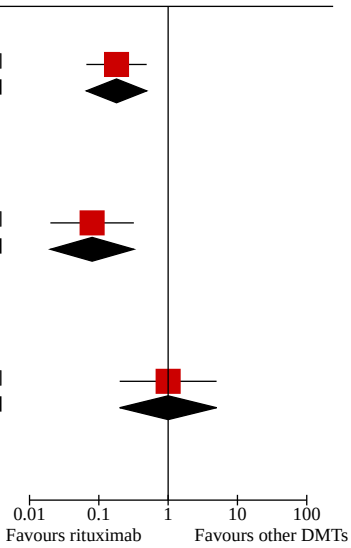
Study or Subgroup	log[Hazard Ratio]	SE	Rituximab Total	Other DMTs Total	Weight	Hazard Ratio IV, Fixed, 95% CI
4.1.1 Rituximab vs interferons or glatiramer						
Spelman 2018 (1)	-0.1508	0.2567	321	532	100.0%	0.86 [0.52 , 1.42]
Subtotal (95% CI)			**321**	**532**	**100.0%**	**0.86 [0.52 , 1.42]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						



Footnotes
(1) Follow-up timepoint: over 24 months.

Analysis 4.2. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 2: Time to relapse over 24 months

Study or Subgroup	log[Hazard Ratio]	SE	Rituximab Total	Other DMTs Total	Weight	Hazard Ratio IV, Fixed, 95% CI
4.2.1 Rituximab vs interferons beta or glatiramer acetate						
Spelman 2018 (1)	-1.7148	0.511	461	922	100.0%	0.18 [0.07 , 0.49]
Subtotal (95% CI)			**461**	**922**	**100.0%**	**0.18 [0.07 , 0.49]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.36 (P = 0.0008)						
4.2.2 Rituximab vs fingolimod						
Alping 2016 (2)	-2.5257	0.7073	69	95	100.0%	0.08 [0.02 , 0.32]
Subtotal (95% CI)			**69**	**95**	**100.0%**	**0.08 [0.02 , 0.32]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.57 (P = 0.0004)						
4.2.3 Rituximab vs natalizumab						
Boremalm 2019 (1)	0	0.8212	48	105	100.0%	1.00 [0.20 , 5.00]
Subtotal (95% CI)			**48**	**105**	**100.0%**	**1.00 [0.20 , 5.00]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi^2 = 5.56, df = 2 (P = 0.06), I^2 = 64.0%						



Footnotes
(1) Over 24 months, results from propensity score model.
(2) Over 18 months, results from propensity score model.

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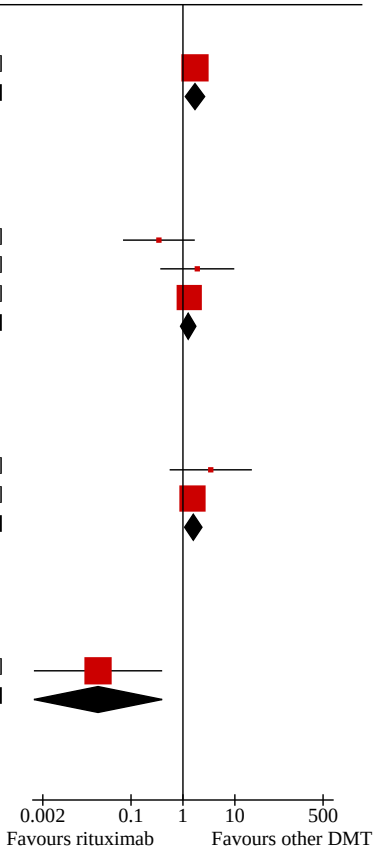
Analysis 4.3. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 3: Common infections

Study or Subgroup	log[OR]	SE	Rituximab Total	Other DMT Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.3.1 Rituximab vs interferons beta or glatiramer acetate						
Luna 2020	0.5342	0.218	3260	2217	100.0%	1.71 [1.11 , 2.62]
Subtotal (95% CI)			**3260**	**2217**	**100.0%**	**1.71 [1.11 , 2.62]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.45 (P = 0.01)						
4.3.2 Rituximab vs fingolimod						
Alping 2016	-1.066	0.8119	114	142	4.6%	0.34 [0.07 , 1.69]
Boremalm 2019	0.636	0.8371	48	88	4.3%	1.89 [0.37 , 9.74]
Luna 2020	0.279	0.1818	3260	1535	91.1%	1.32 [0.93 , 1.89]
Subtotal (95% CI)			**3422**	**1765**	**100.0%**	**1.26 [0.90 , 1.77]**
Heterogeneity: Chi² = 2.86, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 1.34 (P = 0.18)						
4.3.3 Rituximab vs natalizumab						
Boremalm 2019	1.2335	0.9302	48	105	4.4%	3.43 [0.55 , 21.26]
Luna 2020	0.4233	0.2	3260	1588	95.6%	1.53 [1.03 , 2.26]
Subtotal (95% CI)			**3308**	**1693**	**100.0%**	**1.58 [1.08 , 2.32]**
Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						
4.3.4 Rituximab vs ocrelizumab						
Evertsson 2020	-3.7653	1.4509	311	161	100.0%	0.02 [0.00 , 0.40]
Subtotal (95% CI)			**311**	**161**	**100.0%**	**0.02 [0.00 , 0.40]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.60 (P = 0.009)						



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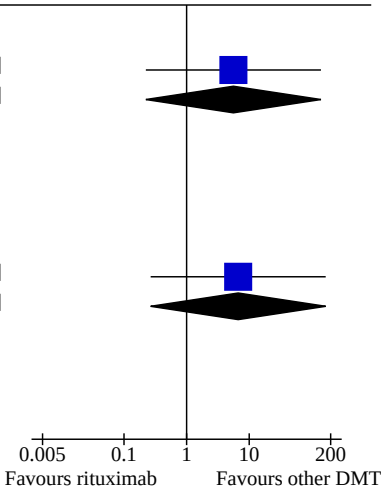
Analysis 4.4. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 4: Mortality

Study or Subgroup	Rituximab Events	Rituximab Total	Other DMTs Events	Other DMTs Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.4.1 Rituximab vs fingolimod						
Boremalm 2019 (1)	1	48	0	88	100.0%	5.59 [0.22 , 139.89]
Subtotal (95% CI)		**48**		**88**	**100.0%**	**5.59 [0.22 , 139.89]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
4.4.2 Rituximab vs natalizumab						
Boremalm 2019 (2)	1	48	0	105	100.0%	6.66 [0.27 , 166.58]
Subtotal (95% CI)		**48**		**105**	**100.0%**	**6.66 [0.27 , 166.58]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%						



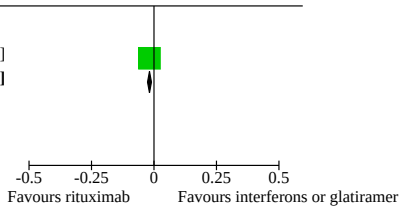
Footnotes

(1) Rituximab group: one suicide due to overdosing of sedative drugs in a person with a severe concomitant psychiatric illness.

(2) Rituximab group: one suicide due to overdosing of sedative drugs in a patient with a severe concomitant psychiatric illness

Analysis 4.5. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 5: Annualised relapse rate (change from baseline) – by type of DMT

Study or Subgroup	RItuximab Mean	RItuximab SD	RItuximab Total	Other DMTs Mean	Other DMTs SD	Other DMTs Total	Weight	Mean Difference IV, Fixed, 95% CI
4.5.1 Rituximab vs interferons beta or glatiramer acetate								
Spelman 2018 (1)	0.004	0.0656	461	0.022	0.0774	922	100.0%	-0.02 [-0.03 , -0.01]
Subtotal (95% CI)			**461**			**922**	**100.0%**	**-0.02 [-0.03 , -0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.52 (P < 0.00001)								

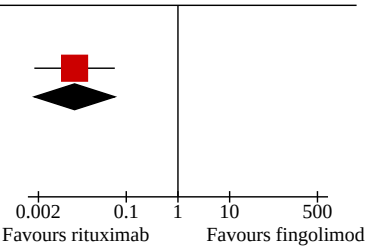


Footnotes

(1) Over 24 months, results from propensity score model.

Analysis 4.6. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 6: T2 MRI lesions

Study or Subgroup	log[OR]	SE	Rituximab Total	Other DMTs Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.6.1 Rituximab vs fingolimod						
Alping 2016 (1)	-4.6052	0.9142	75	107	100.0%	0.01 [0.00 , 0.06]
Subtotal (95% CI)			**75**	**107**	**100.0%**	**0.01 [0.00 , 0.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.04 (P < 0.00001)						



Footnotes

(1) Over 18 months.

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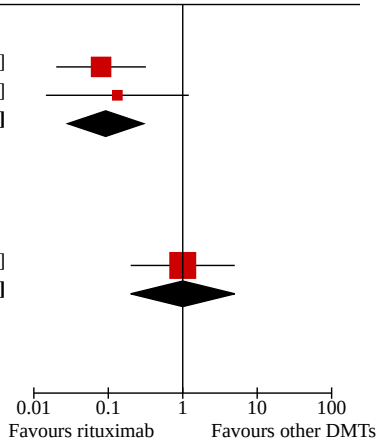
Analysis 4.7. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 7: Gadolinium MRI lesions

Study or Subgroup	log[OR]	SE	Rituximab Total	Other DMTs Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.7.1 Rituximab vs fingolimod						
Alping 2016 (1)	-2.5257	0.7073	69	95	71.7%	0.08 [0.02 , 0.32]
Boremalm 2019	-2.0225	1.1272	43	81	28.3%	0.13 [0.01 , 1.21]
Subtotal (95% CI)			**112**	**176**	**100.0%**	**0.09 [0.03 , 0.30]**
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 3.98 (P < 0.0001)						
4.7.2 Rituximab vs natalizumab						
Boremalm 2019 (2)	0	0.8212	43	95	100.0%	1.00 [0.20 , 5.00]
Subtotal (95% CI)			**43**	**95**	**100.0%**	**1.00 [0.20 , 5.00]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 5.50, df = 1 (P = 0.02), I² = 81.8%						



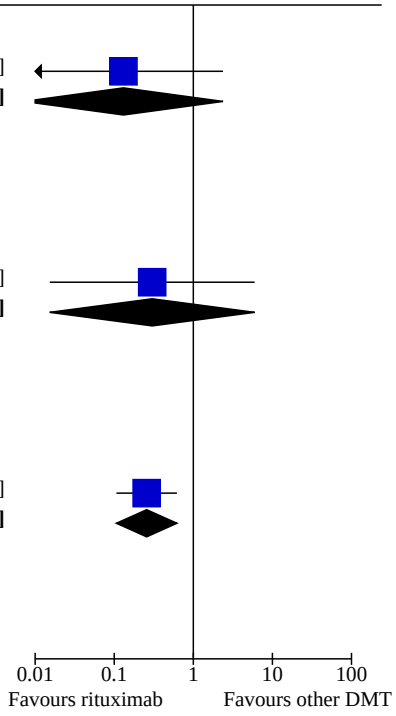
Footnotes

(1) Over 18 months; results from propensity score model.

(2) Results from propensity score model.

Analysis 4.8. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 8: Treatment discontinuation due to adverse events – by type of DMT

Study or Subgroup	Rituximab Events	Rituximab Total	Other DMTs Events	Other DMTs Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.8.1 Rituximab vs fingolimod						
Boremalm 2019	0	48	6	88	100.0%	0.13 [0.01 , 2.37]
Subtotal (95% CI)		**48**		**88**	**100.0%**	**0.13 [0.01 , 2.37]**
Total events:	0		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
4.8.2 Rituximab vs natalizumab						
Boremalm 2019	0	48	3	105	100.0%	0.30 [0.02 , 5.96]
Subtotal (95% CI)		**48**		**105**	**100.0%**	**0.30 [0.02 , 5.96]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
4.8.3 Rituximab vs ocrelizumab						
Evertsson 2020	8	311	15	161	100.0%	0.26 [0.11 , 0.62]
Subtotal (95% CI)		**311**		**161**	**100.0%**	**0.26 [0.11 , 0.62]**
Total events:	8		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.02 (P = 0.002)						
Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%						



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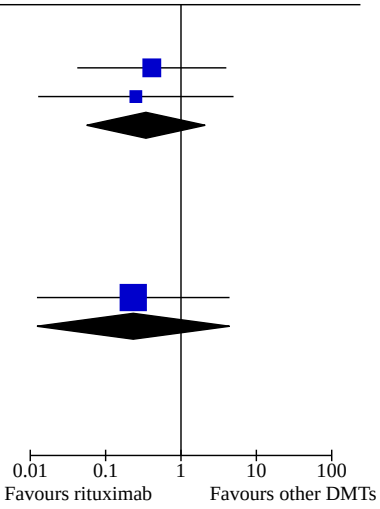
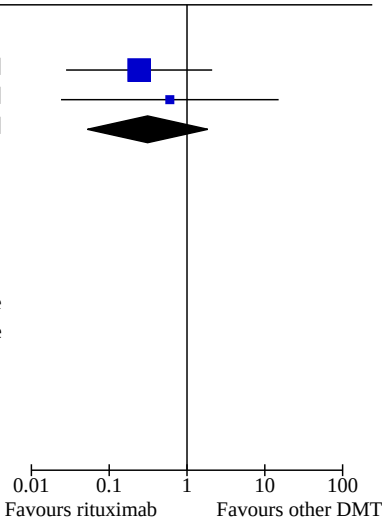
Analysis 4.9. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 9: Grade 3–4 adverse events over 24 months

Study or Subgroup	Rituximab Events	Rituximab Total	Other DMTs Events	Other DMTs Total	Weight	Odds Ratio M-H, Random, 95% CI
4.9.1 Rituximab vs fingolimod						
Alping 2016	1	114	3	142	63.2%	0.41 [0.04 , 4.00]
Boremalm 2019	0	48	3	88	36.8%	0.25 [0.01 , 4.98]
Subtotal (95% CI)		**162**		**230**	**100.0%**	**0.34 [0.06 , 2.09]**
Total events:	1		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
4.9.2 Rituximab vs natalizumab						
Boremalm 2019	0	48	4	105	100.0%	0.23 [0.01 , 4.41]
Subtotal (95% CI)		**48**		**105**	**100.0%**	**0.23 [0.01 , 4.41]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%						



Analysis 4.10. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 10: Cardiovascular events – by type of DMT

Study or Subgroup	Rituximab Events	Rituximab Total	Other DMTs Events	Other DMTs Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.10.1 Rituximab vs fingolimod						
Alping 2016	1	114	5	142	80.7%	0.24 [0.03 , 2.11]
Boremalm 2019	0	48	1	88	19.3%	0.60 [0.02 , 15.05]
Subtotal (95% CI)		**162**		**230**	**100.0%**	**0.31 [0.05 , 1.85]**
Total events:	1		6			
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
4.10.2 Rituximab vs natalizumab						
Boremalm 2019	0	48	0	105		Not estimable
Subtotal (95% CI)		**48**		**105**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



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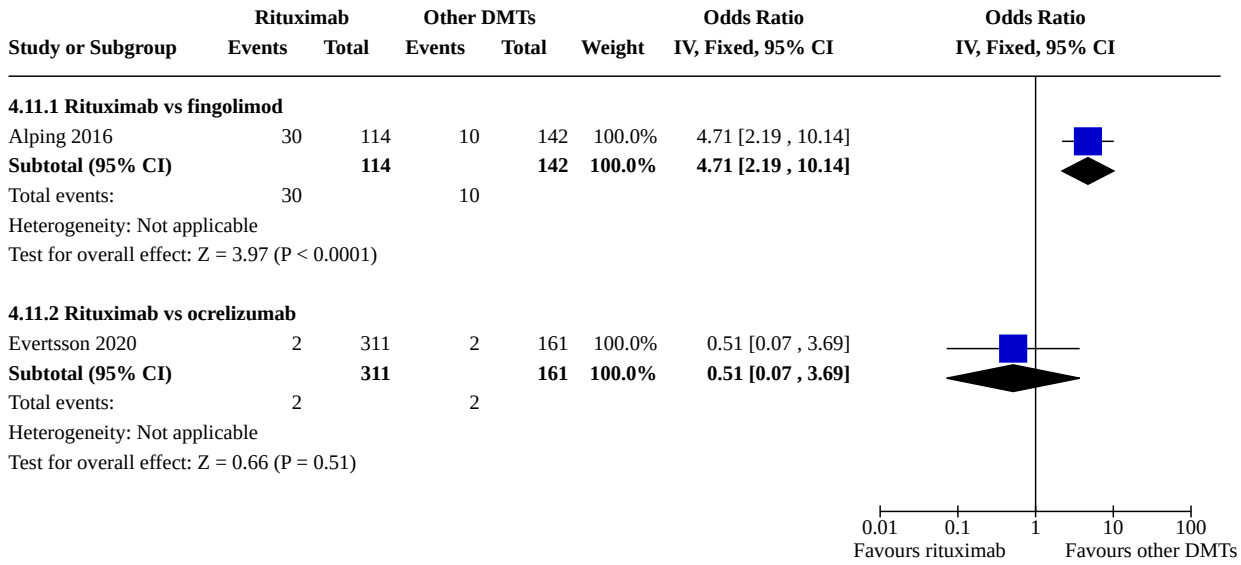
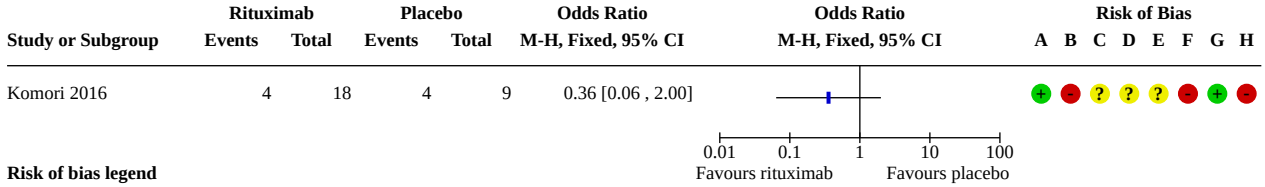
Analysis 4.11. Comparison 4: Comparison: rituximab as 'switching' versus other DMTs for relapsing MS – results from NRSI, Outcome 11: First infusion reactions



Comparison 5. Comparison: rituximab as 'switching' versus placebo for secondary progressive MS – results from RCTs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Serious adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2 Cancer	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.3 Cardiovascular events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 5.1. Comparison 5: Comparison: rituximab as 'switching' versus placebo for secondary progressive MS – results from RCTs, Outcome 1: Serious adverse events



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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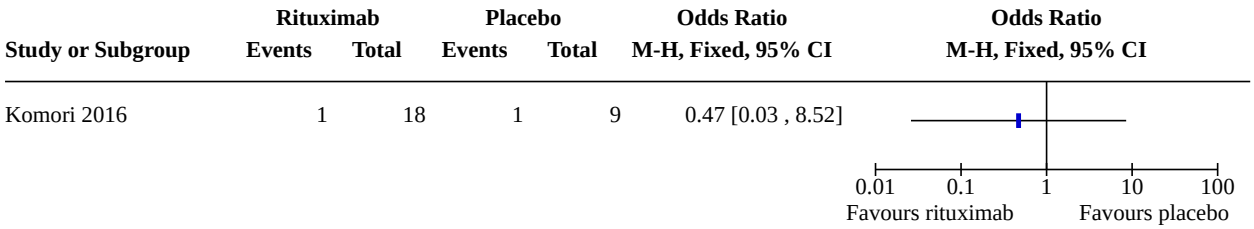
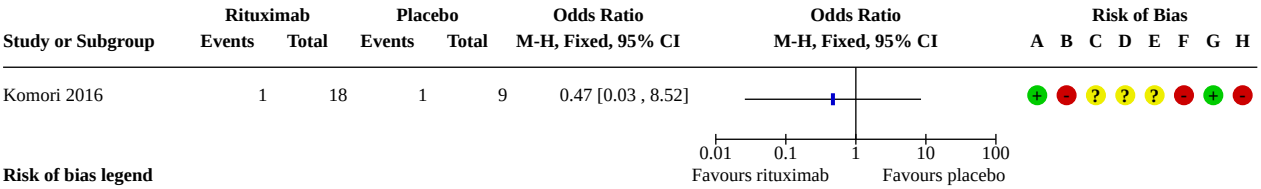
Analysis 5.2. Comparison 5: Comparison: rituximab as 'switching' versus placebo for secondary progressive MS – results from RCTs, Outcome 2: Cancer



Analysis 5.3. Comparison 5: Comparison: rituximab as 'switching' versus placebo for secondary progressive MS – results from RCTs, Outcome 3: Cardiovascular events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 6. Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from RCTs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Serious adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1.1 Rituximab vs glatiramer acetate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2 Common infections – by different DMTs	2		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
6.2.1 Rituximab vs glatiramer acetate	1	84	Odds Ratio (IV, Fixed, 95% CI)	3.00 [0.30, 30.08]
6.2.2 Rituximab vs cyclophosphamide	1	69	Odds Ratio (IV, Fixed, 95% CI)	0.39 [0.14, 1.11]
6.3 Annualised relapse rate	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.3.1 Rituximab vs glatiramer acetate	1	84	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.09, 0.47]

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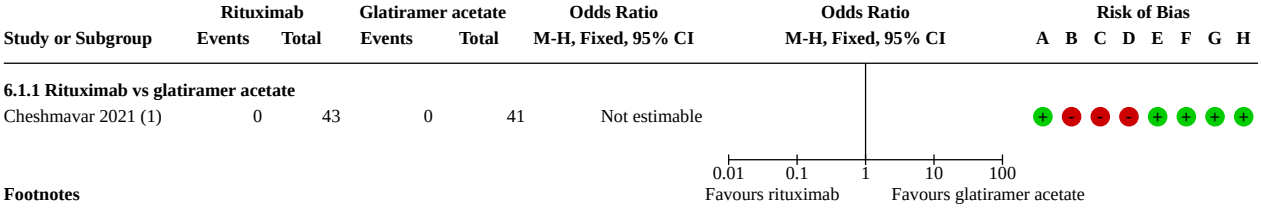
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 Gadolinium MRI lesions	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
6.5 Treatment discontinuation due to adverse events	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
6.5.1 Rituximab vs glatiramer acetate	1	84	Odds Ratio (IV, Fixed, 95% CI)	0.95 [0.13, 7.09]
6.6 Opportunistic infections	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
6.6.1 Rituximab vs glatiramer acetate	1	84	Odds Ratio (IV, Fixed, 95% CI)	Not estimable

Analysis 6.1. Comparison 6: Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from RCTs , Outcome 1: Serious adverse events



Footnotes

(1) Follow-up timepoint: over 12 months.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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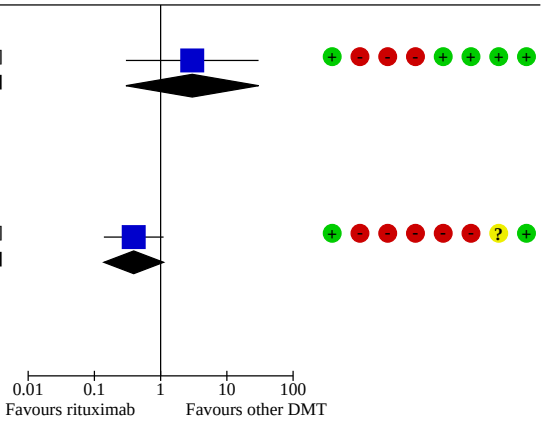
Analysis 6.2. Comparison 6: Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from RCTs , Outcome 2: Common infections – by different DMTs

Study or Subgroup	Rituximab Events	Rituximab Total	Other DMTs Events	Other DMTs Total	Weight	Odds Ratio IV, Fixed, 95% CI
6.2.1 Rituximab vs glatiramer acetate						
Cheshmavar 2021 (1)	3	43	1	41	100.0%	3.00 [0.30 , 30.08]
Subtotal (95% CI)		**43**		**41**	**100.0%**	**3.00 [0.30 , 30.08]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
6.2.2 Rituximab vs cyclophosphamide						
Etemadifar 2019 (2)	9	39	13	30	100.0%	0.39 [0.14 , 1.11]
Subtotal (95% CI)		**39**		**30**	**100.0%**	**0.39 [0.14 , 1.11]**
Total events:	9		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						

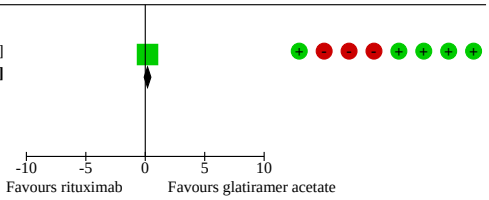


Footnotes
(1) Follow-up timepoint: over 12 months.
(2) Follow-up timepoint: over 24 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.3. Comparison 6: Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from RCTs , Outcome 3: Annualised relapse rate

Study or Subgroup	Rituximab Mean	Rituximab SD	Rituximab Total	Glatiramer acetate Mean	Glatiramer acetate SD	Glatiramer acetate Total	Weight	Mean Difference IV, Fixed, 95% CI
6.3.1 Rituximab vs glatiramer acetate								
Cheshmavar 2021 (1)	0.56	0.73	43	0.37	0.58	41	100.0%	0.19 [-0.09 , 0.47]
Subtotal (95% CI)			**43**			**41**	**100.0%**	**0.19 [-0.09 , 0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.32 (P = 0.19)								



Footnotes
(1) Follow-up timepoint: over 12 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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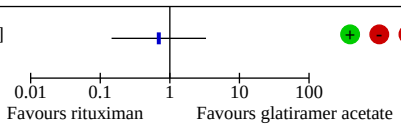
Analysis 6.4. Comparison 6: Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from RCTs , Outcome 4: Gadolinium MRI lesions

Study or Subgroup	Rituximab Events	Rituximab Total	Glatiramer acetate Events	Glatiramer acetate Total	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Cheshmavar 2021 (1)	3	43	4	41	0.69 [0.15 , 3.31]		+ - - - + + + +

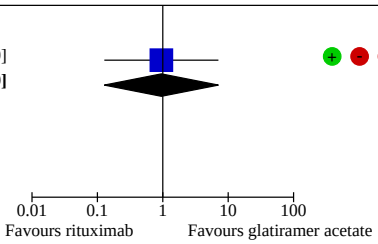


Footnotes
(1) Follow-up timepoint: over 12 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.5. Comparison 6: Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from RCTs , Outcome 5: Treatment discontinuation due to adverse events

Study or Subgroup	Rituximab Events	Rituximab Total	Glatiramer acetate Events	Glatiramer acetate Total	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
6.5.1 Rituximab vs glatiramer acetate								
Cheshmavar 2021 (1)	2	43	2	41	100.0%	0.95 [0.13 , 7.09]		+ - - - + + + +
Subtotal (95% CI)		**43**		**41**	**100.0%**	**0.95 [0.13 , 7.09]**		
Total events:	2		2					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.05 (P = 0.96)								



Footnotes
(1) Follow-up timepoint: over 12 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

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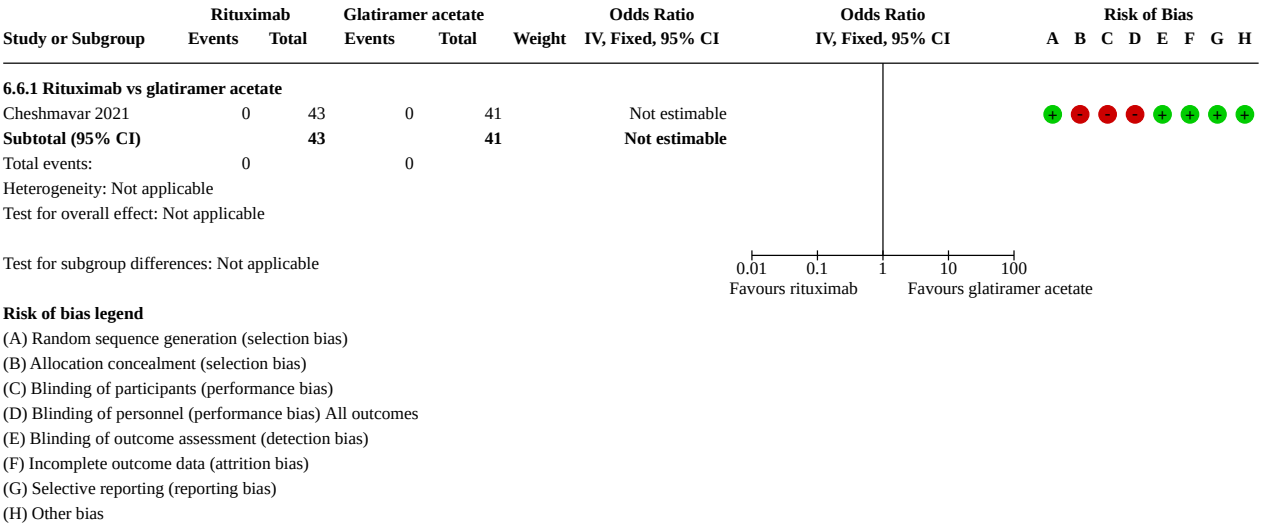
Analysis 6.6. Comparison 6: Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from RCTs , Outcome 6: Opportunistic infections

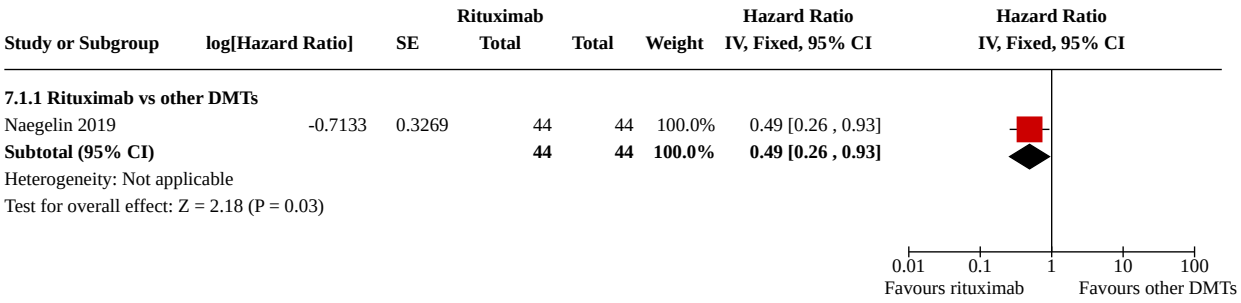


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of personnel (performance bias) All outcomes
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 7. Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from NRSIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Time to disability worsening over 36 months in secondary progressive MS	1		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
7.1.1 Rituximab vs other DMTs	1	88	Hazard Ratio (IV, Fixed, 95% CI)	0.49 [0.26, 0.93]

Analysis 7.1. Comparison 7: Comparison: rituximab as 'switching' versus other DMTs for secondary progressive MS – results from NRSIs, Outcome 1: Time to disability worsening over 36 months in secondary progressive MS



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Comparison 8. Comparison: rituximab as 'switching' versus other DMTs for grouped data as relapsing or progressive MS – results from NRSIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Relapse over 24 months – by type of DMT (unadjusted data)	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
8.1.1 Rituximab vs fingolimod	1	453	Odds Ratio (IV, Fixed, 95% CI)	0.35 [0.14, 0.88]
8.1.2 Rituximab vs dimethyl fumarate	1	524	Odds Ratio (IV, Fixed, 95% CI)	0.23 [0.10, 0.55]
8.1.3 Rituximab vs natalizumab	1	633	Odds Ratio (IV, Fixed, 95% CI)	0.54 [0.22, 1.32]
8.2 Common infections – by type of DMT	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
8.2.1 Rituximab vs fingolimod	1	454	Odds Ratio (IV, Fixed, 95% CI)	1.06 [0.34, 3.30]
8.2.2 Rituximab vs dimethyl fumarate	1	524	Odds Ratio (IV, Fixed, 95% CI)	2.39 [0.63, 9.00]
8.2.3 Rituximab vs natalizumab	1	633	Odds Ratio (IV, Fixed, 95% CI)	4.22 [1.00, 17.84]
8.3 Cancer – by type of DMT	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
8.3.1 Rituximab vs fingolimod	1	5807	Odds Ratio (IV, Fixed, 95% CI)	0.60 [0.35, 1.03]
8.3.2 Rituximab vs natalizumab	1	5857	Odds Ratio (IV, Fixed, 95% CI)	0.74 [0.42, 1.31]
8.4 T2 MRI lesions – by DMT (unadjusted data)	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
8.4.1 Rituximab vs fingolimod	1	453	Odds Ratio (IV, Fixed, 95% CI)	0.40 [0.25, 0.62]
8.4.2 Rituximab vs dimethyl fumarate	1	524	Odds Ratio (IV, Fixed, 95% CI)	0.46 [0.30, 0.72]
8.4.3 Rituximab vs natalizumab	1	633	Odds Ratio (IV, Fixed, 95% CI)	0.63 [0.41, 0.98]
8.5 Gadolinium MRI lesions (unadjusted data)	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
8.5.1 Rituximab vs dimethyl fumarate	1	524	Odds Ratio (IV, Fixed, 95% CI)	0.05 [0.01, 0.37]
8.5.2 Rituximab vs fingolimod	1	453	Odds Ratio (IV, Fixed, 95% CI)	0.04 [0.00, 0.27]
8.5.3 Rituximab vs natalizumab	1	633	Odds Ratio (IV, Fixed, 95% CI)	0.09 [0.01, 0.67]
8.6 Discontinuation due to adverse events – by type of DMT	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
8.6.1 Rituximab vs fingolimod	1	453	Odds Ratio (IV, Fixed, 95% CI)	0.28 [0.13, 0.60]

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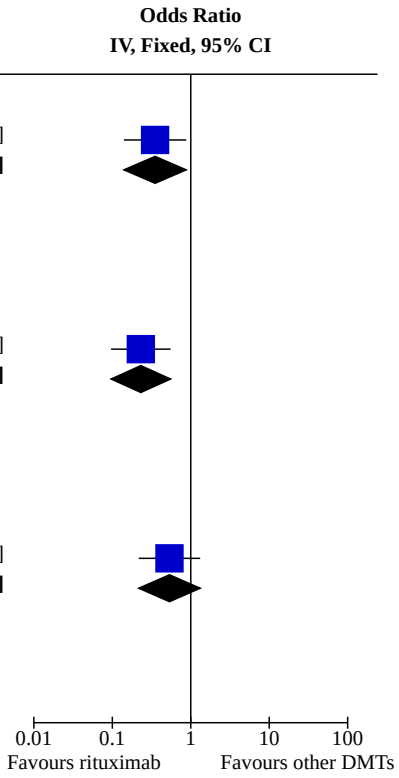
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.6.2 Rituximab vs dimethyl fumarate	1	524	Odds Ratio (IV, Fixed, 95% CI)	0.30 [0.15, 0.60]
8.6.3 Rituximab vs natalizumab	1	633	Odds Ratio (IV, Fixed, 95% CI)	1.10 [0.48, 2.52]
8.7 Cardiovascular events – by DMT	1		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
8.7.1 Rituximab vs fingolimod	1	441	Odds Ratio (IV, Fixed, 95% CI)	0.16 [0.01, 3.04]
8.7.2 Rituximab vs dimethyl fumarate	1	523	Odds Ratio (IV, Fixed, 95% CI)	Not estimable
8.7.3 Rituximab vs natalizumab	1	633	Odds Ratio (IV, Fixed, 95% CI)	0.82 [0.03, 20.29]

Analysis 8.1. Comparison 8: Comparison: rituximab as 'switching' versus other DMTs for grouped data as relapsing or progressive MS – results from NRSIs, Outcome 1: Relapse over 24 months – by type of DMT (unadjusted data)

Study or Subgroup	Rituximab Events	Rituximab Total	Other DMTs Events	Other DMTs Total	Weight	Odds Ratio IV, Fixed, 95% CI
8.1.1 Rituximab vs fingolimod						
Vollmer 2020a	6	182	24	271	100.0%	0.35 [0.14 , 0.88]
Subtotal (95% CI)		**182**		**271**	**100.0%**	**0.35 [0.14 , 0.88]**
Total events:	6		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.24 (P = 0.02)						
8.1.2 Rituximab vs dimethyl fumarate						
Vollmer 2020a	6	182	44	342	100.0%	0.23 [0.10 , 0.55]
Subtotal (95% CI)		**182**		**342**	**100.0%**	**0.23 [0.10 , 0.55]**
Total events:	6		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.29 (P = 0.0010)						
8.1.3 Rituximab vs natalizumab						
Vollmer 2020a	6	182	27	451	100.0%	0.54 [0.22 , 1.32]
Subtotal (95% CI)		**182**		**451**	**100.0%**	**0.54 [0.22 , 1.32]**
Total events:	6		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						



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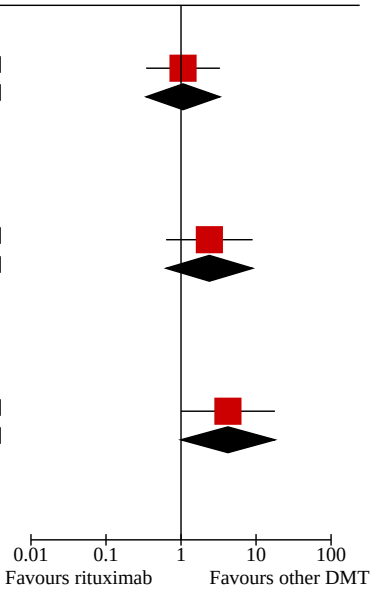
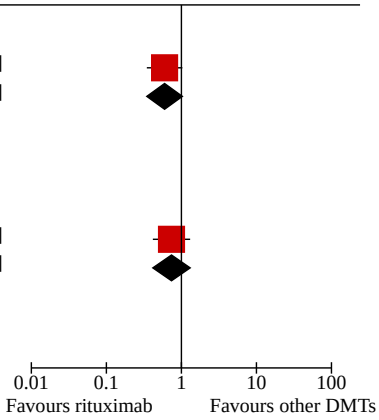
Analysis 8.2. Comparison 8: Comparison: rituximab as 'switching' versus other DMTs for grouped data as relapsing or progressive MS – results from NRSIs, Outcome 2: Common infections – by type of DMT

Study or Subgroup	log[OR]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
8.2.1 Rituximab vs fingolimod						
Vollmer 2020a	0.0616	0.5776	182	272	100.0%	1.06 [0.34 , 3.30]
Subtotal (95% CI)			**182**	**272**	**100.0%**	**1.06 [0.34 , 3.30]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.92)						
8.2.2 Rituximab vs dimethyl fumarate						
Vollmer 2020a	0.87	0.6772	182	342	100.0%	2.39 [0.63 , 9.00]
Subtotal (95% CI)			**182**	**342**	**100.0%**	**2.39 [0.63 , 9.00]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
8.2.3 Rituximab vs natalizumab						
Vollmer 2020a	1.4395	0.7357	182	451	100.0%	4.22 [1.00 , 17.84]
Subtotal (95% CI)			**182**	**451**	**100.0%**	**4.22 [1.00 , 17.84]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						



Analysis 8.3. Comparison 8: Comparison: rituximab as 'switching' versus other DMTs for grouped data as relapsing or progressive MS – results from NRSIs, Outcome 3: Cancer – by type of DMT

Study or Subgroup	log[OR]	SE	Rituximab Total	Other DMT Total	Weight	Odds Ratio IV, Fixed, 95% CI
8.3.1 Rituximab vs fingolimod						
Alping 2020	-0.5162	0.2781	4187	1620	100.0%	0.60 [0.35 , 1.03]
Subtotal (95% CI)			**4187**	**1620**	**100.0%**	**0.60 [0.35 , 1.03]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
8.3.2 Rituximab vs natalizumab						
Alping 2020	-0.304	0.2919	4187	1670	100.0%	0.74 [0.42 , 1.31]
Subtotal (95% CI)			**4187**	**1670**	**100.0%**	**0.74 [0.42 , 1.31]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						



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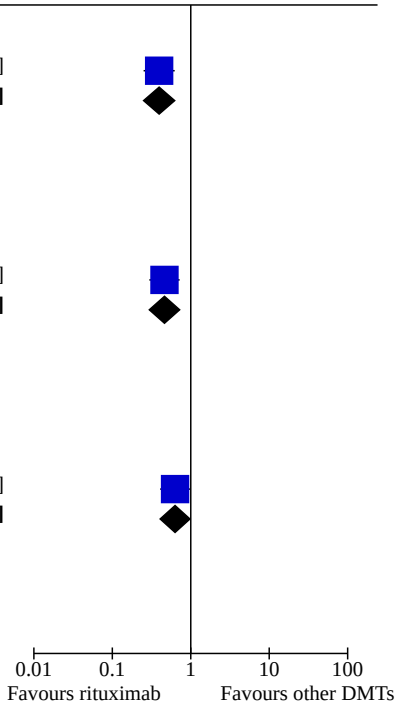
Analysis 8.4. Comparison 8: Comparison: rituximab as 'switching' versus other DMTs for grouped data as relapsing or progressive MS – results from NRSIs, Outcome 4: T2 MRI lesions – by DMT (unadjusted data)

Study or Subgroup	Rituximab Events	Rituximab Total	Other DMTs Events	Other DMTs Total	Weight	Odds Ratio IV, Fixed, 95% CI
8.4.1 Rituximab vs fingolimod						
Vollmer 2020a	32	182	95	271	100.0%	0.40 [0.25 , 0.62]
Subtotal (95% CI)		**182**		**271**	**100.0%**	**0.40 [0.25 , 0.62]**
Total events:	32		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.99 (P < 0.0001)						
8.4.2 Rituximab vs dimethyl fumarate						
Vollmer 2020a	32	182	108	342	100.0%	0.46 [0.30 , 0.72]
Subtotal (95% CI)		**182**		**342**	**100.0%**	**0.46 [0.30 , 0.72]**
Total events:	32		108			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.40 (P = 0.0007)						
8.4.3 Rituximab vs natalizumab						
Vollmer 2020a	32	182	114	451	100.0%	0.63 [0.41 , 0.98]
Subtotal (95% CI)		**182**		**451**	**100.0%**	**0.63 [0.41 , 0.98]**
Total events:	32		114			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.07 (P = 0.04)						



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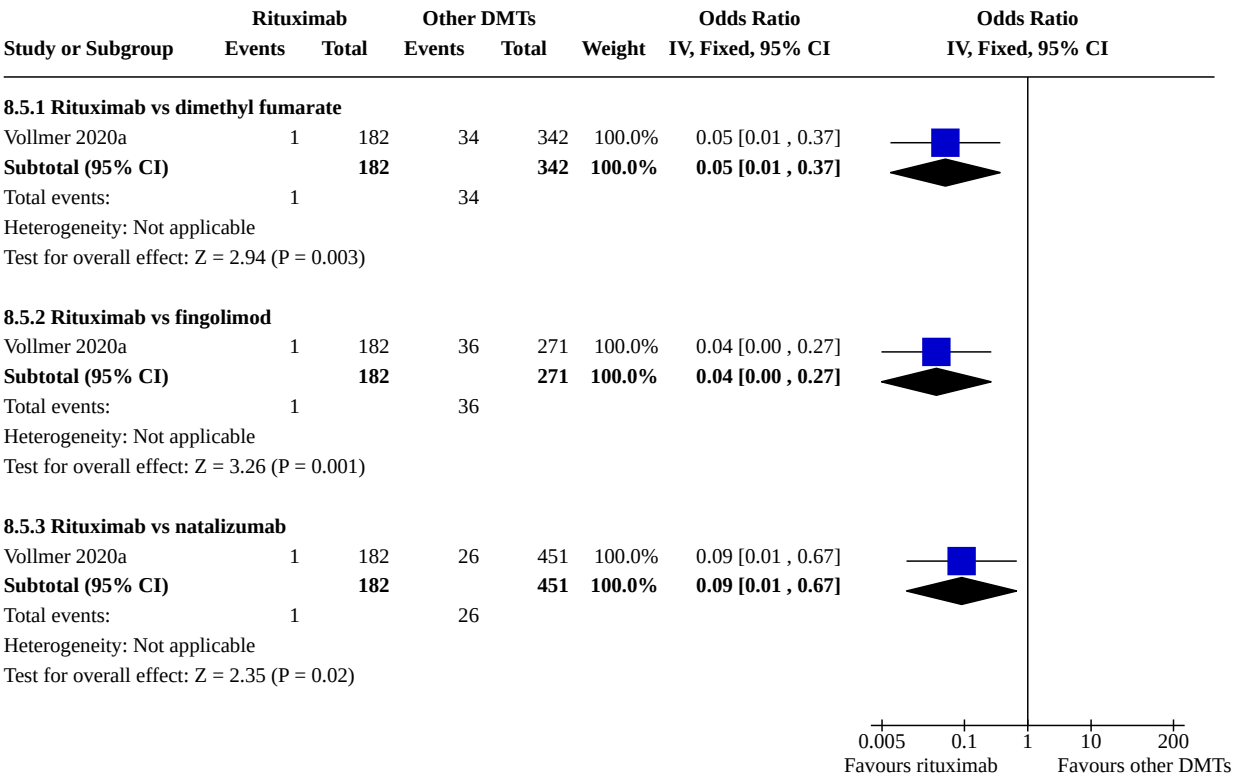
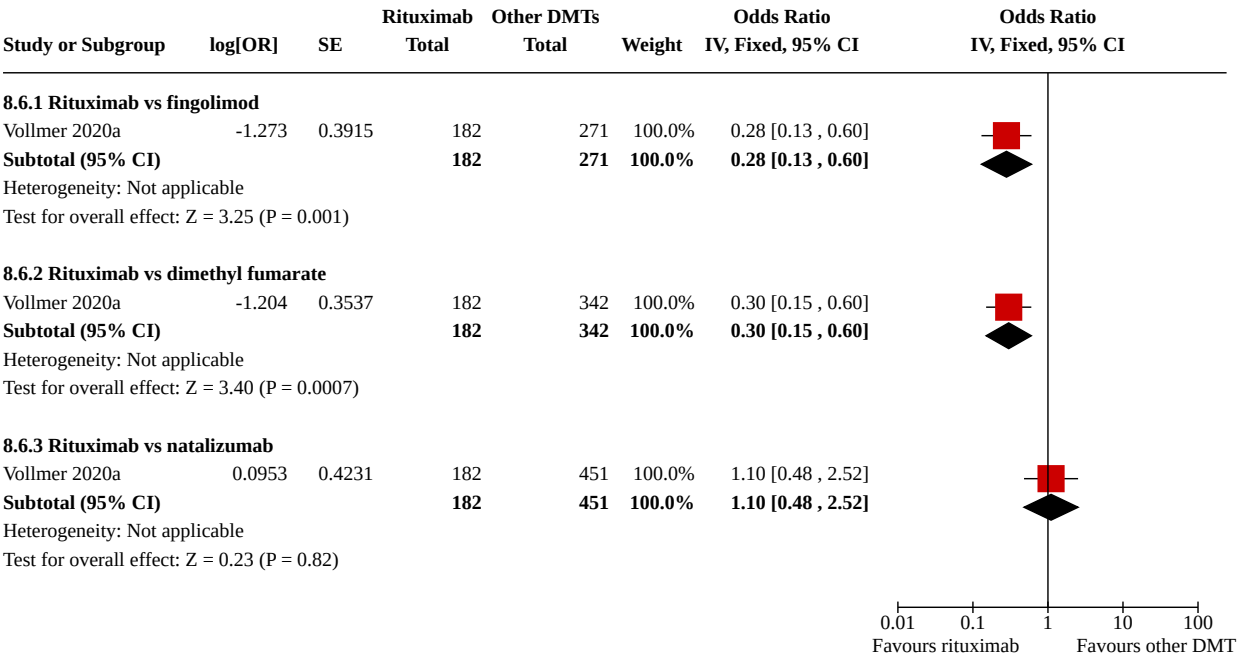
Analysis 8.5. Comparison 8: Comparison: rituximab as 'switching' versus other DMTs for grouped data as relapsing or progressive MS – results from NRSIs, Outcome 5: Gadolinium MRI lesions (unadjusted data)



Analysis 8.6. Comparison 8: Comparison: rituximab as 'switching' versus other DMTs for grouped data as relapsing or progressive MS – results from NRSIs, Outcome 6: Discontinuation due to adverse events – by type of DMT



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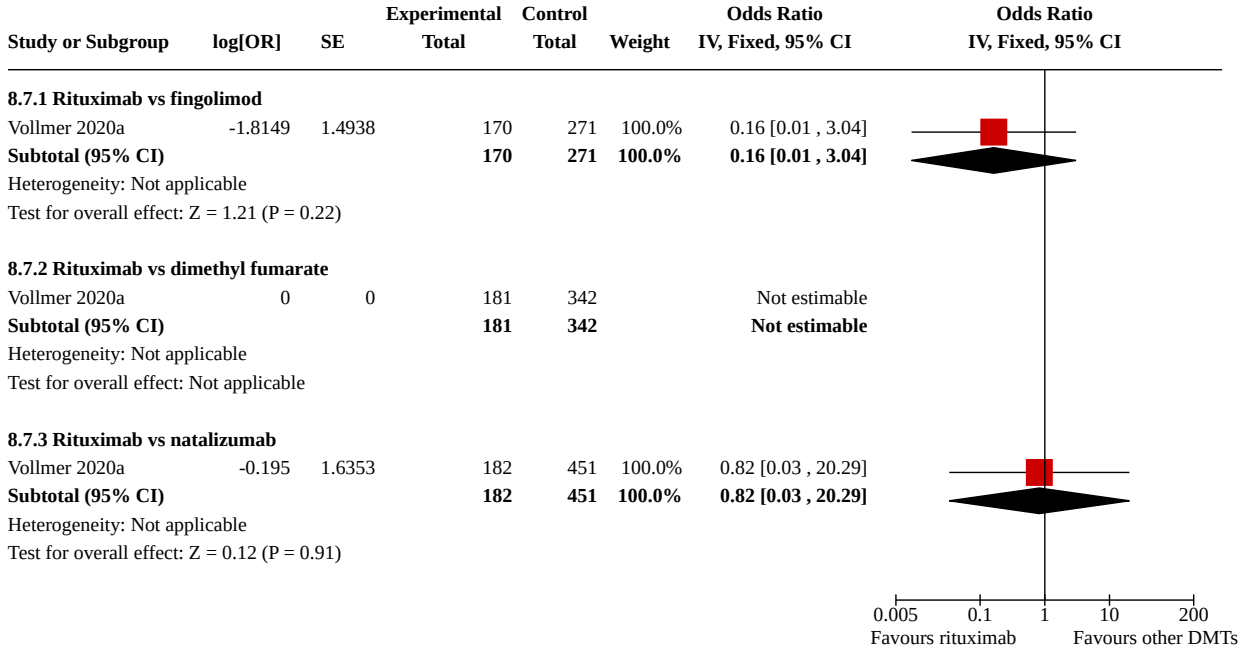
Analysis 8.7. Comparison 8: Comparison: rituximab as 'switching' versus other DMTs for grouped data as relapsing or progressive MS – results from NRSIs, Outcome 7: Cardiovascular events – by DMT



ADDITIONAL TABLES

Table 1. Treatment guidelines for multiple sclerosis

	European ECTRIMS/EAN Guideline (Montalban 2018)	**American Academy of Neurology practice guideline** (Rae-Grant 2018)	**Brazilian Consensus** (Marques 2018)	**The Middle East and North Africa Committee Consensus** (Yamout 2020)
Question 1	In people with CIS, what is the benefit of starting treatment with a DMT compared to no treatment?	In people with CIS, are DMTs superior to placebo in decreasing the risk of conversion to MS?	In people with CIS, are DMTs efficacious in preventing conversion to MS?	Should people with CIS be treated with DMTs?
Recommendation	Offer interferon or glatiramer acetate to people with CIS and an abnormal MRI with lesions suggestive of MS who do not fulfil criteria for MS.	1. Clinicians may recommend at least annual MRI for the first 5 years and follow-up rather than initiating DMT in people with CIS who have not had relapses in the preceding 2 years, and do not have active new MRI lesions on recent imaging. 2. After discussing the risks and benefits, clinicians should prescribe DMT to people with CIS and ≥ 2 brain lesions characteristic of MS who decide they want this therapy.	It seems reasonable to start DMTs only in people with high-risk CIS[a] as well as to choose safer drugs. Efficacy in CIS has been demonstrated with the interferon betas, cladribine, glatiramer acetate, and teriflunomide. Since no direct comparison between these is available, any of these drugs are	If the overall clinical and radiological picture is suggestive of MS, people with CIS and high MRI lesion load (> 9 T2 lesions), or with severe relapses with incomplete recovery, or both, should be treated.

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Table 1. Treatment guidelines for multiple sclerosis *(Continued)*

			deemed appropriate for the treatment of high-risk CIS[a].	
Quality of evidence	Strong	1. Level C: "may" 2. Level B: "should"	Not reported	Not reported
Question 2	In people with RRMS, what is the benefit of treating with a DMT compared to no treatment or another DMT?	In people with RRMS, are DMTs superior to placebo or other DMTs in preventing relapse at 2 years, reducing MRI new disease activity, and preventing disease progression?	In people with relapsing MS, are DMTs efficacious in reducing relapses, MRI disease activity, and disability?	Should people with RRMS be treated with DMTs?
Recommendation	1. Offer early treatment with DMTs to people with active RRMS[b]. 2. For active RRMS, choosing between the wide range of available DMTs, from the modestly effective to the highly efficacious, depends on individual characteristics and comorbidities, disease severity or activity, drug safety profile, and accessibility of the drug, in discussion with the person with active RRMS.	Clinicians should: 1. offer DMTs to people with RRMS with recent clinical relapses or MRI activity; 2. prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS[b]. Clinicians may: 3. recommend azathioprine or cladribine for people with RRMS who do not have access to approved DMTs.	1. It would seem reasonable to start treatment with interferons, glatiramer acetate, pegylated interferon beta, dimethyl fumarate, or teriflunomide, (good safety profile and more easily available, including in the Brazilian public health system). 2. Consider alemtuzumab, cladribine, fingolimod, natalizumab, and ocrelizumab for people with highly active relapsing MS[c].	1. In treatment-naive people, interferons, glatiramer acetate, teriflunomide, and dimethyl fumarate can be initiated. 2. In people with highly active disease[d] fingolimod, siponimod, natalizumab, ocrelizumab, or cladribine may be initiated. 3. In people with rapidly evolving aggressive disease[e] natalizumab, ocrelizumab, or alemtuzumab are recommended after careful risk stratification. 4. Rituximab can be used off-label for highly active disease and rapidly evolving aggressive disease in special populations such as refugees, or in countries where other appropriate options are not available.
Quality of evidence	1. Strong 2. Consensus statement	1. and 2. Level B: "should" 3. Level C: "may"	Not reported	Not reported
Question 3	In people with active SPMS, what is the benefit of	In people with SPMS, are DMTs efficacious?	In people with non-active SPMS, are DMTs efficacious?	Should people with SPMS be treated with DMTs?

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Table 1. Treatment guidelines for multiple sclerosis *(Continued)*

	treating with a DMT compared to no treatment or another DMT?			
Recommendation	Consider treatment with interferons, mitoxantrone, ocrelizumab, or cladribine for people with active SPMS.	1. Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS[b]. 2. Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses or MRI activity and have not been ambulatory (EDSS ≥ 7) for ≥ 2 years.	2. Not prescribing a DMT is an acceptable choice in people with SPMS who no longer present relapses. 2. In cases of rapidly progressive disease, cyclophosphamide, mitoxantrone, and autologous haematopoietic stem cell transplantation may be used as off-label treatments.	1. Consider treatment with ocrelizumab or siponimod in people with active SPMS, aged ≤ 60 years and EDSS ≤ 6.5 (i.e. not needing a wheelchair). 2. In people with rapidly progressive SPMS not responding to ocrelizumab or siponimod or who have no access to these medications, cyclophosphamide, methotrexate, or mycophenolate may be warranted.
Quality of evidence	Weak	1. Level B: "should" 2. Level C: "may"	Not reported	Not reported
Question 4	In people with PPMS, what is the benefit of treating with a DMT compared to no treatment?	In people with PPMS, are DMTs superior to placebo or other DMTs as measured by relapse rate or disease progression?	In people with PPMS, are DMTs efficacious in delaying the progression of disability?	Should people with PPMS be treated with DMTs?
Recommendation	Consider treatment with ocrelizumab for people with PPMS.	Clinicians should offer ocrelizumab to people with PPMS.	Ocrelizumab should be the treatment of choice for people with PPMS, after consideration of the expected benefits and potential risks on a case-by-case basis.	Consider treatment with ocrelizumab for people with PPMS, aged ≤ 55 years, EDSS ≤ 6.5 (i.e. not needing a wheelchair), and disease duration ≤ 10–15 years.
Quality of evidence	Weak	Level B: "should"	Not reported	Not reported
Question 5	1. In people with RRMS treated with interferon or glatiramer acetate and evidence of disease activity at 6 or 12 months, what is the benefit of switching to more efficacious drugs?	In people with RRMS who experience disease activity while on a DMT, is changing to a different DMT superior to continuing the present DMT in terms of relapse and MRI disease activity?	When to consider DMT switching in people with RRMS?	When to consider DMT switching in people with RRMS?

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Table 1. Treatment guidelines for multiple sclerosis *(Continued)*

	2. In people with relapsing MS who stop taking a highly efficacious drug, what is the benefit of further treatment?			
Recommendation	1. Offer a more efficacious drug to people treated with interferon or glatiramer acetate who show evidence of disease activity. 2. Consider starting another highly efficacious drug, taking into account disease activity, half-life and biological activity of the previous drug, and the potential for rebound (particularly with natalizumab).	1. Clinicians should discuss switching from 1 DMT to another in people with MS treated long enough for the treatment to take full effect when they experience ≥ 1 relapse, ≥ 2 new MRI lesions, or increased disability, over a 1-year period of using a DMT. 2. Clinicians should evaluate the degree of disease activity, adherence, AE profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use.	1. If the management of highly active MS[c] with potent DMTs has achieved a satisfactory response and stability for several years, it would be acceptable (though not mandatory) to consider switching to a lower potency DMT. 2. If a person with relapsing MS fails to achieve satisfactory responses, presents intolerance or safety concerns with interferons, dimethyl fumarate, glatiramer acetate, pegylated interferon, teriflunomide, a switch to alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab should be considered.	1. In people with moderately active disease and suboptimal response[f] to interferons, dimethyl fumarate, glatiramer acetate, teriflunomide, treatment escalation to fingolimod, siponimod, natalizumab, ocrelizumab, or cladribine should be considered. 2. Rituximab can be used off-label as an escalation therapy for all levels of MS activity, in special populations such as refugees, or in countries where other appropriate options are not available. 3. In people with evidence of suboptimal response to any of the second-line medications, off-label cyclophosphamide, autologous haematopoietic stem cell transplantation, or mitoxantrone should be considered.
Quality of evidence	1. Strong 2. Consensus statement	1. and 2. Level B: "should"	Not reported	Not reported
Question 6	—	In people with RRMS who experience AEs while on a DMT, is switching necessary?	—	—
Recommendation	—	Clinicians should: 1. discuss a change to non-injectable or less frequently injectable DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs;	—	—

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Table 1. Treatment guidelines for multiple sclerosis *(Continued)*

	2. discuss a medication switch with people with MS for whom AEs negatively influence adherence; 3. discuss switching DMT or reducing dosage or frequency when there are serious infections or persistent laboratory abnormalities; 4. discuss switching to a DMT with a lower risk of progressive multifocal leucoencephalopathy with people with MS taking natalizumab who are or become antibody–positive to John Cunningham (JCV) virus, while on therapy; 5. discuss switching to an alternate DMT for people with MS who develop a malignancy while using azathioprine, methotrexate, mycophenolate, cyclophosphamide, fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate; 6. switch DMTs in people with MS who have persistent natalizumab antibodies.
Quality of evidence	1., 2., 3., 4., 5., and 6. Level B: "should"

[a]High-risk CIS defined by one or more typical MRI T2 lesion(s), provided both the clinical presentation and MRI lesion(s) are suggestive of central nervous system demyelination and not attributable to other diseases.
[b]Active RRMS or highly active MS defined by clinical relapses or MRI activity (active lesions – contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually), or both.
[c]Highly active MS defined as: 1. at least two disabling relapses with incomplete resolution and at least one contrast-enhancing lesion or significant increase in T2 lesion load in the previous year in treatment-naive people; or 2. breakthrough disease activity in the previous year, under an adequate course of at least one DMT (in the absence of intolerance or non-adherence), presenting with at least one relapse in the previous year while on therapy and at least nine MRI T2 lesions or at least one contrast-enhancing lesion.
[d]Highly active disease defined as: 1. at least two relapses in the previous year; 2. relapse severity; 3. incomplete recovery; 4. at least 10 MRI T2 lesions; 5. multiple contrast enhancing lesions.
[e]Rapidly evolving aggressive disease defined as the presence of at least two disabling relapses with incomplete recovery in the previous year and at least 10 MRI T2 lesions.
[f]Suboptimal response to chronic DMTs should be considered after one year of treatment in people with at least one relapse or disability progression or both, or at least two active MRI lesions (gadolinium or new T2-weighted, or both) after one year of adequate treatment and using as baseline an MRI performed six months after treatment initiation.
AE: adverse events; CIS: clinically isolated syndrome; DMT: disease-modifying treatment; ECTRIMS/EAN: European Committee of Treatment of Research in Multiple Sclerosis and European Academy of Neurology; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

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Table 2. Rituximab as 'switching' for multiple sclerosis – results from RCTs and non-randomised studies of intervention

Patient or population: relapsing or progressive forms of multiple sclerosis
Settings: inpatient or outpatient
Intervention: rituximab as 'switching' from another DMT
Comparison: placebo or other DMTs as 'switching' treatment

Intervention	Comparison intervention	Anticipated absolute effects*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Assumed risk with comparator	Corresponding risk with rituximab (95% CI)				
Chance of sustained disability worsening over 24–36 months							
Rituximab	**Interferons or glatiramer acetate**	***RRMS***					
		90 per 1000	**78 per 1000** (48 to 125)	**HR 0.86** (0.52 to 1.42)	853 (1 retrospective cohort study)[a]	⊕⊝⊝⊝ **Very low** [b,c]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on disability worsening at 24 months' follow-up, when compared with interferon beta or glatiramer acetate.
Rituximab	**Other DMTs**	***SPMS***					
		360 per 1000	**196 per 1000** (110 to 340)	**HR 0.49** (0.26 to 0.93)	88 (1 retrospective cohort study)[d]	⊕⊝⊝⊝ **Very low** [e,f]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on disability worsening at 36 months' follow-up, when compared with other DMTs.
Chance of experiencing ≥ 1 relapses over 12–24 months							
Rituximab	**Placebo**	***RRMS***					
		400 per 1000	**202 per 1000** (96 to 383)	**OR 0.38** (0.16 to 0.93)	104 (1 RCT)[g]	⊕⊕⊝⊝ **Low** [f,h]	Our confidence in this result is low, downgraded 1 level for serious risk of bias and 1 level for serious imprecision. Rituximab may result in a large reduction in recurrence of relapse over 12 months' follow-up when compared with placebo

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Table 2. Rituximab as 'switching' for multiple sclerosis – results from RCTs and non-randomised studies of intervention *(Continued)*

Rituximab	**Interferons or glatiramer acetate**	***RRMS***					
		270 per 1000	**55 per 1000** (22 to 143)	**HR 0.18** (0.07 to 0.49)	1383 (1 retrospective cohort study)[a]	⊕⊕⊕⊖ **Moderate** [e]	Our confidence in this result is moderate, downgraded 1 level due to serious risk of bias. Rituximab likely results in a very large reduction in recurrence of relapses over 24 months' follow-up, when compared with interferons or glatiramer. The NNTB is 11 (95% CI 10 to 18).
Rituximab	**Fingolimod**	***RRMS***					
		176 per 1000	**15 per 1000** (4 to 60)	**HR 0.08** (0.02 to 0.32)	256 (1 retrospective cohort study)[i]	⊕⊕⊕⊖ **Moderate** [e]	Our confidence in this result is moderate, downgraded 1 level due to serious risk of bias. Rituximab likely results in a large reduction in recurrence of relapses over 24 months' follow-up, when compared with fingolimod. The NNTB is 6 (95% CI 6 to 9).
Rituximab	**Natalizumab**	***RRMS***					
		60 per 1000	**60 per 1000** (12 to 266)	**HR 1.0** (0.2 to 5.0)	153 (1 retrospective cohort study)[j]	⊕⊖⊖⊖ **Very low** [c,e]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on recurrence of relapses over 24 months' follow-up, when compared with natalizumab.
Rituximab	**Fingolimod**	***MS of all types***					
		89 per 1000	**33 per 1000** (13 to 79)	**OR 0.35** (0.14 to 0.88)	453 (1 retrospective cohort study)[k]	⊕⊖⊖⊖ **Very low** [f,l,m]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias, 1 level for indirectness, and 1 level for serious imprecision. The evidence is very uncertain about the effect of rituximab on recurrence of relapses over 24 months' follow-up, when compared with fingolimod.
Rituximab	**Dimethyl fumarate**	***MS of all types***					
		129 per 1000	**33 per 1000** (15 to 75)	**OR 0.23** (0.10 to 0.55)	524 (1 retrospective cohort study)[k]	⊕⊖⊖⊖ **Very low** [f,l,m]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias, 1 level for indirectness, and 1 level for serious imprecision. The evidence is very uncertain about the effect of rituximab on recurrence of relapses over

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Table 2. Rituximab as 'switching' for multiple sclerosis – results from RCTs and non-randomised studies of intervention *(Continued)*

							24 months' follow-up, when compared with dimethyl fumarate.
Rituximab	**Natalizumab**	***MS of all types***					
		60 per 1000	**33 per 1000** (14 to 78)	**OR 0.54** (0.22 to 1.32)	633 (1 retrospective cohort study)[k]	⊕⊖⊖⊖ **Very low** [f,l,m]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias, 1 level for indirectness, and 1 level for serious imprecision. The evidence is very uncertain about the effect of rituximab on recurrence of relapses over 24 months' follow-up, when compared with natalizumab.
SAEs over 12–24 months							
Rituximab	**Placebo**	***RRMS***					
		143 per 1000	**130 per 1000** (45 to 327)	**OR 0.90** (0.28 to 2.92)	104 (1 RCT)[g]	⊕⊖⊖⊖ **Very low** [h,n]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on SAEs, when compared with placebo.
		SPMS					
		444 per 1000	**224 per 1000** (46 to 615)	**OR 0.36** (0.06 to 2.00)	27 (1 RCT)[o]	⊕⊖⊖⊖ **Very low** [n,p]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on SAEs, when compared with placebo.
Rituximab	**Other DMTs**	***RRMS***					
		No data were available					
Rituximab	**Glatiramer acetate**	***SPMS***					
		0 per 1000	**0 per 1000** (0 to 0)	Not estimable	84 (1 RCT)[q]	—	Cheshmavar 2021 reported 0 SAEs over 12 months' follow-up.
Chance of impaired quality of life: none of the studies reported the outcome.							
Common infections over 12–24 months							

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Table 2. Rituximab as 'switching' for multiple sclerosis – results from RCTs and non-randomised studies of intervention *(Continued)*

Rituximab	**Placebo**	***RRMS***					
		714 per 1000	**695 per 1000** (481 to 848)	**OR 0.91** (0.37 to 2.24)	104 (1 RCT)[g]	⊕⊖⊖⊖ **Very low** [h,n]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on infections, when compared with placebo.
		SPMS					
		667 per 1000	**444 per 1000** (138 to 809)	**OR 0.40** (0.08 to 2.12)	27 (1 RCT)[o]	⊕⊖⊖⊖ **Very low** [n,p]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on infections, when compared with placebo.
Rituximab	**Interferon beta or glatiramer acetate**	***RRMS***					
		36 per 1000	**60 per 1000** (40 to 89)	**OR 1.71** (1.11 to 2.62)	5477 (The national Swedish MS Register linked to national healthcare and census registries)[r]	⊕⊕⊕⊖ **Moderate** [s]	Our confidence in this result is moderate, downgraded 1 level for serious risk of bias in measurement of the outcome. Rituximab likely increases infections when compared with interferons or glatiramer acetate.
Rituximab	**Fingolimod**	***RRMS***					
		56 per 1000	**70 per 1000** (51 to 95)	**OR 1.26** (0.90 to 1.77)	5187 (3 retrospective cohort studies)[i,j,m]	⊕⊕⊖⊖ **Low** [n,t]	Our confidence in this result is low, downgraded 1 level for serious risk of bias and 1 level for imprecision. Heterogeneity: P = 0.24, I^2 = 30%. Rituximab may increase slightly infections when compared with fingolimod.
Rituximab	**Natalizumab**	***RRMS***					
		50 per 1000	**77 per 1000** (51 to 95)	**OR 1.58** (1.08 to 2.32)	5001 (2 non-randomised studies: the nation-	⊕⊕⊕⊖ **Moderate** [t]	Our confidence in this result is moderate, downgraded 1 level for serious risk of bias. Heterogeneity: P = 0.39, I^2 = 0%. Rituximab likely increases the number of participants who have common infections when compared with natalizumab.

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Table 2. Rituximab as 'switching' for multiple sclerosis – results from RCTs and non-randomised studies of intervention *(Continued)*

					al Swedish MS Register linked to national healthcare and census registries, and 2 retrospective cohort studies)[j,r]		
Rituximab	**Ocrelizumab**	***RRMS***					
		62 per 1000	**1 per 1000** (0 to 26)	**OR 0.02** (0.00 to 0.40)	472 (1 retrospective cohort study)[u]	⊕⊖⊖⊖ **Very low** [f,l]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias and 1 level for imprecision. The evidence is very uncertain about the effect of rituximab on the number of participants who have infections when compared with ocrelizumab.
Rituximab	**Glatiramer acetate**	***SPMS***					
		24 per 1000	**70 per 1000** (7 to 429)	**OR 3.00** (0.30 to 30.08)	84 (1 RCT)[q]	⊕⊖⊖⊖ **Very low** [c,v]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on common infections, when compared with glatiramer acetate.
Rituximab	**Cyclophosphamide**	***SPMS***					
		433 per 1000	**230 per 1000** (97 to 459)	**OR 0.39** (0.14 to 1.11)	69 (1 RCT)[w]	⊕⊖⊖⊖ **Very low** [c,x]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias and 1 level for some imprecision. The evidence is very uncertain about the effect of rituximab on the number of participants who have infections, when compared with cyclophosphamide.
Rituximab	**Fingolimod**	***MS of all types***					
		26 per 1000	**27 per 1000** (9 to 80)	**OR 1.06** (0.34 to 3.30)	453 (1 retrospective cohort study)[k]	⊕⊖⊖⊖ **Very low** [l,m,n]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias, 1 level for indirectness, and 1 level for serious imprecision. The evidence is very uncertain about the

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Table 2. Rituximab as 'switching' for multiple sclerosis – results from RCTs and non-randomised studies of intervention *(Continued)*

							effect of rituximab on infections when compared with fingolimod.
Rituximab	**Dimethyl fumarate**	***MS of all types***					
		12 per 1000	**28 per 1000** (7 to 96)	**OR 2.39** (0.63 to 9.00)	453 (1 retrospective cohort study)[k]	⊕⊖⊖⊖ **Very low** [l.m.n]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias, 1 level for indirectness, and 1 level for some imprecision. The evidence is very uncertain about the effect of rituximab on infections when compared with dimethyl fumarate.
Rituximab	**Natalizumab**	***MS of all types***					
		7 per 1000	**27 per 1000** (7 to 107)	**OR 4.22** (1.00 to 17.84)	453 (1 retrospective cohort study)[k]	⊕⊖⊖⊖ **Very low** [f,l,m]	Our confidence in this result is very low, downgraded 2 levels for very serious risk of bias, 1 level for indirectness, and 1 level for some imprecision. The evidence is very uncertain about the effect of rituximab on infections when compared with natalizumab
Cancer over 24–36 months							
Rituximab	**Placebo**	***RRMS***					
		0 per 1000	**0 per 1000** (0 to 0)	**OR 1.55** (0.06 to 39.15)	104 (1 RCT)[g]	⊕⊖⊖⊖ **Very low** [h,n]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on the number of participants who have cancer, when compared with placebo.
		SPMS					
		111 per 1000	**55 per 1000** (4 to 516)	**OR 0.47** (0.03 to 8.52)	27 (1 RCT)[o]	⊕⊖⊖⊖ **Very low** [n,p]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on the number of participants who have cancer, when compared with placebo.
Rituximab	**Fingolimod**	***MS of all types***					

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Table 2. Rituximab as 'switching' for multiple sclerosis – results from RCTs and non-randomised studies of intervention *(Continued)*

		17 per 1000	**10 per 1000** (6 to 18)	**OR 0.60** (0.35 to 1.03)	5807 (The Swedish MS Register linked to the Swedish Cancer Register and the national patient Register)[y]	⊕⊕⊖⊖ **Low** [f,z]	Our confidence in this result is low downgraded 1 level for serious risk of bias and 1 level for some imprecision. Rituximab may reduce the number of participants who have cancer over 36 months, when compared with fingolimod.
Rituximab	**Natalizumab**	***MS of all types***					
		10 per 1000	**8 per 1000** (4 to 13)	**OR 0.74** (0.42 to 1.31)	5857 (The Swedish MS Register linked to the Swedish Cancer Register and the national patient Register)[y]	⊕⊕⊖⊖ **Low** [f,z]	Our confidence in this result is low, downgraded 1 level for serious risk of bias and 1 level for some imprecision. Rituximab may reduce the number of participants who have cancer over 36 months, when compared with natalizumab.
Mortality over 24 months							
Rituximab	**Placebo**	***RRMS***					
		0 per 1000	**0 per 1000** (0 to 0)	**OR 1.55** (0.06 to 39.15)	104 (1 RCT)[g]	⊕⊖⊖⊖ **Very low** [h,n]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on mortality compared with placebo.
Rituximab	**Fingolimod**	***RRMS***					
		0 per 1000	**0 per 1000** (0 to 0)	**OR 5.59** (0.22 to 139.89)	136 (1 retrospective cohort study)[j]	⊕⊖⊖⊖ **Very low** [e,n,aa]	Our confidence in this result is very low, downgraded 1 level for serious risk of bias, 1 level for indirectness, and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on mortality compared with fingolimod.
Rituximab	**Natalizumab**	***RRMS***					

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Table 2. Rituximab as 'switching' for multiple sclerosis – results from RCTs and non-randomised studies of intervention *(Continued)*

	0 per 1000	**0 per 1000** (0 to 0)	**OR 6.66** (0.27 to 166.58)	153 (1 retrospective cohort study)[j]	⊕⊖⊖⊖ **Very low** e,n,aa	Our confidence in this result is very low, downgraded 1 level for serious risk of bias, 1 level for indirectness, and 2 levels for very serious imprecision. The evidence is very uncertain about the effect of rituximab on mortality compared with natalizumab.

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

CI: confidence interval; **DMT:** disease-modifying treatment; **HR:** hazard ratio; **MS:** multiple sclerosis; **NNTB:** number needed to treat for an additional beneficial effect; **OR:** odds ratio; **RCT:** randomised controlled trial; **RRMS:** relapsing-remitting multiple sclerosis; **SAE:** serious adverse event; **SPMS:** secondary progressive multiple sclerosis.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

Event rates in comparator based on the number of events in the included studies.

[a] Spelman 2018.
[b]Bias due to missing data since time to disability worsening was limited to people with a minimum of three Expanded Disability Status Scale scores reported, i.e. 321/461 (70%) participants in the rituximab group and 532/922 (58%) participants in the interferon or glatiramer acetate group.
[c]The optimal information size criterion was not met (few events). Results included both no effect and appreciable benefit or harm.
[d] Naegelin 2019.
[e]Bias due to residual confounding is expected in a retrospective cohort study.
[f]The optimal information size criterion was not met (few events).
[g] Hauser 2008.
[h]High risk of bias for unblinding of personnel and incomplete outcome data. Unclear risk of bias for allocation concealment and blinding of participants.
[i] Alping 2016.
[j] Boremalm 2019.
[k] Vollmer 2020a.
[l]Very serious risk of bias. All known important confounding domains not appropriately measured and controlled for.
[m]Indirectness of population.
[n]The optimal information size criterion was not met (very few events). Results included both no harm and appreciable harm.
[o] Komori 2016.
[p]High risk of bias for inadequate allocation concealment, incomplete outcome data, and other bias. Unclear risk of bias for blinding of participants and outcome assessment.
[q] Cheshmavar 2021.

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[r] Luna 2020.
[s]Quote: "Data are not available on the validity of the registries to measure infections and on different reporting of infections between interventions"(Luna 2020).
[t]All the retrospective cohort studies were at serious risk of bias.
[u] Evertsson 2020.
[v]High risk of bias for inadequate allocation concealment and lack of blinding of participants and personnel.
[w] Etemadifar 2019.
[x]High risk of bias for inadequate allocation concealment, lack of blinding of participants, personnel and outcome assessment, and incomplete outcome data.
[y] Alping 2020.
[z]The register linkage allowed adjustment for many important confounders; however, residual confounding might still be an issue.
[aa]Indirectness of outcome, one suicide in the rituximab group.

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Table 3. PICOS table to summarise the current evidence identified in the review

Intervention: rituximab as first-choice

Comparator	Population	Study design (number of included studies)	Outcomes (☑ evidence identified)
Placebo	Relapsing MS	RCT 0	Critical
		NRSI 0	Disability worsening
			Recurrence of relapse
			SAEs
			Important prioritised
			QoL
			Common infections
			Cancer
			Mortality
			Important
			ARR
			Cognitive decline
			New or enlarging T2 MRI lesions
			New T1 (gadolinium) MRI lesions
			Discontinuation due to AEs
			Grade 3–4 AEs
			Long-term AEs
			Short-term AEs
Other DMTs	Relapsing MS	RCT 0	Critical
	Also see: Summary of findings 1	NRSI 1	Disability worsening
			Recurrence of relapse ☑
			SAEs
			Important prioritised
			QoL
			Common infections
			Cancer
			Mortality ☑
			Important
			ARR

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Table 3. PICOS table to summarise the current evidence identified in the review *(Continued)*

			Cognitive decline New or enlarging T2 MRI lesions New T1 (gadolinium) MRI lesions ☑ Discontinuation due to AEs ☑ Grade 3–4 AEs ☑ Long-term AEs Short-term AEs
Placebo	Progressive MS (primary) *Also see:* Summary of findings 2	RCT 1 NRSI 0	Critical Disability worsening ☑ Recurrence of relapse ☑ SAEs ☑ Important prioritised QoL Common infections ☑ Cancer ☑ Mortality ☑ Important ARR Cognitive decline New or enlarging T2 MRI lesions New T1 (gadolinium) MRI lesions Discontinuation due to AEs ☑ Grade 3–4 AEs ☑ Long-term AEs Short-term AEs ☑ **(infusion-related)**
Other DMTs	Progressive MS	RCT 0 NRSI 0	Critical Disability worsening Recurrence of relapse SAEs Important prioritised QoL Common infections Cancer

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Table 3. PICOS table to summarise the current evidence identified in the review *(Continued)*

			Mortality
			Important
			ARR
			Cognitive decline
			New or enlarging T2 MRI lesions
			New T1 MRI lesions
			Discontinuation due to AEs
			Grade 3–4 AEs
			Long-term AEs
			Short-term AEs
Intervention: rituximab as 'switching'			
Comparator	**Population**	**Study design (number of included studies)**	**Outcomes**
Placebo	Relapsing MS *Also see:* Summary of findings 3	RCT 1 NRSI 0	Critical Disability worsening Recurrence of relapse ☑ SAEs ☑
			Important prioritised QoL Common infections ☑ Cancer ☑ Mortality ☑
			Important ARR ☑ Cognitive decline New or enlarging T2 MRI lesions New T1 (gadolinium) MRI lesions ☑ Discontinuation due to AEs ☑ Grade 3–4 AEs ☑ Long-term AEs ☑ (CV events; opportunistic infections) Short-term AEs ☑ (infusion-related)
Other DMTs	Relapsing MS	RCT 0 NRSI 5	Critical Disability worsening ☑ (1 NRSI)

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Table 3. PICOS table to summarise the current evidence identified in the review *(Continued)*

	Also see: Summary of findings 4		Recurrence of relapse ☑ (3 NRSI) SAEs Important prioritised QoL Common infections ☑ (4 NRSI) Cancer Mortality ☑ (1 NRSI) Important ARR ☑ (1 study) Cognitive decline New or enlarging T2 MRI lesions ☑ (1 NRSI) New T1 (gadolinium) MRI lesions ☑ (2 NRSI) Discontinuation due to AEs ☑ (2 NRSI) Grade 3–4 AEs ☑ (2 NRSI) Long-term AEs ☑ (CV events (2 NRSI)) Short-term AEs ☑ (infusion-related) (2 NRSI)
Placebo	Progressive MS (secondary) *Also see:* Table 2	RCT 1 NRSI 0	Critical Disability worsening Recurrence of relapse SAEs ☑ Important prioritised QoL Common infections Cancer ☑ Mortality Important ARR Cognitive decline New or enlarging T2 MRI lesions New T1 (gadolinium) MRI lesions Discontinuation due to AEs Grade 3–4 AEs Long-term AEs ☑ (CV events)

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Table 3. PICOS table to summarise the current evidence identified in the review *(Continued)*

			Short-term AEs
Other DMTs	Progressing MS (secondary) *Also see:* Table 2	RCT 2 NRSI 1	Critical Disability worsening ☑ (1 NRSI) Recurrence of relapse SAEs ☑ (1 RCT)
			Important prioritised QoL Common infections ☑ (2 RCTs) Cancer Mortality
			Important ARR ☑ (1 RCT) Cognitive decline New or enlarging T2 MRI lesions New T1 (gadolinium) MRI lesions ☑ (1 RCT) Discontinuation due to AEs ☑ (1 RCT) Grades 3–4 AEs Long-term AEs ☑ (opportunistic infections, 1 RCT) Short-term AEs
Other DMTs	Relapsing + progressing MS *Also see:* Table 2	RCT 0 NRSI 2	Critical Disability worsening Recurrence of relapse ☑ (1 NRSI) SAEs
			Important prioritised QoL Common infections ☑ (1 NRSI) Cancer ☑ (1 NRSI) Mortality
			Important ARR Cognitive decline New or enlarging T2 MRI lesions ☑ (1 NRSI) New T1 (gadolinium) MRI lesions ☑ (1 NRSI)

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Table 3. PICOS table to summarise the current evidence identified in the review *(Continued)*

	Discontinuation due to AEs ☑ (1 NRSI)
	Grades 3–4 AEs
	Long-term AEs ☑ (CV events, 1 NRSI)
	Short-term AEs

AE: adverse event; ARR: annualised relapse rate; CV: cardiovascular events; MRI: magnetic resonance imaging; MS: multiple sclerosis; NRSI: non-randomised study of intervention; QoL: quality of life; RCT: randomised controlled trial; SAE: serious adverse event.

APPENDICES

Appendix 1. Database searches for primary studies

1. The Cochrane Central Register of Controlled Trials (CENTRAL)

((mabthera OR rituximab OR rituxan OR (monoclonal NEAR antibod*) OR (MeSH descriptor, Antibodies, Monoclonal, this term only in MeSH products)) AND ((MeSH descriptor, multiple sclerosis, demyelinating diseases, this term only in MeSH products) OR MS)

2. MEDLINE (PubMed)

1. "Rituximab"[Mesh]
2. "IDEC C2B8"[All Fields]
3. Rituxan[All Fields]
4. rituximab[All Fields]
5. mabthera[All Fields]
6. "anti cd20"[All Fields]
7. immunotherap*
8. monoclonal antibod*[all fields]
9. "Immunotherapy"[Mesh:NoExp]
10. "Antibodies,Monoclonal"[Mesh:NoExp]
11. 1/10 OR
12. "Demyelinating Diseases"[Mesh:NoExp]
13. "Demyelinating Autoimmune Diseases, CNS" [Mesh:NoExp]
14. Demyelinating Diseases*[all fields]
15. Demyelinating Disorder*[all fields]
16. "Multiple Sclerosis"[Mesh]
17. "Multiple Sclerosis, Chronic Progressive"[Mesh]
18. "Multiple Sclerosis, Relapsing-Remitting"[Mesh]
19. "Multiple sclerosis"[all fields]
20. 12/19 OR
21. 11 AND 20

3. Embase

1. 'multiple sclerosis'/exp OR 'demyelinating disease'/de
2. ((demyelinating NEAR/3 disorder*):ti,ab,kw) OR ((demyelinating NEAR/3 disease*):ti,ab,kw) OR 'first demyelinating':ti,ab,kw OR cis:ti,ab,kw OR (('clinically isolated' NEAR/2 'syndrome*'):ti,ab,kw)
3. 1 OR 2
4. rituximab:ti,ab,kw OR 'idec c2b8':ti,ab,kw OR rituxan:ti,ab,kw OR mabthera:ti,ab,kw OR 'anti cd20':ti,ab,kw OR immunotherap*:ti,ab,kw OR ((monoclonal NEAR/2 antibod*):ti,ab,kw)
5. 'rituximab'/exp OR 'immunotherapy'/de OR 'monoclonal antibody'/de
6. 4 OR 5
7. 3 AND 6

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4. CINAHL (via EBSCO)

((TI ("multiple sclerosis" OR "multiple sclerosis, chronic progressive" OR "multiple sclerosis, relapsing remitting" OR "demyelinating diseases" OR "demyelinating autoimmune diseases") OR AB ("multiple sclerosis" OR "multiple sclerosis, chronic progressive" OR "multiple sclerosis, relapsing remitting" OR "demyelinating diseases" OR "demyelinating autoimmune diseases") OR SU ("multiple sclerosis" OR "multiple sclerosis, chronic progressive" OR "multiple sclerosis, relapsing remitting" OR "demyelinating diseases" OR "demyelinating autoimmune diseases")) AND (MH ("rituximab" OR "rituxan" OR "mabthera" OR "anti cd20" OR "immunotherap*" OR "monoclonal antibod*") OR TI ("rituximab" OR "rituxan" OR "mabthera" OR "anti cd20" OR "immunotherap*" OR "monoclonal antibod*") OR AB ("rituximab" OR "rituxan" OR "mabthera" OR "anti cd20" OR "immunotherap*" OR "monoclonal antibod*"))

5. Search terms for the trials registers

(multiple sclerosis) AND (rituximab OR rituxan OR mabthera)

Appendix 2. ROBINS-I: review authors' judgements about each risk of bias item for each included non-randomised study

Alcalá 2019

Type of study: retrospective multicentre cohort study – The GITEM Registry (Spain)

Participants: active relapsing MS (n = 55) switching from fingolimod due to failure or experiencing adverse effects with previously aggressive disease

Treatment group: rituximab (n = 27)

Comparison group: alemtuzumab (n = 28)

Outcome timing: 12 months

Median follow-up: 20.9 months (IQR 11.8–38.7). Median time with alemtuzumab: 18.1 months (IQR 11.8–31.4); median time with rituximab: 32.0 months (IQR 10.6–48.6)

Outcomes assessed

O1. Number of participants with sustained disability worsening defined as increase in 1 point in EDSS (if EDSS < 6) or in 0.5 point (if EDSS ≥ 6) persisting after 6 months

O2. Number of participants with clinical relapse defined by the presence of new suggesting neurological symptoms, maintained for more than 24 hours, in the absence of intercurrent processes and accompanied by objective changes in neurological examination

O3. Number of participants who discontinued treatment due to adverse events

O4. Number of participants with SAEs: no SAEs reported

O5. Number of participants with infusion-related reactions

O6. Number of participants with opportunistic infections: none of the participants developed opportunistic infections

O7. Number of participants with common infections (respiratory and urinary)

O8. Number of participants with cancer

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Outcome	Intervention effect	Domains							Overall Risk of Bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1, O2, O3	Assignment	Serious[a]	Serious[b]	Serious[c]	Low[d]	Low[e]	Serious[f]	Serious[g]	**Critical**
O4, O5, O6, O7, O8	Adhering	Serious[a]	Serious[b]	Serious[c]	NI[h]	Low[e]	Serious[f]	Serious[g]	**Critical**

Explanatory footnotes

[a]Only counts available (no adjustment for baseline confounders). Different follow-up periods between the comparison groups (median 18 months in alemtuzumab group and 32 months in rituximab group).

[b]Selection bias (immortal time bias). The start of follow-up, defined as the date of the first prescription, was considerably later after first relapse for the rituximab group (11 years) than the alemtuzumab group (8 years) and the rituximab group had been previously treated with a greater number of drugs (i.e. survived previous treatments). No statistical techniques for correcting selection bias were used.

[c]Retrospective clinical data were collected. Intervention status is not well-defined: dose, frequency, intensity of alemtuzumab not reported.

[d]Deviations from intended intervention if had occurred (not reported) were part of usual practice.

[e]Data were reasonably complete at 1 year.

[f]Outcome assessors aware of the intervention assigned. The methods of outcome assessment were not comparable across the intervention groups: different follow-up periods (that is different outcome measurement criteria), different frequency of clinical visits and imaging tests.

[g]Outcomes were analysed in different ways in the methods and results sections of the article. Quote: "Kaplan–Meier survival analysis for the median time to a relapse and to increase of disability was run". In the results section, only the number of participants with the event was reported.

[h]No information reported on whether there was deviation from the intended intervention.

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Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Alping 2016

Type of study: retrospective multicentre cohort study – The Swedish MS Register

Participants: relapsing MS (n = 256) switching from natalizumab, due to JC virus antibody positivity

Treatment group: rituximab (n = 114)

Treatment group: fingolimod (n = 142)

Outcome timing: 18 months

Outcomes assessed

O1. Time to new clinical relapse

O2. Number of participants with new MRI T2 lesions

O3. Number of participants with new MRI gadolinium-enhancing positive T1 lesions

O4. Number of participants with SAEs

O5. Number of participants with grade 3–5 adverse events

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Outcome	Intervention effect	Domains							Overall Risk of Bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1, O2, O3	Assignment	Moderate[a]	Low[b]	Moderate[c]	Low[d]	Low[e]	Moderate[f]	Low[g]	**Moderate**
O4, O5	Adhering	Moderate[a]	Low[b]	Moderate[c]	NI[h]	Low[e]	Moderate[f]	Low[g]	**Moderate**

Explanatory footnotes

[a]Bias due to confounding by indication expected. Important confounding domains were appropriately measured and controlled for. Data for potential baseline confounding variables were obtained from in-depth medical chart review. Logistic regression analyses for number of participants with MRI lesions within the first 18 months of treatment, and Cox proportional hazards model analyses of time to event for clinical relapses, adverse events, and discontinuation of therapy within the first 18 months of treatment, both comparing rituximab to fingolimod and compensating for the continuous variables age, time receiving natalizumab, wash-out time, and follow-up time (logistic regression only), and the categorical variables sex, baseline EDSS, and study centre. For the Cox proportional hazards models time was counted from the first administration of rituximab or fingolimod.

[b]Bias to selection unlikely. The source population was people with MS ever recorded in the Swedish MS register, at the Karolinska (Stockholm, to 24 February 2015), Sahlgrenska (Gothenburg, to 18 April 2015), and Norrland's (Umeå, to 12 April 2015) University Hospitals. The study population was identified through the Swedish MS register (www.neuroreg.se) and cross-checked against the local clinical records systems. The number of participants excluded due to insufficient follow-up or compliance was low (6/344; 1.7%) (Figure 1).

[c]Bias due to classification of interventions since retrospective clinical data were collected. The intervention groups were clearly defined.

[d]Deviations from intended intervention were part of usual practice.

[e]Data were reasonably complete. Information about missing data for outcomes were described. Missing data for baseline confounders were reported.

[f]Lack of blind outcome assessment. Geographical imbalances in the recording of outcomes may have been, given the lack of formal study visits. Clinical guidelines for follow-up differed to some degree between different interventions.

[g]Reported results correspond to all intended outcomes reported in the methods section of the article.

[h]No information is reported on whether there is deviation from the intended intervention.

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Alping 2020

Type of study: retrospective multicentre cohort study – The Swedish MS register linked to the Swedish Cancer register and other national healthcare and census registers

Participants: all types of MS (n = 6136) switching from other DMTs, matched to people from a general population without MS.

Treatment group: rituximab (n = 4187 therapy initiation)

Treatment group: fingolimod (n = 1620 therapy initiation)

Treatment group: natalizumab (n = 1670 therapy initiation)

General population: n = 37,801

Outcome timing: mean follow-up: rituximab 2.30 years; fingolimod 3.96 years; natalizumab 3.94 years; general population 3.03 years

Outcome assessed

O1. Time to first invasive cancer (reference: rituximab)

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Outcome	Intervention effect	Domains							Overall Risk of Bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1	Adhering	Moderate[a]	Low[b]	Moderate[c]	NI[d]	Low[e]	Low[f]	Low[g]	**Moderate**

Explanatory footnotes

[a]Bias due to confounding expected. The register linkage allowed adjustment for many important confounders. However, residual confounding might still be an issue. No data were available on diet, alcohol use, workplace exposure to carcinogens, obesity, sunlight exposure, or smoking, all of which are well-known risk factors for cancer. Several general health markers and demographic variables were included to limit unmeasured confounding by proxy. Inverse probability of treatment weighting-adjusted Cox regression model adjusted for age; sex; birth region; education; previous invasive

cancer; arrhythmia; major acute cardiovascular event; and use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, and immunosuppressive agents. Time since therapy start as the timescale. In the study intervention, switches were unrelated to the outcome that is an unexpected harm.

[b]By linking the national registers to the Swedish MS register, the study included almost all people with MS in Sweden's treated with rituximab, fingolimod, or natalizumab, limiting the risk of selection bias.

[c]Bias due to classification of interventions since retrospective clinical data were collected. The intervention groups were clearly defined.

[d]No information is reported on whether there is deviation from the intended intervention.

[e]The registers made it possible to follow patients without attrition and were suitable for studying rare safety outcomes in a population-based setting.

[f]Outcomes were identified in the national cancer register and included time to first invasive cancer. The International Classification of Diseases for Oncology codes was used for the identification of the specific cancers.

[g]Reported results corresponded to all intended outcomes reported in the methods section of the article.

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Boremalm 2019

Type of study: retrospective multicentre cohort study – The Swedish MS Register

Participants: active relapsing MS (n = 241) switching from interferon beta or glatiramer acetate due to relapse or MRI contrast-enhancing lesions or both (escalation therapy)

Treatment group: rituximab (n = 48)

Treatment group: fingolimod (n = 88)

Treatment group: natalizumab (n = 105)

Outcome timing: 24 months

Median follow-up: rituximab: 33.6 (IQR 25.2–43.2) months; fingolimod: 31.2 (IQR 20.4–45.6) months; natalizumab 33.6 (IQR 22.8–54.0) months

Outcomes assessed

O1. Time to new clinical relapse

O2. Number of participants with new gadolinium-enhancing positive T1 lesions

O3. Number of participants who discontinued treatment due to adverse events

O4. Number of participants with grade 3–5 adverse events

O5. Number of participants with common infections

O6. Number of participants with hypogammaglobulinaemia

O7. Number of participants with cardiovascular events

O8. Number of deaths

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Outcome	Intervention effect	Domains							Overall Risk of Bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1, O2, O3	Assignment	Moderate[a]	Low[b]	Moderate[c]	Low[d]	Low[e]	Moderate[f]	Low[g]	**Moderate**
O4, O5, O6, O7, O8	Adhering	Moderate[a]	Low[b]	Moderate[c]	NI[h]	Low[e]	Moderate[f]	Low[g]	**Moderate**

Explanatory footnotes

[a]Bias due to confounding by indication expected. Important baseline confounding variables were obtained from participants' medical records at each centre. Cox proportional hazards model analyses of time to event for relapse, adverse events, and discontinuation of therapy comparing natalizumab to rituximab. Analyses adjusted for the continuous variables age at inclusion, duration since debut, EDSS at baseline, time receiving last DMT before switch, time from disease activity to switch, and the categorical variables sex and centre (except for discontinuation of therapy because treatment allocation correlated to centre and too few had interrupted rituximab treatment). Radiological activity was measured, but it was not included in Cox models due to the limited number of participants in the treatment groups and a high and uneven percentage of participants lacking MRI data prior to baseline.
[b]Bias to selection unlikely. The source population was all people with MS from the Swedish MS registry. Participants with relapsing MS who, due to breakthrough disease activity, switched from interferon or glatiramer acetate to natalizumab, rituximab, or fingolimod between 1 January 2011 and 31 December 2015. The number of participants excluded, due to missing or incomplete patient data or due to uncertainty regarding compliance to treatment, was low (13/470; 2.8%) (Figure 1).

[c]Bias due to classification of interventions since retrospective clinical data were collected. The intervention groups were not clearly defined.

[d]Deviations from intended intervention were part of usual practice.

[e]Data were reasonably complete. Information about missing data for outcomes were described. Missing data for baseline confounders were reported.

[f]Lack of blind outcome assessment. Geographical imbalances in the recording of outcomes may have been, given the lack of formal study visits. Clinical guidelines for follow-up differed to some degree between different interventions.

[g]Reported results correspond to all intended outcomes reported in the methods section of the article.

[h]No information reported on whether there was deviation from the intended intervention.

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Evertsson 2020

Type of study: retrospective multicentre cohort study – The Swedish MS Register and the Rocky Mountain Multiple Sclerosis Clinic US database

Participants: relapsing and secondary progressive MS (n = 472)

Treatment group: rituximab (n = 311)

Treatment group: ocrelizumab (n = 161)

Outcome timing: 12 months

Median follow-up: rituximab: 33.6 (IQR 25.2–43.2) months; fingolimod: 31.2 (IQR 20.4–45.6) months; natalizumab 33.6 (IQR 22.8–54.0) months

Outcomes assessed

O1. Number of participants who discontinued treatment due to adverse events

O2. Number of participants with common infections

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Outcome	Intervention effect	Domains							Overall Risk of Bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1	Assignment	Serious[a]	Serious[b]	Moderate[c]	Low[d]	Low[e]	Moderate[f]	Low[g]	**Serious**
O2	Adhering	Serious[a]	Serious[b]	Moderate[c]	NI[h]	Low[e]	Moderate[f]	Low[g]	**Serious**

Explanatory footnotes

[a]Bias due to confounding by indication expected. Important confounding domains were not appropriately measured and controlled for.

[b]Bias due to selection of participants into the study due to the selection of participants into the study was based on characteristic of participants after the start of intervention. Not adjusted for selection bias.

[c]Bias due to classification of interventions since retrospective clinical data were collected. The intervention groups were defined.

[d]Deviations from intended intervention were part of usual practice.

[e]Data were reasonably complete.

[f]Lack of blind outcome assessment. Geographical imbalances in the recording of outcomes may have been, given the lack of formal study visits. Clinical guidelines for follow-up differed to some degree between different interventions.

[g]Reported results correspond to all intended outcomes reported in the methods section of the article.

[h]No information is reported on whether there is deviation from the intended intervention.

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Granqvist 2018

Type of study: retrospective multicentre cohort – The national Swedish MS Register and local medical records

Participants: relapsing MS (n = 488) who received diagnoses from 1 January 2012 to 31 October 2015 and started their first DMT

Treatment group: rituximab

Treatment group: interferon beta or glatiramer acetate

Treatment group: dimethyl fumarate

Treatment group: fingolimod

Treatment group: natalizumab

Median follow-up: rituximab: 18.8 (IQR 12.3–28.0) months; interferon beta or glatiramer acetate 15.3 (IQR 8.6–26.3) months; dimethyl fumarate 14.2 (IQR 8.6–18.9) months; fingolimod: 12.1 (IQR 7.9–22.3) months; natalizumab 19.0 (IQR 11.4–27.5) months

Outcomes assessed

O1. Time to new clinical relapse

O2. Number of participants with new MRI gadolinium-enhancing positive T1 lesions

O3. Number of participants who discontinued treatment due to adverse events

O4. Number of participants with grade 3–5 adverse events

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Outcome	Intervention effect	Domains							Overall Risk of Bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1, O2, O3	Assignment	Moderate[a]	Low[b]	Moderate[c]	Low[d]	Low[e]	Moderate[f]	Low[g]	**Moderate**
O4	Adhering	Moderate[a]	Low[b]	Moderate[c]	NI[h]	Low[e]	Moderate[f]	Low[g]	**Moderate**

Explanatory footnotes

[a]Bias due to confounding by indication expected. Data for potential baseline confounding variables were obtained from medical chart review. The potential confounding variables age, sex, baseline EDSS score, MS duration after debut and diagnosis, relapse in the year before treatment initiation, region, and follow-up time were examined through sequential regression models. Propensity scores were estimated for each treatment group in comparison with rituximab and were separately adjusted for as stratified quintiles in the regression models.

[b]Bias to selection unlikely. The source population comprised all individuals in Stockholm and Västerbotten Counties who received a diagnosis of relapsing MS from 1 January 2012 to 31 October 2015, starting their first DMT (i.e. first-line treatment). Participants were identified through a national Internet-based MS registry (www.neuroreg.se) from which data were collected along with social security numbers used to access corresponding local medical records. The number of participants excluded due to lacked follow-up was low (3/593; 0.5%) (Figure 1).

[c]Bias due to classification of interventions since retrospective clinical data were collected. Doses, timing, and frequency of interventions reported.

[d]Deviations from intended intervention were part of usual practice.

[e]Data were reasonably complete.

[f]Lack of blinded outcome assessment. There may have been geographical imbalances in the recording of outcomes given the lack of formal study visits. Clinical guidelines for follow-up differed to some degree between different interventions.

[g]Reported results correspond to all intended outcomes reported in the methods section of the article.

[h]Adherence was not examined or adjusted for in the study. No information on other deviations was reported.

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Luna 2020

Type of study: retrospective multicentre cohort – The national Swedish MS Register linked to national healthcare and census registries

Participants: relapsing MS (n = 6421) who started treatment between 1 January 2011 and 31 December 2017

Treatment episodes: rituximab (n = 3260)

Treatment episodes: interferon beta or glatiramer acetate (n = 2217)

Treatment episodes: fingolimod (n = 1535)

Treatment episodes: natalizumab (n = 1588)

End of follow-up: 31 December 2017

Outcome assessed

O1. Time to serious infections requiring hospitalisation

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Outcome	Intervention effect	Domains							Overall risk of bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1	Adhering	Moderate[a]	Moderate[b]	Moderate[c]	Moderate[d]	Moderate[e]	Moderate[f]	Low[g]	**Moderate**

Explanatory footnotes

[a]Bias due to confounding expected. Important baseline confounding variables were available; however, data were lacking on other potential confounders including body mass index, smoking status, and varicella vaccination status. Hazard ratios adjusted for age, sex, educational level, country of birth, sick leave, disability pension, hospitalisations in the previous 5 years, history of infections, cancer, antidepressant use, antipsychotic use, major adverse cardiovascular events, arrhythmia, year of treatment start, region of treating clinic, relapses last year, MS duration, EDSS, MS Impact Scale-29, EuroQol 5-Dimension scale, and Symbol Digit Modalities Test.

[b]The use of national registries, which enabled inclusion of almost all people with MS in Sweden likely avoided the risk for selection bias.

[c]Bias due to classification of interventions since retrospective clinical data were collected. Dose and frequency of the intervention were not clearly defined.

[d]Use of antibiotics was much more common than serious infections, but the pattern of rates was similar: highest with rituximab, followed by natalizumab and fingolimod. The prescription of antibiotics may be sensitive to lack of blinding and surveillance (e.g. association with frequency of visits or over prescription for participants believed to be at particular risk). The rate of prescribed herpes antivirals was about 70% higher among participants receiving fingolimod and natalizumab than receiving rituximab or interferon beta and glatiramer acetate. We could not exclude that these different prescription patterns may have influenced treatment outcomes differently.

[e]Minor infections were likely missed. Multiple imputation was applied to account for missing data, creating 25 imputed data sets using fully conditional specifications. Sensitivity analyses were not performed.

[f]The authors of the article reported: "We are limited in what data we can show for the identified serious infections". Data were not available on the validity of the registries to measure infections and on different reporting of infections between interventions.

[g]Reported results correspond to all intended outcomes reported in the methods section of the article.

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Naegelin 2019

Type of study: retrospective cohort

Participants: secondary progressive MS

Treatment group: rituximab (≥ 1 dose). Cohort recruited at the MS Centres in Basel or Lugano, Switzerland

Treatment group: participants who had never been treated with rituximab. Cohort recruited at the MS Centres in Basel or Amsterdam, the Netherlands

Follow-up time: mean 3.5 years for the rituximab group; 4.8 years for the control group

Outcome assessed

O1. Time to confirmed disability worsening.

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Outcome	Intervention effect	Domains							Overall Risk of Bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1	Assignment	Moderate[a]	Serious[b]	Moderate[c]	Low[d]	Low[e]	Moderate[f]	Low[g]	**Serious**

Explanatory footnotes

[a]Bias due to confounding by indication is expected. Participants in the rituximab group tended to be younger, had a higher EDSS score, and showed more MRI lesion activity than the control group, favouring indication to treatment with rituximab. A higher proportion of the control participants had not been treated with DMTs in the year before baseline suggesting a bias toward a less aggressive disease course in the control group. Propensity scores were used to match 1:1 the rituximab-treated and the control groups for sex, age, EDSS score, and disease duration at baseline, in combination with covariate adjustment in the statistical models. Data of baseline confounding variables were obtained from medical chart review.

[b]Selection into the study was likely related to intervention and outcome.

[c]Bias due to classification of interventions since retrospective clinical data were collected. Doses, timing, and frequency of interventions not reported.

[d]In the control group, 14/59 (24%) participants switched to other treatments. Deviations from intended intervention were part of usual practice.

[e]Data were reasonably complete.

[f]Lack of blinded outcome assessment. Imbalances between the centres in measuring EDSS and in recording of outcomes may have occurred, given the lack of formal study visits. Clinical guidelines for follow-up differed between different interventions.

[g]Reported results correspond to all intended outcomes reported in the methods section of the article.

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Spelman 2018

Type of study: retrospective cohort – The Swedish MS Register

Participants: relapsing MS (n = 1383)

Treatment group: rituximab (n = 461)

Treatment group: interferon beta or glatiramer acetate (n = 922)

Recruitment: April 2005 to November 2015

Follow-up: 24 months

Outcome assessed

O1. Time to disability worsening

O2. Time to first relapse on therapy

O3. Annualised relapse rate

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Outcome	Intervention effect	Domains							Overall Risk of Bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1	Assignment	Moderate[a]	Moderate[b]	Moderate[c]	Low[d]	Serious[e]	Moderate[f]	Low[g]	**Serious**
O2, O3	Assignment	Moderate[a]	Moderate[b]	Moderate[c]	Low[d]	Low[e]	Moderate[f]	Low[g]	**Moderate**

Explanatory footnotes

[a]Bias due to confounding is expected. Data for baseline confounding variables were obtained from the nationwide Swedish register. Propensity scores were used to match 2:1 the rituximab-treated and the interferon/glatiramer acetate groups using a 5-to-1 digit matching algorithm with a 0.01 calliper. The independent explanatory variables used to calculate the propensity score were sex, age, EDSS, disease duration at baseline, number of prebaselines DMT start, the proportion of disease duration on treatment, the number of DMT starts as a proportion of disease duration, relapse activity in the 12- and 24-months prebaseline, the index year of the DMT start, and the number of assessments per year of follow-up. Lesion number on MRI at baseline was not included in the propensity score due to inadequate data availability. The propensity score was calculated using a binomial logistic regression model. A sensitivity analysis was used to test statistical models for the influence of unobserved confounding.

[b]Bias due to selection of participants into the study due to the selection of participants who had a minimum of 3-month persistence on the index DMT and who had a full set of baseline data for all variables used in the derivation of the baseline score. The authors used sensitivity analysis to reject the inference of a treatment effect in favour of selection effects.

[c]Bias due to classification of interventions since retrospective clinical data were collected. The intervention groups were clearly defined.

[d]Deviations from intended intervention were part of usual practice.

[e]Bias due to missing data since time to disability worsening was limited to patients with a minimum of three EDSS scores (included baseline score), i.e. 321/461 (70%) participants in the rituximab group and 532/922 (58%) participants in the interferon or glatiramer acetate group.

[f]Lack of blinded outcome assessment. Geographical imbalances in the recording of outcomes may have been, given the lack of formal study visits. Clinical guidelines for follow-up differed to some degree between rituximab and interferon or glatiramer acetate. Treatment arms were matched on index year meaning that the groups were contemporaneous.

[g]Reported results correspond to all intended outcomes reported in the methods section of the article.

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Vollmer 2020a

Type of study: retrospective cohort

Setting: The Rocky Mountain MS Center at the University of Colorado, US

Participants: all types of MS (n = 1246)

Treatment group: rituximab (n = 182)

Treatment group: fingolimod (n = 271)

Treatment group: dimethyl fumarate (n = 342)

Treatment group: natalizumab (n = 451)

Recruitment: January 2010 to October 2013

Follow-up time: 24 months

Outcome assessed

O1. Number of participants with relapse

O2. Number of participants with new MRI T2 lesion

O3. Number of participants with new MRI gadolinium-enhancing positive T1 lesions

O4. Number of participants who discontinued therapy due to adverse events

O5. Number of participants with common infections

O6. Number of participants with cardiovascular events

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Outcome	Intervention effect	Domains							Overall risk of bias
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
O1, O2, O3	Assignment	Serious[a]	Moderate[b]	Moderate[c]	Low[d]	Low[e]	Moderate[f]	Low[g]	**Serious**
O4	Assignment	Moderate[h]	Moderate[b]	Moderate[c]	NI[i]	Low[e]	Moderate[f]	Low[g]	**Moderate**
O5, O6	Adhering	Moderate[a]	Moderate[b]	Moderate[c]	NI[i]	Low[e]	Moderate[f]	Low[g]	**Moderate**

Explanatory footnotes

[a]Bias due to confounding is expected. Baseline characteristics were collected from chart review of electronic medical records at the time of DMT start date. Baseline MRI data were collected from the closest MRI prior to DMT initiation. They did not match participants with relapsing MS and reported unadjusted beneficial outcomes (relapse and MRI lesions) and adjusted treatment discontinuation due to adverse events.

[b]Bias to selection unlikely. The source population was all people with MS who initiated rituximab, fingolimod, dimethyl fumarate, or natalizumab at the Rocky Mountain MS Center between January 2010 and October 2013. 4% of participants were excluded in the natalizumab group since data on the first two years of treatment were not available. For each participant, start of follow-up and start of intervention coincided.

[c]Bias due to classification of interventions since retrospective clinical data were collected. The rituximab group only was clearly defined.

[d]Deviations from intended intervention were part of usual practice.

[e]Data were reasonably complete.

[f]Bias due to measurement of included outcomes since the outcome assessors were not blinded to intervention. Imbalances in the recording of outcomes may have occurred, given the lack of formal study visits. Clinical guidelines for follow-up differed to some degree between different interventions. MRIs were not obtained consistently at routine intervals and differing magnetic strength may were used. This may have affected the likelihood of detecting MRI lesions.

[g]Reported results correspond to all intended outcomes reported in the methods section of the article.

[h]Adjusted odds ratios for discontinuation due to adverse events at ≤ 24 months were available.

[i]Adherence was not examined or adjusted for in the study. No information on other deviations was reported.

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DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; IQR: interquartile range; JC: John Cunningham; MRI: magnetic resonance imaging; MS: multiple sclerosis; n: number of participants; NI: no information; SAE: serious adverse event.

HISTORY

Protocol first published: Issue 2, 2021

Date	Event	Description
18 February 2021	Amended	Republishing the protocol, broken links in Appendix 2 fixed

CONTRIBUTIONS OF AUTHORS

Concept development: GF

Title registration: GF, JK, CDG

Drafting of protocol: GF

Editing of protocol: GF, JK, CDG

Title and abstract review: GF, JK, CDG

Data abstraction: GF, JK

Data entry: GF, CDG

Data analysis: CDG

Drafting the review: GF

Editing and revising the review: GF, JK, CDG

DECLARATIONS OF INTEREST

GF: none.

JK: none.

CDG: none.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied, Other

  No sources of support supplied

External sources

- Multiple Sclerosis International Federation (MSIF), Other

  Contribution to the review was partly supported by the not-for-profit organisation MSIF to the Editorial Base of the Group hosted by the IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy. MSIF had no role in the design, conduct, or publication of the review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In the review, we redefined 'Primary outcomes' as 'Critical outcomes' and 'Secondary outcomes' as 'Prioritised important outcomes' to be included in the summary of findings tables, or as 'Additional important outcomes', which were not included in the summary of findings tables.

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- In the protocol, we had planned to evaluate methods for monitoring and detecting adverse events in included studies. This was removed.
- Studies with multiple treatment groups. For multiple arm trials involving the same agent at different doses compared to a control treatment, we had planned to convert the treatment arms into a single arm by merging the different doses. This was removed because we found no studies involving the same agent at different doses.
- We had planned to evaluate potential publication bias using funnel plots. This was removed because there were fewer than 10 studies available for meta-analysis.
- In the protocol section 'Selective non-reporting bias', we reported that: "If a study appeared to be carried out appropriately and the authors were known and trustworthy, we will see if there is correspondence between the outcome measurements and analyses described in the Methods section of the published paper and those reported in the Results section". During the review development process, we did not assess if a study author was "known and trustworthy". The only approach we used was to check for consistencies between the outcome measurements and analyses described in 'Methods' and those reported in 'Results' of the included study.
- Measures of treatment effect. We used odds ratios to estimate treatment effect for included outcomes, and hazard ratios for time to events. In the few cases in which we combined two or more study results, there were not the conditions to apply the Peto's method, and we applied the inverse variance method.
- We had planned subgroup analyses for active or inactive multiple sclerosis. These were removed because few studies provided the information.
- We had planned a sensitivity analysis on the exclusion of studies at high or critical risk of bias. This was removed because we judged most of the randomised controlled trials at high risk of bias, critical in one non-randomised studies of interventions (NRSI), and serious in four NRSIs.
- In the protocol, we had planned to present four summary of findings tables and additional tables for comparisons versus placebo. In the review phase, due to the large number of treatment comparisons, we decided to present two summary of findings, one for 'rituximab as first choice treatment for MS' and one for 'rituximab when switching from another disease-modifying treatment'. The two summary of findings tables were based on the critical and important outcomes identified in the review protocol and included comparisons of rituximab versus placebo or other disease-modifying treatments in relapsing MS, progressive MS, and MS of all types.
- In the protocol, we had planned to apply no limitation with respect to study outcomes for study selection. This was changed. We stated that we included studies that assessed critical and important outcomes prespecified in the protocol.

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