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Ocrelizumab for multiple sclerosis (Review)

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TABLE OF CONTENTS

[Intervention Review]

Ocrelizumab for multiple sclerosis

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ABSTRACT

Background

Ocrelizumab is a humanised anti-CD20 monoclonal antibody developed for the treatment of multiple sclerosis (MS). It was approved by the Food and Drug Administration (FDA) in March 2017 for using in adults with relapsing-remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS). Ocrelizumab is the only disease-modifying therapy (DMT) approved for PPMS. In November 2017, the European Medicines Agency (EMA) also approved ocrelizumab as the first drug for people with early PPMS. Therefore, it is important to evaluate the benefits, harms, and tolerability of ocrelizumab in people with MS.

Objectives

To assess the benefits, harms, and tolerability of ocrelizumab in people with RRMS and PPMS.

Search methods

We searched MEDLINE, Embase, CENTRAL, and two trials registers on 8 October 2021. We screened reference lists, contacted experts, and contacted the main authors of studies.

Selection criteria

All randomised controlled trials (RCTs) involving adults diagnosed with RRMS or PPMS according to the McDonald criteria, comparing ocrelizumab alone or associated with other medications, at the approved dose of 600 mg every 24 weeks for any duration, versus placebo or any other active drug therapy.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

Four RCTs met our selection criteria. The overall population included 2551 participants; 1370 treated with ocrelizumab 600 mg and 1181 controls. Among the controls, 298 participants received placebo and 883 received interferon beta-1a. The treatment duration was 24 weeks in one study, 96 weeks in two studies, and at least 120 weeks in one study. One study was at high risk of allocation concealment and blinding of participants and personnel; all four studies were at high risk of bias for incomplete outcome data.

For RRMS, compared with interferon beta-1a, ocrelizumab was associated with: 1. lower relapse rate (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.52 to 0.73; 2 studies, 1656 participants; moderate-certainty evidence); 2. a lower number of participants with disability progression (hazard ratio (HR) 0.60, 95% CI 0.43 to 0.84; 2 studies, 1656 participants; low-certainty evidence); 3. little to no difference in the number of participants with any adverse event (RR 1.00, 95% CI 0.96 to 1.04; 2 studies, 1651 participants; moderate-certainty evidence); 4. little to no difference in the number of participants with any serious adverse event (RR 0.79, 95% CI 0.57 to 1.11; 2 studies, 1651 participants; low-certainty evidence); 5. a lower number of participants experiencing treatment discontinuation caused by adverse events (RR 0.58,

95% CI 0.37 to 0.91; 2 studies, 1651 participants; low-certainty evidence); 6. a lower number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging (MRI) (RR 0.27, 95% CI 0.22 to 0.35; 2 studies, 1656 participants; low-certainty evidence); 7. a lower number of participants with new or enlarging T2-hyperintense lesions on MRI (RR 0.63, 95% CI 0.57 to 0.69; 2 studies, 1656 participants; low-certainty evidence) at 96 weeks.

For PPMS, compared with placebo, ocrelizumab was associated with: 1. a lower number of participants with disability progression (HR 0.75, 95% CI 0.58 to 0.98; 1 study, 731 participants; low-certainty evidence); 2. a higher number of participants with any adverse events (RR 1.06, 95% CI 1.01 to 1.11; 1 study, 725 participants; moderate-certainty evidence); 3. little to no difference in the number of participants with any serious adverse event (RR 0.92, 95% CI 0.68 to 1.23; 1 study, 725 participants; low-certainty evidence); 4. little to no difference in the number of participants experiencing treatment discontinuation caused by adverse events (RR 1.23, 95% CI 0.55 to 2.75; 1 study, 725 participants; low-certainty evidence) for at least 120 weeks. There were no data for number of participants with gadolinium-enhancing T1 lesions on MRI and number of participants with new or enlarging T2-hyperintense lesions on MRI.

Authors' conclusions

For people with RRMS, ocrelizumab probably results in a large reduction in relapse rate and little to no difference in adverse events when compared with interferon beta-1a at 96 weeks (moderate-certainty evidence). Ocrelizumab may result in a large reduction in disability progression, treatment discontinuation caused by adverse events, number of participants with gadolinium-enhancing T1 lesions on MRI, and number of participants with new or enlarging T2-hyperintense lesions on MRI, and may result in little to no difference in serious adverse events (low-certainty evidence).

For people with PPMS, ocrelizumab probably results in a higher rate of adverse events when compared with placebo for at least 120 weeks (moderate-certainty evidence). Ocrelizumab may result in a reduction in disability progression and little to no difference in serious adverse events and treatment discontinuation caused by adverse events (low-certainty evidence).

Ocrelizumab was well tolerated clinically; the most common adverse events were infusion-related reactions and nasopharyngitis, and urinary tract and upper respiratory tract infections.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of ocrelizumab for multiple sclerosis?

Key messages

– Ocrelizumab is a recently approved medicine to treat people with multiple sclerosis (MS). In relapsing-remitting MS (where people experience flare-ups of symptoms), ocrelizumab probably substantially reduces flare-ups, may substantially reduce worsening of symptoms, and probably makes little or no difference to unwanted effects compared with interferon beta-1a (a standard treatment for MS), 96 weeks after treatment starts.

– Compared to placebo (a dummy medicine) after 120 weeks of treatment for primary progressive MS (where people's symptoms worsen gradually), ocrelizumab may reduce worsening of symptoms. Ocrelizumab probably increases unwanted effects but makes little or no difference to the number of serious unwanted effects.

– We need more, better-designed studies to test the effectiveness of ocrelizumab and measure unwanted effects.

What is multiple sclerosis?

MS is a condition where the body's immune system mistakenly attacks the nerves in the brain and spinal cord (the central nervous system). This damage prevents messages travelling from the central nervous system to other parts of the body. It causes a range of potential symptoms from pins and needles to difficulties with balance and walking.

There are several types of MS. In relapsing-remitting MS, people have 'flare-ups' of disease followed by periods of recovery. In primary progressive MS, people's symptoms gradually worsen over time.

What is ocrelizumab?

Ocrelizumab is a medicine that has been recently approved to treat relapsing-remitting MS and primary progressive MS. It is a disease-modifying therapy, which is a type of medicine that treats the underlying symptoms of MS. Ocrelizumab targets white blood cells in the body's immune system. It sticks to a type of these cells called B cells, and stops them attacking the central nervous system. This prevents inflammation and nerve damage, reducing the number and severity of relapses and slowing the worsening of symptoms.

What did we want to find out?

We wanted to find out if ocrelizumab is more effective than any other medicine or placebo in people with relapsing-remitting MS and primary progressive MS.

We were interested in how many people:

– had symptom flare-ups;

– had worsening symptoms;

– experienced unwanted effects; and

– stopped treatment due to unwanted effects.

What did we do?

We searched for studies that compared ocrelizumab against any other medicine or placebo for people with a confirmed diagnosis of relapsing-remitting MS or primary progressive MS. People in the studies could be any age or sex, could have mild or severe symptoms, and could have had MS for any length of time.

We compared and summarised their results, and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found four studies with 2551 people with MS. The largest study included 732 people and the smallest included 163 people. The studies were in countries around the world, but mostly in the USA. One study lasted for 24 weeks; two studies for 96 weeks; and one study for at least 120 weeks. Pharmaceutical companies funded the four studies.

Three studies compared ocrelizumab with interferon beta-1a in people with relapsing-remitting MS. Interferon beta-1a is an older type of disease-modifying therapy. One study compared ocrelizumab with placebo for people with primary progressive MS.

Main results

Ocrelizumab compared with interferon beta-1a for people with relapsing-remitting MS, after 96 weeks of treatment:

– probably substantially reduces the number of people who had flare-ups;

– may substantially reduce the number of people whose symptoms got worse;

– probably makes little or no difference to unwanted effects; and

– may substantially reduce the number of people who stopped having treatment due to unwanted effects.

Ocrelizumab compared with placebo for people with primary progressive MS, after 120 weeks of treatment:

– may reduce the number of people whose symptoms got worse;

– probably increases unwanted effects; and

– may make little or no difference to the number of serious unwanted effects and the number of people who stopped having treatment due to unwanted effects.

What are the limitations of the evidence?

Our confidence in the results is moderate to low for several reasons. First, people dropped out of the studies unevenly, which meant more people had one treatment than the other. Second, there was not enough information about some of our points of interest to allow us to draw conclusions for outcomes, there was not enough information available for us to be confident in the results. Finally, changes in symptoms shown by scans could have been due to causes other than disease progression.

How up-to-date is this evidence?

The evidence is up-to-date to 8 October 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Ocrelizumab compared to interferon beta-1a for relapsing-remitting multiple sclerosis

Ocrelizumab compared to interferon beta-1a for relapsing-remitting multiple sclerosis

Patient or population: people with relapsing-remitting multiple sclerosis
Setting: outpatients
Intervention: ocrelizumab
Comparison: interferon beta-1a

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with interferon beta-1a	Risk with ocrelizumab				
Number of participants experiencing ≥ 1 relapse Follow-up: 96 weeks	**Study population**		**RR 0.61** (0.52 to 0.73)	1656 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
	403 per 1000	234 per 1000 (201 to 274)				
Number of participants experiencing disability progression Follow-up: 96 weeks	**Study population**		**HR 0.60** (0.43 to 0.84)	1656 (2 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	—
	105 per 1000	69 per 1000 (50 to 94)				
Number of participants with any adverse events Follow-up: 96 weeks	**Study population**		**RR 1.00** (0.96 to 1.04)	1651 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
	833 per 1000	833 per 1000 (800 to 866)				
Number of participants with any serious adverse events Follow-up: 96 weeks	**Study population**		**RR 0.79** (0.57 to 1.11)	1651 (2 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	—
	87 per 1000	69 per 1000 (50 to 97)				
Number of participants experiencing treatment discontinuation caused by adverse events Follow-up: 96 weeks	**Study population**		**RR 0.58** (0.37 to 0.91)	1651 (2 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	—
	61 per 1000	35 per 1000 (22 to 55)				
Number of participants with gadolinium-enhancing T1 lesions on MRI	**Study population**		**RR 0.27** (0.22 to 0.35)	1656 (2 RCTs)	⊕⊕⊖⊖ **Low**[a,c]	—

Follow-up: 96 weeks	331 per 1000	89 per 1000 (73 to 116)				
Number of participants with new or enlarging T2-hyperintense lesions on MRI Follow-up: 96 weeks	**Study population** 616 per 1000	388 per 1000 (351 to 425)	**RR 0.63** (0.57 to 0.69)	1656 (2 RCTs)	⊕⊕⊝⊝ **Low**[a,c]	—

*__The risk in the intervention 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; **HR:** hazard ratio; **MRI:** magnetic resonance imaging; **RCT:** randomised controlled trial; **RR:** risk 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 certainty: 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]Downgraded one level due to study limitation (a high rate of dropouts existed and reasons of dropouts were unbalanced between arms).
[b]Downgraded one level due to imprecision (total number of events (i.e. the number of participants experiencing disability progression, the number of participants with any serious adverse events and the number of participants experiencing treatment discontinuation caused by adverse events) was fewer than 300 (the threshold rule-of-thumb value), and thus the available evidence did not meet the optimal information size (OIS) criteria. Wide 95% confidence intervals).
[c]Downgraded one level due to indirectness (changes in MRI (gadolinium-enhancing T1 lesions or new or newly enlarging T2-hyperintense lesions) were not consistently proved closely related to changes in disability progression).

Summary of findings 2. Ocrelizumab compared to placebo for primary progressive multiple sclerosis

Ocrelizumab compared to placebo for primary progressive multiple sclerosis

Patient or population: people with primary progressive multiple sclerosis
Setting: outpatients
Intervention: ocrelizumab
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with ocrelizumab				

Number of participants experiencing disability progression Follow-up: ≥ 120 weeks	**Study population**		**HR 0.75** (0.58 to 0.98)	731 (1 RCT)	⊕⊕⊝⊝ **Low**[a,b]	—
	357 per 1000	296 per 1000 (239 to 367)				
Number of participants with any adverse events Follow-up: ≥ 120 weeks	**Study population**		**RR 1.06** (1.01 to 1.11)	725 (1 RCT)	⊕⊕⊕⊝ **Moderate**[a]	—
	900 per 1000	954 per 1000 (909 to 999)				
Number of participants with any serious adverse events Follow-up: ≥ 120 weeks	**Study population**		**RR 0.92** (0.68 to 1.23)	725 (1 RCT)	⊕⊕⊝⊝ **Low**[a,b]	—
	222 per 1000	204 per 1000 (151 to 273)				
Number of participants experiencing treatment discontinuation caused by adverse event Follow-up: ≥ 120 weeks	**Study population**		**RR 1.23** (0.55 to 2.75)	725 (1 RCT)	⊕⊕⊝⊝ **Low**[a,b]	—
	33 per 1000	41 per 1000 (18 to 92)				
Number of participants with gadolinium-enhancing T1 lesions on MRI Follow-up: ≥ 120 weeks	—		—	—	—	No data available.
Number of participants with new or enlarging T2-hyperintense lesions on MRI Follow-up: ≥ 120 weeks	—		—	—	—	No data available.

*__The risk in the intervention 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; **HR:** hazard ratio; **RCT:** randomised controlled trial; **RR:** risk 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 certainty: 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]Downgraded one level due to study limitation (a high rate of dropouts existed and reasons of dropouts were unbalanced between arms).

[b]Downgraded one level due to imprecision (total number of events (i.e. the number of participants experiencing disability progression, the number of participants with any serious adverse events, and the number of participants experiencing treatment discontinuation caused by adverse events) was fewer than 300 (the threshold rule-of-thumb value), and thus the available evidence did not meet the optimal information size (OIS) criteria. Wide 95% confidence intervals).

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) that can cause neurological relapses that may partially or fully resolve, as well as disability accumulation. Neurodegeneration is a fundamental aspect of MS pathogenesis as loss of axons, dendrites, and neurons is a major cause of permanent neurological disability in people with MS (Dutta 2011). Current studies support inflammatory cascade as the underlying cause of oligodendrocytes and myelin sheath loss during earlier stages in MS (Dhib-Jalbut 2007). Epidemiological studies have shown that the distribution of MS can be attributed to differences in genetic, particularly the HLA-DR15 haplotype, and environmental factors and their interactions. The prevalence of MS is lowest at the equator and increases with north and south latitude (Koch-Henriksen 2010). With an incidence of 2 per 100,000 in Asia and more than 100 per 100,000 in Northern Europe and North America, the burden of MS is similarly affected by unevenness in longevity and comorbidity (Howard 2016).

The most common clinical manifestations of MS are optic neuritis, brainstem and spinal cord syndromes, and other less common symptoms, including cortical presentations such as dominant parietal lobe syndromes (Dobson 2019). Clinical manifestations are often varied because of the site of neurological involvement. The International Advisory Committee on Clinical Trials of Multiple Sclerosis has reviewed the disease phenotypes, including consideration of disease activity based on clinical relapses, disease progression, and imaging findings. About 85% of people have a relapsing-remitting (RRMS) course, characterised by a course of deteriorations and remissions. The course of secondary progressive MS (SPMS) is characterised by gradual deterioration after an initial relapsing disease course with or without acute deteriorations during the progressive course (Lublin 2014). Primary progressive MS (PPMS) is a part of progressive MS phenotypes; it enters a progressive course from onset without a relapsing course (Lublin 2014).

Current immunomodulatory drugs for the treatment of RRMS include interferon beta-1a, interferon beta-1b, peginterferon beta-1a, glatiramer acetate, alemtuzumab, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, ocrelizumab, daclizumab (withdrawn in 2018), cladribine, siponimod, ozanimod, and ponesimod (NIDDK 2021; Rotstein 2019). Ocrelizumab is the only immunomodulatory agent approved for PPMS (Rotstein 2019). The reduction in relapse and disability progression risk varies between disease-modifying therapies (DMT) (Fogarty 2017). At present, MS is incurable. DMTs are targeted to reduce the risk of relapses and disability progression.

Description of the intervention

Ocrelizumab is a humanised anti-CD20 monoclonal antibody which was approved by the US Food and Drug Administration (FDA) in 2017 for the treatment of RRMS or PPMS (FDA 2017). While a series of DMTs have been approved for RRMS, ocrelizumab is the only DMT approved for PPMS (Syed 2018). This capability has attracted the attention of researchers interested in studying the benefits, harms, and tolerability of ocrelizumab. Treatment with ocrelizumab is associated with adverse events, such as infusion-related reactions, upper respiratory tract infection, nasopharyngitis, urinary tract infection, and headache.

How the intervention might work

CD20, an activated-glycosylated phosphoprotein, is a cell surface antigen found on pre-B cells and mature and memory B-cells (Sorensen 2016). Bubien and colleagues have suggested that B-cells play a central role in the pathogenesis of MS. During antigen recognition by immature and mature B-cells, CD20 is transduced through the B-cell antigen receptor (Bubien 1993). The following mechanisms of B-cell depletion have been suggested:

1. "complement-dependent cytotoxicity characterised by the formation of pores in the cell membrane, causing breakdown of the cell membrane leading to cell lysis" (Sorensen 2016);
2. "antibody-dependent cellular cytotoxicity involving macrophages, natural killer cells, and cytotoxic T cells that act together to cause cell destruction" (Sorensen 2016);
3. "apoptosis, which occurs through cross-linking membrane CD20 on the target cell surface" (Clynes 2000; Reff 1994; Sorensen 2016).

Animal experiments suggest that the depletion of B-cell may cause changes in the cytokine network, reducing pathogenic T-cell responses and contributing to the favourable effect of anti-CD20 treatment in MS (Li 2015). Ocrelizumab, as a humanised anti-CD20 monoclonal antibody, depletes B-cells ranging from pro-B-cells to short-lived plasmablasts. Palanichamy 2014 proposes that anti-CD20 treatment not only depletes B-cells, it also depletes CD20+ T cells. Memory B-cells mediate autoproliferation of peripheral Th1 cells in an HLA-DR-dependent manner in people carrying the HLA-DR15 haplotype. Depletion of B cells in vitro and therapeutically in vivo by anti-CD20 effectively reduces autoproliferation of T-cells (Jelcic 2018).

For MS, B-cell-depleting treatment-related monoclonal anti-CD20 antibodies includes rituximab, ocrelizumab, and ofatumumab. Compared with rituximab, ocrelizumab more effectively causes a pathogenic response in vivo; it also increases the antibody-dependent cell-mediated cytotoxicity and reduces the complement-dependent cytotoxicity (Sorensen 2016). Compared with rituximab, ocrelizumab has lower immunogenicity and is less likely to induce human anti-human antibodies in repeated injections (Sorensen 2016).

Why it is important to do this review

Ocrelizumab was approved by the US FDA to treat adults with RRMS and PPMS in March 2017. This was the first drug approved by the FDA for PPMS. In November 2017, the European Medicines Agency (EMA) approved ocrelizumab as the first medicine to receive a positive endorsement for treatment of people with early-stage PPMS. Therefore, it is important to assess the benefit–risk ratio of ocrelizumab for people with MS.

OBJECTIVES

To assess the benefits, harms, and tolerability of ocrelizumab in people with RRMS and PPMS.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with blinded assessment of participants, personnel, and outcomes.

Types of participants

Participants with a confirmed diagnosis of RRMS or PPMS, according to published criteria (McDonald 2001; Polman 2005; Polman 2011; Thompson 2018), regardless of age, sex, degree of disability, or duration of the disease. And we excluded participants with other clinically significant autoimmune disorder or previous immunosuppressive before.

Types of interventions

Experimental intervention: ocrelizumab alone or associated with other medications at the approved dose of 600 mg every 24 weeks for any course duration.

Comparator: placebo, any other active drug therapy (i.e. corticosteroids, plasmapheresis, beta interferons, glatiramer acetate, natalizumab, alemtuzumab, daclizumab, mitoxantrone, fingolimod, dimethyl fumarate, or teriflunomide).

Concomitant interventions were allowed only if used equally in all arms of the trial.

Types of outcome measures

We assessed the following outcomes at the end of the treatment period.

Primary outcomes

Benefits

1. Number of participants experiencing at least one relapse at one year and after, or at the end of the study. 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).
2. Number of participants experiencing disability progression at 24 weeks to week 96. Disability progression is defined as an increase from the baseline Expanded Disability Status Scale (EDSS) score of at least 1.0 point (or 0.5 points if the baseline EDSS score was greater than 5.5) that was sustained for at least 24 weeks.

Harms

1. Number of participants experiencing any adverse event.
2. Number of participants experiencing any serious adverse event. A serious adverse event was defined as any adverse event that, at any dose, fulfilled at least one of the following criteria: was fatal; was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; was medically significant or required intervention to prevent one or other of the outcomes listed above.
3. Number of participants experiencing treatment discontinuation caused by adverse events.

Secondary outcomes

1. Change in quality of life at one year and after, or at the end of the study. The following scales were accepted: 36-item Short-Form Health Survey (SF-36) scores (Ware 1992), Multiple Sclerosis Quality of Life (MSQoL-54) questionnaire scores (Vickrey 1995), Multiple Sclerosis Quality of Life Inventory (MSQLI) (Fischer 1999), or Functional Assessment of Multiple Sclerosis (FAMS) (Cella 1996).
2. Number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging (MRI) at one year and after, or at the end of the study.
3. Number of participants with new or enlarging T2-hyperintense lesions on MRI at one year and after, or at the end of the study.
4. Brain volume changed at one year and after, or at the end of the study.

Search methods for identification of studies

Electronic searches

We searched the following on 8 October 2021:

1. Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (2021 Issue 9);
2. MEDLINE (PubMed) (from 1966);
3. Embase (Embase.com) (from 1974);
4. ClinicalTrials.gov (www.clinicaltrials.gov) for all prospectively registered trials (from 2000);
5. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch) (from 2005).

The full search strategies are listed in Appendix 1, Appendix 2, Appendix 3, Appendix 4, and Appendix 5.

Searching other resources

In addition, we used the following methods.

1. We screened reference lists of relevant review articles and primary studies found.
2. We contacted experts in the field to identify further published or unpublished trials.
3. We contacted the main authors of studies if data reported in the original articles were incomplete.

Data collection and analysis

Selection of studies

Three review authors (ML, JZ, and JL) independently screened titles and abstracts of the citations retrieved by the literature search to obtain titles and abstracts of studies possibly relevant to the review. We obtained full copies of potentially relevant studies for further assessment. We also independently evaluated the eligibility of these studies on the basis of information available in the published data. We excluded irrelevant studies. We resolved disagreements through discussion.

Data extraction and management

Three review authors (ML, JZ and JL) independently extracted data from selected trials using standardised forms, and entered the data into Review Manager 5 (Review Manager 2020).

We extracted the following information from individual studies.

1. Publication details (i.e. year, data, country, journal, authors).
2. Study design and setting: inclusion criteria, exclusion criteria, number of randomised participants and characteristics of participants.
3. Details of intervention (i.e. doses, frequency, scheme, length).
4. Description of outcomes.
5. Risk of bias: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias.
6. Data analyses.
7. Declarations of interest and funding source.

We resolved disagreements by discussion among the review authors.

Assessment of risk of bias in included studies

Three review authors (ML, JZ, and YZ) independently assessed the risks of bias in included studies, using the Cochrane risk of bias criteria (Higgins 2021). We assessed the following domains.

1. Sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other potential sources of bias.

We judged each domain as being at low, high, or unclear risk of bias. And we resolved any disagreements by discussion among all review authors. We judged the overall risk of bias of each included study according to the following criteria.

1. Low risk of bias (plausible bias unlikely to seriously alter the results) if all the above items were met.
2. Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more items were assessed as unclear.
3. High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more items were not met.

Measures of treatment effect

We analysed data using Review Manager 5 (Review Manager 2020). We expressed results for dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs). We calculated mean differences (MD) with 95% CIs for continuous data. We used hazard ratio (HR) with 95% CIs if calculating time-to-event data.

Unit of analysis issues

We included studies with parallel-group design: participants randomly assigned to intervention or control were analysed at the individual allocation level. We planned to include cross-over studies by considering only data from the first half of the cross-over trial, but the search found no cross-over studies. We performed each separate analysis based on the preset outcomes and different periods of follow-up (24 and 96 weeks).

Dealing with missing data

We contacted authors of identified studies to obtain additional information. If additional information was not obtained, we analysed the available data.

Assessment of heterogeneity

We evaluated clinical and methodological heterogeneity across included studies by comparing characteristics of participants, interventions, and study designs.

We evaluated statistical heterogeneity among included studies using a Chi^2 test with an alpha of 0.1, and with the I^2 test. A P value of less than 0.1 and an I^2 statistic more than 50% was an indication of substantial statistical heterogeneity (Higgins 2021); we examined potential sources of clinical and methodological heterogeneity.

Assessment of reporting biases

We did not use funnel plots to explore possible publication bias due to an insufficient number of included studies.

Data synthesis

We used Review Manager 5 to conduct formal meta-analysis (Review Manager 2020). The selection of a fixed-effect or random-effects model was mainly based on the results of the Chi^2 test and I^2 statistic for heterogeneity (Higgins 2021). If the I^2 statistic indicated substantial statistical heterogeneity, we explored potential causes of heterogeneity first, to determine whether a subgroup analyses was needed. If the substantial heterogeneity still could not be explained, we adopted a random-effects model. If the I^2 statistic indicated no significant statistical heterogeneity, we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroups analyses.

1. Different dosages of ocrelizumab.
2. Different duration of treatment.
3. Different degrees of disability.
4. Different co-interventions.
5. Different types of interferon beta-1a.

However, we did not carry out subgroup analyses to consider dosages of ocrelizumab, baseline degree of disability, cointerventions, and types of interferon beta-1a due to lack of available data.

Sensitivity analysis

We planned to perform sensitivity analysis by excluding trials at high risk of bias (i.e. non-random sequence generation and inadequate allocation concealment, lack of blinded outcome assessor, lack of blinded participants/personnel, or a combination of these). However, because of the limited number of studies, we deemed this analysis inappropriate.

Summary of findings and assessment of the certainty of the evidence

In the summary of findings tables, we included trials with a follow-up period longer than 12 months. We created two summary of findings tables comparing intravenous ocrelizumab at the

approved dose of 600 mg every 24 weeks; one versus subcutaneous interferon beta-1a 44 µg three times weekly for RRMS at 96 weeks (Summary of findings 1), and one versus placebo for PPMS at 120 weeks (Summary of findings 2).

In Summary of findings 1, we included seven outcomes.

1. Number of participants experiencing at least one relapse.
2. Number of participants experiencing disability progression.
3. Number of participants with any adverse event.
4. Number of participants with any serious adverse events.
5. Number of participants experiencing treatment discontinuation caused by adverse events.
6. Number of participants with gadolinium-enhancing T1 lesions on MRI.
7. Number of participants with new or enlarging T2-hyperintense lesions on MRI.

In Summary of findings 2, we included six outcomes.

1. Number of participants experiencing disability progression.
2. Number of participants with any adverse event.
3. Number of participants with any serious adverse events.
4. Number of participants experiencing treatment discontinuation caused by adverse events.
5. Number of participants with gadolinium-enhancing T1 lesions on MRI.
6. Number of participants with new or enlarging T2-hyperintense lesions on MRI.

We used the five GRADE parameters (risk of bias, inconsistency, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence as it related to the studies that contributed data to the meta-analyses for prespecified outcomes. We used the methods and recommendations described in Section 8 and Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021) using the GRADEpro GDT (GRADEpro GDT). We justified all decisions to downgrade or upgrade the certainty of studies in the footnotes and made comments to aid readers' understanding of the review when necessary.

RESULTS

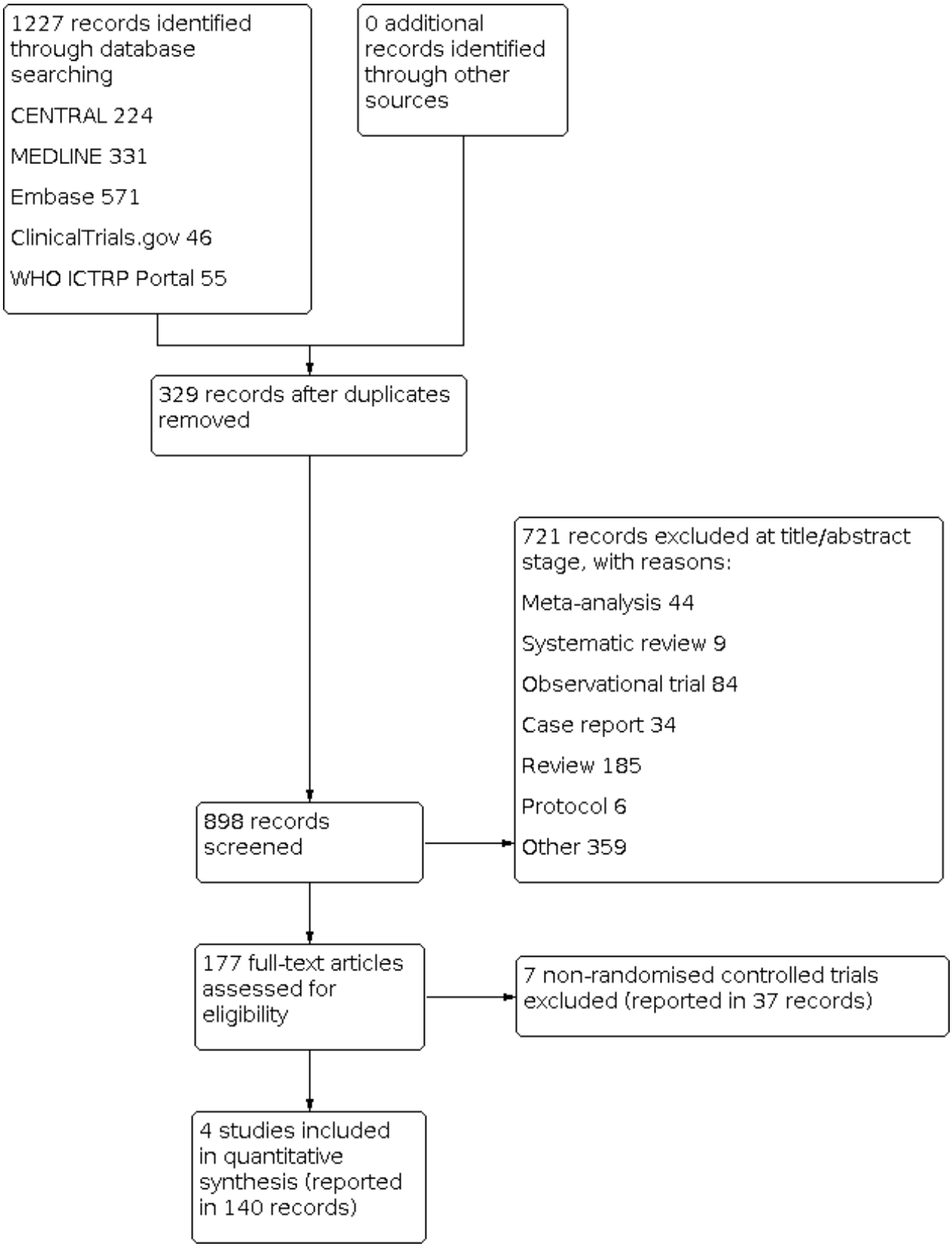
Description of studies

See: Characteristics of included studies table.

Results of the search

The search strategies retrieved 1227 references. A total of 177 references were potentially eligible. After reading the full texts, we included these 140 records. They referred to four RCTs and 136 ancillary reports about these four primary studies. The flow diagram of the process of study identification and selection is presented in Figure 1.

Figure 1. Study flow diagram.



Included studies

The four RCTs included 2551 participants (Kappos 2011; OPERA I 2017; OPERA II 2017; ORATORIO 2017). Kappos 2011 was a multicentric RCT comparing ocrelizumab versus intramuscular interferon beta-1a or placebo for people with RRMS according to the McDonald criteria (McDonald 2001). OPERA I 2017 and OPERA II 2017 were multicentric RCTs comparing ocrelizumab versus subcutaneous interferon beta-1a for people with RRMS according to the McDonald criteria (Polman 2011). ORATORIO 2017 was a multicentric RCT comparing ocrelizumab versus placebo for people with PPMS according to the McDonald criteria (Polman 2005).

For people with RRMS, we identified three RCTs including 1819 participants (Kappos 2011; OPERA I 2017; OPERA II 2017). Kappos 2011 was a multi-arm trial. OPERA I 2017 and OPERA II 2017 were two identical double-arm trials. We did not merge multi-arm trials involving ocrelizumab at different doses compared to interferon beta treatment or placebo and presented separate data for each arm. Kappos 2011 included two cycles, we included the first cycle, which was a randomised designed. The RCTs used the following regimens.

1. Kappos 2011 was a phase II trial. The ocrelizumab 600 mg group had a dual infusion of 300 mg for days 1 and 15. The placebo group received placebo on days 1 and 15. The interferon beta-1a group received intramuscular interferon beta-1a (Avonex, Biogen Idec Inc) once a week for 24 weeks.
2. OPERA I 2017 (from 31 August 2011 to 14 February 2013) was a phase III trial. Participants received intravenous ocrelizumab 600 mg (two 300-mg infusions on days 1 and 15 for the first dose and as a single 600-mg infusion thereafter) every 24 weeks or subcutaneous interferon beta-1a (Rebif, EMD Serono) 44 µg three times weekly for 96 weeks.
3. OPERA II 2017 (from 20 September 2011 to 28 March 2013) was a phase III trial. Participants received intravenous ocrelizumab 600 mg (two 300-mg infusions on days 1 and 15 for the first dose and as a single 600-mg infusion thereafter) every 24 weeks or subcutaneous interferon beta-1a (Rebif, EMD Serono) 44 µg three times weekly for 96 weeks.

For people with PPMS, we included one RCT including 732 participants (ORATORIO 2017).

1. ORATORIO 2017 (from 3 March 2011 to 27 November 2012) was a phase III trial. Participants received intravenous ocrelizumab 600 mg (administered as two 300-mg infusions 14 days apart) every 24 weeks or matching placebo every 24 weeks for at least 120 weeks.

Details of these RCTs are available in the Characteristics of included studies table.

Excluded studies

We excluded none of the potentially eligible studies.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

The risk of bias of each study is detailed in the Characteristics of included studies table. Figure 2 and Figure 3 present the risk of bias summary along with review authors' judgements about each risk of bias item for each included study.

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

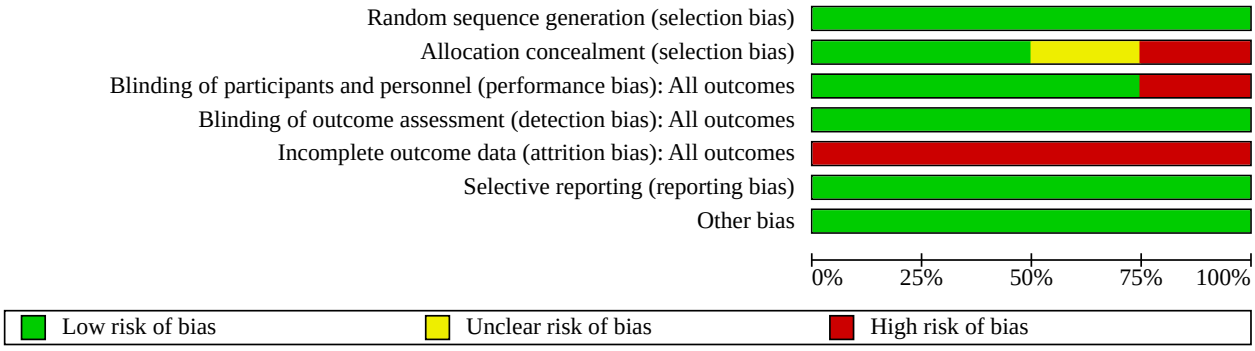
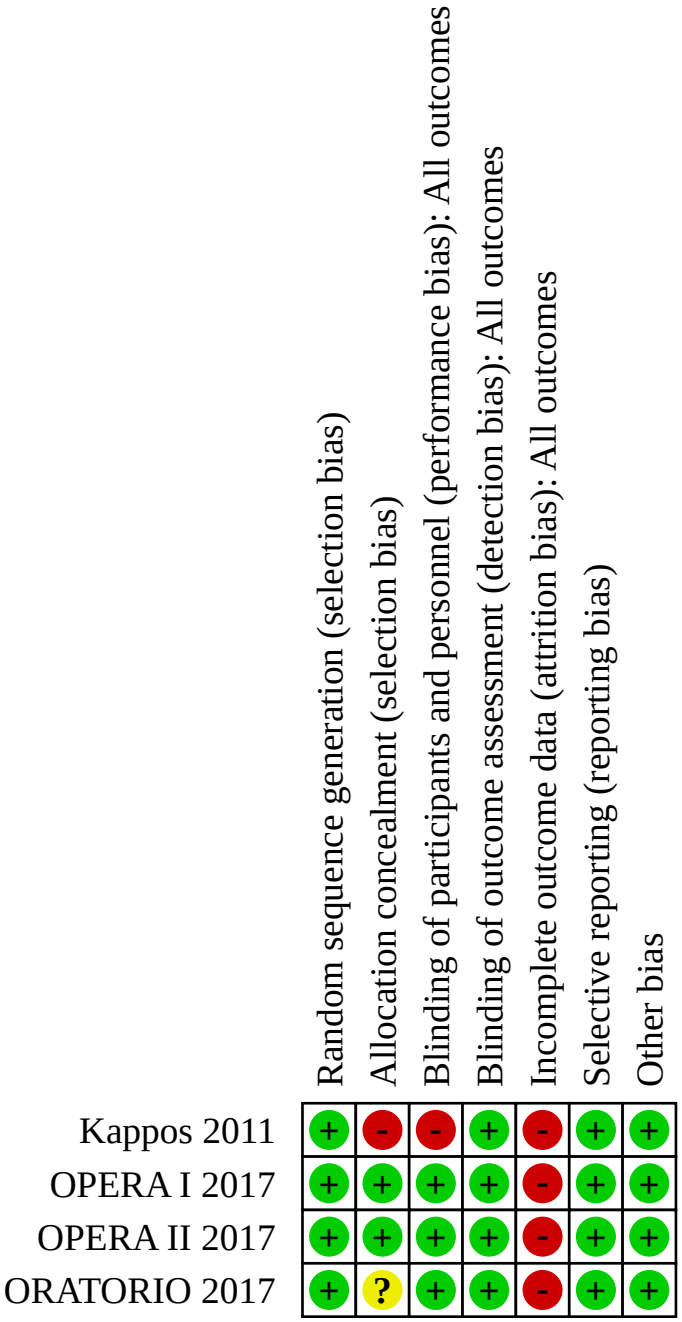


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All four included trials were reported as randomised with the use of an independent interactive Web-response system. Thus, the four studies were at low risk of bias for random sequence generation.

For allocation concealment, we classified Kappos 2011 at high risk of bias because the participants in the interferon beta-1a group were not blinded to allocation. We classified two studies at low risk of bias because they provided an adequate method to ensure allocation concealment (OPERA I 2017; OPERA II 2017). We

classified ORATORIO 2017 at unclear risk of bias because it did not provide enough information to allow judgement.

Blinding

We considered Kappos 2011 at high risk of performance bias (participants and personnel) because the treating investigator had access to benefits and harms data and interferon beta-1a group was open label. We considered the other three studies at low risk of performance bias (OPERA I 2017; OPERA II 2017; ORATORIO 2017).

We considered all studies at low risk of detection bias (outcome assessment) because blinded raters evaluated the benefits and harms outcomes.

Incomplete outcome data

All four trials provided sufficient details about the number of, and the reasons for, dropouts. In Kappos 2011, the dropout rate was unbalanced between the four groups (ocrelizumab 600 mg: 8.9%; ocrelizumab 2000 mg: 12.7%; interferon beta-1a: 7.27%; placebo: 0%). In OPERA I 2017, the dropout rate was unbalanced between the ocrelizumab group (10.7%) and the interferon beta-1a group (17.3%). In OPERA II 2017, the dropout rate was unbalanced between the ocrelizumab group (13.7%) and the interferon beta-1a group (23.4%). In ORATORIO 2017, the dropout rate was unbalanced between the ocrelizumab group (18.0%) and the placebo group (29.0%). Due to these imbalances, we classified all four trials at high risk of attrition bias.

Selective reporting

All four trials reported all specified primary and secondary outcomes. We classified them at low risk of reporting bias.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Ocrelizumab compared to interferon beta-1a for relapsing-remitting multiple sclerosis; **Summary of findings 2** Ocrelizumab compared to placebo for primary progressive multiple sclerosis

We defined three main comparisons, ocrelizumab versus interferon beta-1a for RRMS, ocrelizumab versus placebo for RRMS, and ocrelizumab versus placebo for PPMS.

We reported the main results concerning benefit and withdrawals due to adverse events of ocrelizumab at the approved dose of 600 mg compared to interferon beta-1a for RRMS at 96 weeks in Summary of findings 1 and compared to placebo for PPMS at 120 weeks in Summary of findings 2.

Comparison 1: ocrelizumab 600 mg versus interferon beta-1a for relapsing-remitting multiple sclerosis

Kappos 2011, OPERA I 2017, and OPERA II 2017 compared ocrelizumab versus interferon beta-1a for treating RRMS (see Summary of findings 1).

Primary outcomes: benefits

Number of participants experiencing at least one relapse

Three trials reported the number of participants experiencing at least one relapse (Kappos 2011; OPERA I 2017; OPERA II 2017). Kappos 2011 assessed the number of participants experiencing at least one relapse at 24 weeks. There was little to no difference between groups (RR 0.33, 95% CI 0.09 to 1.14; P = 0.08; 109 participants). OPERA I 2017 and OPERA II 2017 assessed the number of participants experiencing at least one relapse at 96 weeks. The rate of participants experiencing at least one relapse was lower with ocrelizumab than with interferon beta-1a (RR 0.61, 95% CI 0.52 to 0.73; P < 0.00001; I^2 = 0%; 1656 participants; fixed-effect model; moderate-certainty evidence) (Analysis 1.1).

Number of participants experiencing disability progression

Two trials reported the number of participants experiencing 24-week confirmed disability progression at 96 weeks (OPERA I 2017; OPERA II 2017). The rate was lower with ocrelizumab than with interferon beta-1a (HR 0.60, 95% CI 0.43 to 0.84; P = 0.003; I^2 = 0%; 1656 participants; fixed-effect model) (Analysis 1.2). (We used HR to calculate this outcome due to time-to-event data.)

Primary outcomes: harms

Three trials reported adverse events and serious adverse events (Kappos 2011; OPERA I 2017; OPERA II 2017).

Number of participants experiencing any adverse event

Kappos 2011 assessed the number of participants experiencing any adverse events at 24 weeks. There was little to no difference between groups (RR 1.11, 95% CI 0.81 to 1.53; P = 0.51; 109 participants). OPERA I 2017 and OPERA II 2017 assessed the number of participants experiencing any adverse events at 96 weeks. There was little to no difference between groups (RR 1.00, 95% CI 0.96 to 1.04; P = 0.99; I^2 = 0%; 1651 participants; fixed-effect model) (Analysis 1.3).

Number of participants experiencing any serious adverse events

Kappos 2011 assessed the number of participants experiencing any serious adverse events at 24 weeks. There was little to no difference between groups (RR 0.49, 95% CI 0.05 to 5.26; P = 0.56; 109 participants). OPERA I 2017 and OPERA II 2017 assessed the number of participants experiencing any serious adverse events at 96 weeks. There was little to no difference between groups (RR 0.79, 95% CI 0.57 to 1.11; P = 0.17; I^2 = 0%; 1651 participants; fixed-effect model) (Analysis 1.4).

Number of participants experiencing treatment discontinuation caused by adverse events

Three trials reported the number of participants experiencing treatment discontinuation caused by adverse events (Kappos 2011; OPERA I 2017; OPERA II 2017). Kappos 2011 assessed the number of participants experiencing treatment discontinuation caused by adverse events at 24 weeks. There was little to no difference between groups (RR 1.96, 95% CI 0.18 to 21.02; P = 0.58; 109 participants). OPERA I 2017 and OPERA II 2017 assessed the number of participants experiencing treatment discontinuation caused by adverse events at 96 weeks. There rate of participants experiencing treatment discontinuation caused by adverse events was lower with ocrelizumab than with interferon beta-1a (RR 0.58, 95% CI 0.37

to 0.91; P = 0.02; I^2 = 0%; 1651 participants; fixed-effect model) (Analysis 1.5).

Secondary outcomes

Change in quality of life

Two trials reported the change in SF-36 Physical Component Summary score from baseline to week 96 (OPERA I 2017; OPERA II 2017). The change in score was better with ocrelizumab than with interferon beta-1a (MD 0.93, 95% CI 0.02 to 1.83; P = 0.04; I^2 = 0%; 1656 participants; fixed-effect model; Analysis 1.6)

Number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging

Three trials reported the number of participants with gadolinium-enhancing T1 lesions on MRI (Kappos 2011; OPERA I 2017; OPERA II 2017). Kappos 2011 assessed the number of participants with gadolinium-enhancing T1 lesions on MRI at 24 weeks. The rate was lower with ocrelizumab than with interferon beta-1a (RR 0.44, 95% CI 0.25 to 0.77; P = 0.004; 109 participants). OPERA I 2017 and OPERA II 2017 assessed the number of participants with gadolinium-enhancing T1 lesions on MRI at 96 weeks. The rate was lower with ocrelizumab than with interferon beta-1a (RR 0.27, 95% CI 0.22 to 0.35; P < 0.00001; I^2 = 0%; 1656 participants; fixed-effect model) (Analysis 1.7).

Number of participants with new or enlarging T2-hyperintense lesions on magnetic resonance imaging

Two trials reported the number of participants with new or enlarging T2-hyperintense lesions on MRI at 96 weeks (OPERA I 2017; OPERA II 2017). The rate was lower with ocrelizumab than with interferon beta-1a (RR 0.63, 95% CI 0.57 to 0.69; P < 0.00001; I^2 = 0%; 1656 participants; fixed-effect model; Analysis 1.8).

Mean percentage change in brain-volume from week 24 to the end of the study

Two trials reported the mean percentage change in brain-volume from week 24 to week 96 (OPERA I 2017; OPERA II 2017). The mean percentage change was less with ocrelizumab than with interferon beta-1a (MD 0.14, 95% CI 0.05 to 0.23; P = 0.003; I^2 = 0%; 1656 participants; fixed-effect model; Analysis 1.9).

Comparison 2: ocrelizumab 600 mg versus placebo for relapsing-remitting multiple sclerosis

We were unable to conduct meta-analysis because only one study was included. Thus, we have provided a descriptive summary of the results. Kappos 2011 compared ocrelizumab versus placebo for treating RRMS at 24 weeks.

Primary outcomes: benefits

Number of participants experiencing at least one relapse

Kappos 2011 reported the number of participants experiencing at least one relapse at 24 weeks. The rate was lower with ocrelizumab than with placebo (RR 0.18, 95% CI 0.06 to 0.60; P = 0.005; 109 participants; Analysis 2.1).

Number of participants experiencing disability progression

Kappos 2011 did not assess the number of participants experiencing disability progression.

Primary outcomes: harms

Number of participants experiencing any adverse event

Kappos 2011 reported the number of participants experiencing any adverse events at 24 weeks. There was little to no difference between groups (RR 0.88, 95% CI 0.67 to 1.15; P = 0.35; 109 participants; Analysis 2.2).

Number of participants experiencing any serious adverse events

Kappos 2011 reported the number of participants experiencing any serious adverse events at 24 weeks. There was little to no difference between groups (RR 0.49, 95% CI 0.05 to 5.26; P = 0.56; 109 participants; Analysis 2.3).

Number of participants experiencing treatment discontinuation caused by adverse events

Kappos 2011 reported the number of participants experiencing treatment discontinuation caused by adverse events at 24 weeks. There was little to no difference between groups (RR 4.91, 95% CI 0.24 to 99.97; P = 0.30; 109 participants; Analysis 2.4).

Secondary outcomes

Change in quality of life

Kappos 2011 did not assess quality of life.

Number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging

Kappos 2011 reported the number of participants with gadolinium-enhancing T1 lesions on MRI at 24 weeks. The rate was lower with ocrelizumab than with placebo (RR 0.34, 95% CI 0.20 to 0.58; P < 0.0001; 109 participants; Analysis 2.5).

Number of participants with new or enlarging T2-hyperintense lesions on magnetic resonance imaging

Kappos 2011 did not assess number of participants with new or enlarging T2-hyperintense lesions on MRI.

Mean percentage change in brain-volume from week 24 to the end of the study

Kappos 2011 did not assess mean percentage change in brain-volume from week 24 to the end of the study.

Comparison 3: ocrelizumab 600 mg versus placebo for primary progressive multiple sclerosis

We were unable to conduct meta-analysis because only one study was included. Thus, we have provided a descriptive summary of the results. ORATORIO 2017 compared ocrelizumab versus placebo for treating PPMS for at least 120 weeks (see Summary of findings 2).

Primary outcomes: benefits

Number of participants experiencing at least one relapse

This outcome is not applicable to PPMS.

Number of participants experiencing disability progression

ORATORIO 2017 reported that the number of participants with 24-week confirmed disability progression was 29.6% with ocrelizumab and 35.7% with placebo. The rate of participants experiencing 24-week confirmed disability progression was lower with ocrelizumab than with placebo (HR 0.75, 95% CI 0.58 to 0.98; P = 0.03; 731

participants; Analysis 3.1). (We used HR to calculate this outcome due to time-to-event data.)

Primary outcomes: harms

Number of participants experiencing any adverse event

ORATORIO 2017 reported that in the ocrelizumab group, 462/486 (95.1%) participants experienced any adverse events and in the placebo group, 215/239 (90.0%) participants experienced any adverse events. The rate was higher with ocrelizumab than with placebo (RR 1.06, 95% CI 1.01 to 1.11; P = 0.02; 725 participants; Analysis 3.2).

Number of participants experiencing any serious adverse events

ORATORIO 2017 reported that in the ocrelizumab group, 99/486 (20.4%) participants experienced any serious adverse events and in the placebo group, 53/239 (22.2%) participants experienced any serious adverse events. There was little to no difference between groups (RR 0.92, 95% CI 0.68 to 1.23; P = 0.57; 725 participants; Analysis 3.3).

Number of participants experiencing treatment discontinuation caused by adverse events

ORATORIO 2017 reported that 20/486 (4.1%) participants in the ocrelizumab group experienced treatment discontinuation caused by adverse events and 8/239 (3.3%) participants in the placebo group experienced treatment discontinuation caused by adverse events. There was little to no difference between groups (RR 1.23, 95% CI 0.55 to 2.75; P = 0.62; 725 participants; Analysis 3.4).

Secondary outcomes

Change in quality of life

ORATORIO 2017 reported the change in SF-36 Physical Component Summary score from baseline to week 120. There was little to no difference between groups (adjusted MD 0.38, 95% CI −1.04 to 1.80; P = 0.60; 732 participants; Analysis 3.5).

Number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging

ORATORIO 2017 did not assess number of participants with gadolinium-enhancing T1 lesions on MRI.

Number of participants with new or enlarging T2-hyperintense lesions on magnetic resonance imaging

ORATORIO 2017 did not assess number of participants with new or enlarging T2-hyperintense lesions on MRI.

Mean percentage change in brain-volume from week 24 to the end of the study

ORATORIO 2017 reported that the adjusted mean percentage change in brain volume from week 24 to week 120 was lower with ocrelizumab than with placebo (MD 0.19, 95% CI 0.01 to 0.37; P = 0.03; 732 participants; Analysis 3.6).

DISCUSSION

Summary of main results

This systematic review aimed to evaluate the benefits, harms, and tolerability of ocrelizumab compared with placebo or any other drug treatments for RRMS or PPMS.

For RRMS, based on the results of two RCTs, compared to interferon beta-1a, ocrelizumab 600 mg:

1. probably reduces the relapse rate at 96 weeks;
2. may reduce the number of participants with disability progression at 96 weeks;
3. probably results in little to no difference in the number of participants with any adverse events at 96 weeks;
4. may result in little to no difference in the number of participants with any serious adverse events at 96 weeks;
5. may reduce the number of participants experiencing treatment discontinuation caused by adverse events at 96 weeks;
6. may reduce the number of participants with gadolinium-enhancing T1 lesions on MRI at 96 weeks;
7. may reduce the number of participants with new or enlarging T2-hyperintense lesions on MRI at 96 weeks.

For PPMS, based on the results of one RCT, compared to placebo, ocrelizumab 600 mg:

1. may reduce the number of participants with disability progression at 120 weeks;
2. probably increases the number of adverse events at 120 weeks;
3. may result in little to no difference in the number of participants with any serious adverse event at 120 weeks;
4. may result in little to no difference in the number of participants experiencing treatment discontinuation caused by adverse events at 120 weeks.

Overall completeness and applicability of evidence

In this review, we included three RCTs that evaluated the benefit of ocrelizumab as monotherapy versus interferon beta-1a or placebo for RRMS and one RCT that compared ocrelizumab versus placebo for PPMS. For RRMS, two identical RCTs contributed to the main evidence. Participants randomly received intravenous ocrelizumab 600 mg every 24 weeks or subcutaneous interferon beta-1a 44 µg three times weekly for 96 weeks. For PPMS, participants randomly received intravenous ocrelizumab 600 mg or placebo every 24 weeks for at least 120 weeks. It is important to note that MS is a chronic disease, and treatment of MS requires adequate duration of medication and follow-up to determine benefits, harms, and tolerability outcomes, adding to the uncertainty of these findings.

We selected outcome measures that evaluated benefits (relapse rate, disability progression), harms (adverse events and serious adverse events), tolerability (treatment discontinuation caused by adverse events), and MRI appearance (gadolinium-enhancing T1 lesions and new or newly enlarging T2-hyperintense lesions). We performed meta-analyses using the available data from the studies. The small number of included studies and the absence of data on people receiving treatment over a longer time (e.g. 144 weeks or longer) might increase the uncertainty of these findings. Besides, changes in MRI were not consistently proved closely related to changes in disability progression. Further, the studies only included people with RRMS and PPMS, and we found no evidence for other forms of MS.

In summary, the above limitations may affect the applicability of the evidence. The available evidence is limited to these specific interventions and patients, and requires us to be cautious in interpreting the results.

Quality of the evidence

As shown in Summary of findings 1 and Summary of findings 2, the certainty of evidence for each outcome ranged from low to moderate.

The certainty of evidence for all included outcomes for RRMS at 96 weeks were downgraded due to a high rate of dropouts and unbalanced dropouts between ocrelizumab and interferon beta-1a groups. The certainty of evidence for disability progression, any serious adverse events, and discontinuation caused by adverse events were downgraded due to insufficient information size and wide 95% CIs. The quality of evidence for two MRI outcomes were downgraded due to indirectness. Overall, we gave a GRADE rating of moderate for relapses and any adverse events, and low for disability progression, any serious adverse events, discontinuation caused by adverse events, MRI gadolinium-enhancing T1 lesions and MRI new or newly enlarging T2-hyperintense lesions.

The certainty of evidence for all included outcomes for PPMS for at least 120 weeks were downgraded due to a high rate of dropouts and unbalanced dropouts between ocrelizumab and placebo groups. The certainty of evidence for disability progression, any serious adverse events, and discontinuation caused by adverse events were downgraded due to insufficient information size and wide 95% CIs. Overall, we gave a GRADE rating of moderate for any adverse events, and low for disability progression, any serious adverse events, and discontinuation caused by adverse events.

Potential biases in the review process

To avoid the introduction of bias, we strictly followed the recommendations on searching, study selection, quality assessment, data collection, and data analysis from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). The search strategy for the studies was broad and sensitive, which suggests the likelihood that all RCTs were identified. The authors of this review had no conflicts of interest.

The limitation of this review include:

1. lack of outcome data in the included studies;
2. publication bias was not assessed by funnel plot analysis because fewer than 10 studies were included in the meta-analysis.

Agreements and disagreements with other studies or reviews

This review included four RCTs and evaluated the benefits, harms, and tolerability of ocrelizumab in RRMS and PPMS. We found similar reviews that included and evaluated the use of ocrelizumab in MS, and these reviews differed slightly in their analytical approach, but overall, they reached similar conclusions (McCool 2019; Ng 2020).

AUTHORS' CONCLUSIONS

Implications for practice

For people with relapsing-remitting multiple sclerosis (RRMS), ocrelizumab probably results in a large reduction in relapse rate and probably results in little to no difference in adverse events when compared with interferon beta-1a at 96 weeks (moderate-certainty evidence). Ocrelizumab may result in a large reduction in disability progression, treatment discontinuation caused by adverse events, number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging (MRI), and number of participants with new or enlarging T2-hyperintense lesions on MRI; and may result in little to no difference in serious adverse events (low-certainty evidence).

For people with PPMS, ocrelizumab probably results in a higher rate of adverse events when compared with placebo for at least 120 weeks (moderate-certainty evidence). Ocrelizumab may result in a reduction in disability progression and may result in little to no difference in serious adverse events and treatment discontinuation caused by adverse events (low-certainty evidence).

Ocrelizumab was well tolerated clinically, with infusion-related reactions and nasopharyngitis, and urinary tract and upper respiratory tract infections being the most common adverse events.

Based on these results, clinicians may consider ocrelizumab as an effective and safe treatment to be offered to people with RRMS and PPMS.

Implications for research

The included trials did not report all the critical and important outcomes which should be addressed in the planning of future research. The feasibility of using ocrelizumab in combination with modified therapies for other diseases remains to be further tested. More randomised, double-blind, large-sample controlled trials are required in the future to evaluate the benefits, harms, and tolerability of ocrelizumab for RRMS and PPMS. In particular, treatment duration and follow-up needs to be longer. Further studies could result in increased certainty in the evidence, as the current evidence offers only low to moderate certainty in the outcomes of interest.

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The following people conducted the editorial process for this article.

1. Sign-off Editor (final editorial decision): Robert Boyle, Network Editor, Cochrane.
2. Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Colleen Ovelman, Cochrane Central Editorial Service.
3. Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service.
4. Copy Editor (copy editing and production): Anne Lawson, Copy Edit Support, Cochrane.

5. Peer-reviewers (provided comments and recommended an editorial decision): Michael Zhong Central Clinical School, Monash University (clinical review), Natalie Parks, MD, MSc, FRCPC Division of Neurology Dalhousie University Halifax (clinical review), Prof. Tomas Kalincik, CORe, University of Melbourne MS Centre (clinical review) Jennifer Hilgart, Associate Editor, Cochrane (methods review), Robin Featherstone, Information Specialist, Cochrane Central Editorial Service (search review), Margaret Anderson, Cochrane Information Specialist for Developmental, Psychosocial and Learning Problems (search review).

The background and methods sections of this review were based on a standard template used by Cochrane Multiple Sclerosis and Rare Diseases of the CNS Review Group.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Kappos 2011

Study characteristics	
Methods	International multicentre, randomised, parallel, double-blind, placebo-controlled, dose-finding study with ocrelizumab
Participants	Date of randomisation: study dates not reported Number of participation randomised: 218 Number of centres: 58 from North America, 120 from east-central Europe and Asia, 34 from western Europe, and 8 from Latin America Inclusion criteria: aged 18–55 years; diagnosis of RRMS, had ≥ 2 documented relapses within 3 years before screening, ≥ 1 of which occurred within the past year; EDSS score 1–6 points at baseline; evidence of previous multiple sclerosis inflammatory disease activity with ≥ 6 T2 lesions per MRI, or 2 relapses in the year before screening Exclusion criteria: secondary progressive multiple sclerosis or PPMS; disease duration > 15 years in people with an EDSS of ≤ 2; history or presence of other neurological or systemic autoimmune disorders; treatment with rituximab or lymphocyte-depleting therapies; use of lymphocyte trafficking blockers within previous 24 weeks; use of beta-interferons, glatiramer acetate, intravenous immunoglobulin, plasmapheresis, and immunosuppressive treatments within previous 12 weeks; use of systemic glucocorticoids within previous 4 weeks; intolerance to interferon beta-1a.
Interventions	Ocrelizumab 600 mg group (55 participants, mean age 35.6 (SD 8.5) years, 64% female): a dual infusion of 300 mg for the first treatment cycle (days 1 and 15), and then infusions of 600 mg for the subsequent treatment cycles (weeks 24, 48, and 72) Ocrelizumab 2000 mg group (55 participants, mean age 38.5 (SD 8.7) years, 69% female): a dual infusion of 1000 mg (days 1 and 15) for the first treatment cycle, and then an infusion of 1000 mg for the subsequent treatment cycles Placebo group (54 participants, mean age 38.0 (SD 8.8) years, 67% female): placebo on days 1 and 15 of the first treatment cycle Interferon beta-1a group (54 participants, mean age 38.1 (SD 9.3) years, 59% female): intramuscular interferon beta-1a 30 µg (Avonex, Biogen Idec) once a week for the first 24 weeks.
Outcomes	Primary outcomes: total number of gadolinium-enhancing T1 lesions observed on brain MRI scans for weeks 12, 16, 20, and 24 Secondary outcomes: annualised protocol-defined relapse rate; proportion of relapse-free participants; total number of gadolinium-enhancing T1 lesions (all data points from 4 to 24 weeks); total number of new gadolinium-enhancing T1 lesions; change in total volume of T2 lesions from baseline to week 24; safety and tolerability of 2 dose regimens of ocrelizumab versus placebo and interferon beta-1a at week 24; and safety of ocrelizumab therapy up to 96 weeks.
Notes	Funded by F Hoffmann-La Roche Ltd, Biogen Idec Inc

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A randomisation list was generated by an independent group within Roche. This list was provided to an interactive voice response system, which

Kappos 2011 *(Continued)*

		then randomised patients (1:1:1:1) to one of the four treatment groups stratified by geographical region."
Allocation concealment (selection bias)	High risk	Quote: "The list was not disclosed to the study centres, monitors, project statisticians, or to the project team at Roche and Genentech. All individuals directly involved in this study remain blinded to the dose of ocrelizumab. Project statisticians remained blinded until data lock and statistical analysis at week 24." "We masked treatment assignment for patients in the placebo and both ocrelizumab groups throughout the study. In the interferon beta-1a group, only the raters were masked to allocation."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "A fourth study group with interferon beta-1a was included as an active, open label, rater-masked control." "The treating investigator had access to safety and efficacy data, and made all treatment decisions on the basis of patients' clinical responses and laboratory findings." "We masked treatment assignment for patients in the placebo and both ocrelizumab groups throughout the study. In the interferon beta-1a group, only the raters were masked to allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A fourth study group with interferon beta-1a was included as an active, open label, rater-masked control." "A trained and certified examining investigator, who had no access to other study or patient-related information, did a full neurological examination, including assessment of walking capacity, and assigned the functional systems and EDSS." "We masked treatment assignment for patients in the placebo and both ocrelizumab groups throughout the study. In the interferon beta-1a group, only the raters were masked to allocation." "We obtained brain MRI (proton density and T2-weighted images, T1-weighted images before and after gadolinium enhancement) scans at baseline and thereafter at intervals of 4 weeks to week 24, and centrally reviewed and analysed the scans with no clinical information to ensure they were masked." "All individuals directly involved in this study remain blinded to the dose of ocrelizumab. Project statisticians remained blinded until data lock and statistical analysis at week 24."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 220 randomly assigned patients, 204 (93%) completed the 24-week study period."
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Low risk	–

OPERA I 2017

Study characteristics

OPERA I 2017 *(Continued)*

Methods	Phase III, randomised, multicentre, double-blind, double-dummy, active-controlled, parallel-group trials comparing of ocrelizumab with subcutaneous interferon beta-1a
Participants	Date of randomisation: 31 August 2011 to 14 February 2013 Number of participation randomised: 821 Number of centres: 141 trial sites across 32 countries Inclusion criteria: aged 18–55 years; diagnosis of MS (2010 revised McDonald criteria; McDonald 2001); EDSS score ≤ 5.5 (range 0–10, higher scores indicating greater disability); ≥ 2 documented clinical relapses within the previous 2 years or 1 clinical relapse within the year before screening; MRI of the brain showing abnormalities consistent with MS; and no neurological worsening for ≥ 30 days before both screening and baseline. Exclusion criteria: diagnosis of PPMS; previous treatment with any B-cell-targeted therapy or other immunosuppressive medication; disease duration > 10 years in combination with EDSS score ≤ 2.0 at screening
Interventions	Ocrelizumab (410 participants, mean age 37.1 (SD 9.3) years, 65.9% female): ocrelizumab 600 mg by intravenous infusion every 24 weeks (2 × 300-mg infusions on days 1 and 15 for the first dose and a single 600-mg infusion thereafter) Interferon beta-1a (411 participants, mean age 36.9 (SD 9.3) years, 66.2% female): interferon beta-1a 44 µg (Rebif, EMD Serono) subcutaneously 3 times weekly for 96 weeks
Outcomes	Primary outcome: annualised relapse rate by 96 weeks Secondary outcomes: proportion of participants with disability progression confirmed at 12 weeks in a pooled time-to-event analysis of both trials through week 96, in which disability progression was defined as an increase from the baseline EDSS score of ≥ 1.0 point (or 0.5 points if the baseline EDSS score was > 5.5) that was sustained for ≥ 12 weeks; the total (cumulative) mean number of gadolinium-enhancing lesions identified on T1-weighted MRI of the brain at weeks 24, 48, and 96; total number of new or newly enlarging hyperintense lesions on T2-weighted MRI of the brain at weeks 24, 48, and 96; pooled analysis of the proportion of participants with disability improvement confirmed at 12 weeks to week 96, which was defined as a reduction from the baseline EDSS score of ≥ 1.0 point (or 0.5 points if the baseline EDSS score was > 5.5) that was sustained for ≥ 12 weeks in participants with a baseline EDSS score of ≥ 2.0; pooled time-to-event analysis of the rate of disability progression confirmed at 24 weeks to week 96; the total number of new hypointense lesions on T1-weighted MRI of the brain at weeks 24, 48, and 96; change in the Multiple Sclerosis Functional Composite score from baseline to week 96; the percentage change in brain volume from week 24 to week 96; the change in the physical-component summary score of the Medical Outcomes Study SF-36 (range 0–100, higher scores indicating better physical health-related quality of life) from baseline to week 96; proportion of participants with a baseline EDSS score of ≥ 2.0 who had no evidence of disease activity (defined as no relapse, no disability progression confirmed at 12 weeks or at 24 weeks, no new or newly enlarging lesions on T2-weighted MRI, and no gadolinium-enhancing lesions on T1-weighted MRI) by week 96. The analysis of percentage change in brain volume was performed with the use of SIENA/X software. Additional secondary endpoints were the pharmacokinetics, pharmacodynamics, and immunogenicity of ocrelizumab; and the safety profile of ocrelizumab.
Notes	Funded by F Hoffmann-La Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally with the use of an independent interactive Web-response system."

OPERA I 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients in each group received a matching subcutaneous or intravenous placebo, as appropriate." "Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Data were collected by the site investigators, queries were responded to by site personnel, and the data were analyzed by the sponsor; the aggregated and individual results of the participants were reviewed by the sponsor and steering committee. An independent data and safety monitoring committee reviewed ongoing safety data and provided guidance on trial continuation, modification, or termination." "The examining investigator conducted the neurologic assessments, including the Multiple Sclerosis Functional Composite and the EDSS. The EDSS assessment and data collection were captured with the use of a real-time, electronic data-entry system in conjunction with an algorithm and central consistency check and feedback on the basis of expert review. MRI scans were analyzed centrally at an MRI reading center by personnel who were unaware of the treatment assignments."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "In the OPERA I trial, 366 of 410 patients (89.3%) in the ocrelizumab group and 340 of 411 (82.7%) in the interferon beta-1a group completed the 96-week treatment."
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Low risk	–

OPERA II 2017

Study characteristics	
Methods	Phase III, randomised, multicentre, double-blind, double-dummy, active-controlled, parallel-group trials comparing of ocrelizumab with subcutaneous interferon beta-1a
Participants	Date of randomisation: 20 September 2011 to 28 March 2013 Number of participation randomised: 835 Number of centres: 166 trial sites across 24 countries Inclusion criteria: aged 18–55 years; diagnosis of MS (2010 revised McDonald criteria; McDonald 2001); EDSS score ≤ 5.5 (range 0–10, higher scores indicating greater disability); ≥ 2 documented clinical relapses within the previous 2 years or 1 clinical relapse within the year before screening; MRI of the brain showing abnormalities consistent with MS; and no neurological worsening for ≥ 30 days before both screening and baseline Exclusion criteria: diagnosis of PPMS; previous treatment with any B-cell-targeted therapy or other immunosuppressive medication; disease duration > 10 years in combination with an EDSS score ≤ 2.0 at screening

OPERA II 2017 *(Continued)*

Interventions	Ocrelizumab (417 participants, mean age 37.2 (SD 9.1) years, 65.0% female): ocrelizumab 600 mg by intravenous infusion every 24 weeks (2 × 300-mg infusions on days 1 and 15 for the first dose and a single 600-mg infusion thereafter) Interferon beta-1a (418 participants, mean age 37.4 (SD 9.0) years, 67.0% female): interferon beta-1a 44 µg (Rebif, EMD Serono) subcutaneously 3 times weekly for 96 weeks
Outcomes	Primary outcomes: annualised relapse rate by 96 weeks Secondary outcomes: proportion of participants with disability progression confirmed at 12 weeks in a pooled time-to-event analysis of both trials through week 96, in which disability progression was defined as an increase from the baseline EDSS score of ≥ 1.0 point (or 0.5 points if the baseline EDSS score was > 5.5) that was sustained for ≥ 12 weeks; total (cumulative) mean number of gadolinium-enhancing lesions identified on T1-weighted MRI of the brain at weeks 24, 48, and 96; total number of new or newly enlarging hyperintense lesions on T2-weighted MRI of the brain at weeks 24, 48, and 96; pooled analysis of the proportion of participants with disability improvement confirmed at 12 weeks to week 96, which was defined as a reduction from the baseline EDSS score of ≥ 1.0 point (or 0.5 points if the baseline EDSS score was > 5.5) that was sustained for ≥ 12 weeks in participants with a baseline EDSS score of ≥ 2.0; pooled time-to-event analysis of the rate of disability progression confirmed at 24 weeks to week 96; total number of new hypointense lesions on T1-weighted MRI of the brain at weeks 24, 48, and 96; change in the Multiple Sclerosis Functional Composite score from baseline to week 96; percentage change in brain volume from week 24 to week 96; change in the physical-component summary score of the Medical Outcomes Study SF-36 (range 0–100, higher scores indicating better physical health-related quality of life) from baseline to week 96; proportion of participants with a baseline EDSS score of ≥ 2.0 who had no evidence of disease activity (defined as no relapse, no disability progression confirmed at 12 weeks or at 24 weeks, no new or newly enlarging lesions on T2-weighted MRI, and no gadolinium-enhancing lesions on T1-weighted MRI) by week 96. The analysis of percentage change in brain volume was performed with the use of SIENA/X software. Additional secondary endpoints were the pharmacokinetics, pharmacodynamics, and immunogenicity of ocrelizumab; and the safety profile of ocrelizumab
Notes	Funded by F Hoffmann-La Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally with the use of an independent interactive Web-response system."
Allocation concealment (selection bias)	Low risk	Quote: "Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients in each group received a matching subcutaneous or intravenous placebo, as appropriate." "Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Data were collected by the site investigators, queries were responded to by site personnel, and the data were analyzed by the sponsor; the aggregated and individual results of the participants were reviewed by the sponsor and steering committee. An independent data and safety monitoring committee reviewed ongoing safety data and provided guidance on trial continuation, modification, or termination." "The examining investigator conducted the neurologic assessments, including the Multiple Sclerosis Functional Composite and the EDSS. The EDSS assessment and data collection were captured with the use of a real-time, electronic data-entry system in conjunction with an algorithm and central consis-

OPERA II 2017 *(Continued)*

		tency check and feedback on the basis of expert review. MRI scans were analyzed centrally at an MRI reading center by personnel who were unaware of the treatment assignments."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "In the OPERA II trial, 360 of 417 patients (86.3%) and 320 of 418 (76.6%), respectively, completed the 96-week treatment."
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Low risk	–

ORATORIO 2017

Study characteristics	
Methods	A phase 3, multicentre, randomised, parallel, double-blind, placebo-controlled study
Participants	Date of randomisation: 3 March 2011 to 27 December 2012 Number of participation randomised: 732 Inclusion criteria: aged 18–55 years; diagnosis of PPMS (2005 revised McDonald criteria; McDonald 2001); EDSS score 3.0–6.5 at screening; score on the pyramidal functions component of the Functional Systems Scale of ≥ 2; duration of multiple sclerosis symptoms of < 15 years in people with an EDSS score > 5.0 at screening or < 10 years in people with an EDSS score ≤ 5.0 at screening; documented history or the presence at screening of an elevated IgG index or ≥ 1 IgG oligoclonal band detected in the cerebrospinal fluid Exclusion criteria: history of RRMS, secondary progressive multiple sclerosis, or progressive relapsing multiple sclerosis; contraindications to MRI; contraindications to or unacceptable adverse effects from oral or intravenous glucocorticoids; previous treatment with B-cell-targeted therapies and other immunosuppressive medications
Interventions	Ocrelizumab (488 participants, mean age 44.7 (SD 7.9) years, 48.6% female): ocrelizumab 600 mg by intravenous infusion every 24 weeks (administered as 2 × 300-mg infusions 14 days apart) Placebo (244 participants, mean age 44.4 (SD 8.3) years, 50.8% female) every 24 weeks
Outcomes	Primary outcomes: percentage of participants with disability progression confirmed at 12 weeks, defined as an increase in the EDSS of ≥ 1.0 point from baseline that was sustained on subsequent visits for ≥ 12 weeks if the baseline score was ≤ 5.5 or an increase of ≥ 0.5 points that was sustained for ≥ 12 weeks if the baseline score was > 5.5 Secondary outcomes: percentage of participants with disability progression confirmed at 24 weeks; change in performance on the timed 25-foot walk from baseline to week 120; change in the total volume of brain lesions on T2-weighted MRI from baseline to week 120; change in brain volume from week 24 to week 120; change in the Physical Component Summary score of the Medical Outcomes Study SF-36
Notes	Funded by F Hoffmann-La Roche

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

ORATORIO 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization that was stratified according to geographic region and age was performed centrally by an independent interactive Web-response system."
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomly assigned in a 2:1 ratio to receive 600 mg of ocrelizumab by intravenous infusion or matching placebo every 24 weeks." "The trial was event-driven, such that double-blind treatment was administered for a minimum of five doses (120 weeks)." "Patients who completed the blinded treatment phase were eligible to enter the open-label extension phase of the trial, after the database lock and unblinding of trial results."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The trial was event-driven, such that double-blind treatment was administered for a minimum of five doses (120 weeks)." "Data were collected by the investigators and analyzed by the sponsor; the results were reviewed by the sponsor and steering committee. An independent data and safety monitoring committee reviewed safety data on an ongoing basis and provided guidance on trial continuation, modification, or termination." "Each trial center had separate treating and examining investigators." "An independent, trained investigator who was unaware of the trial-group assignments and was certified in administering the EDSS conducted the neurologic examination and scored the EDSS. EDSS assessment and data collection were captured with the use of a real time, electronic tablet data-entry system. Multiple Sclerosis Functional Composite analysis was performed by the examining investigator or a qualified designee who was unaware of the trial group assignments. MRI scans were analyzed independently at a central MRI reading center by staff members who were unaware of the trial group assignments."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 402 patients (82%) who were assigned to ocrelizumab and 174 (71%) assigned to placebo reached 120 weeks in the trial."
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Low risk	–

SF-36: 36-item Short-Form Health Survey; EDSS: Expanded Disability Status Scale; IgG: immunoglobulin G; MRI: magnetic resonance imaging; MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis.

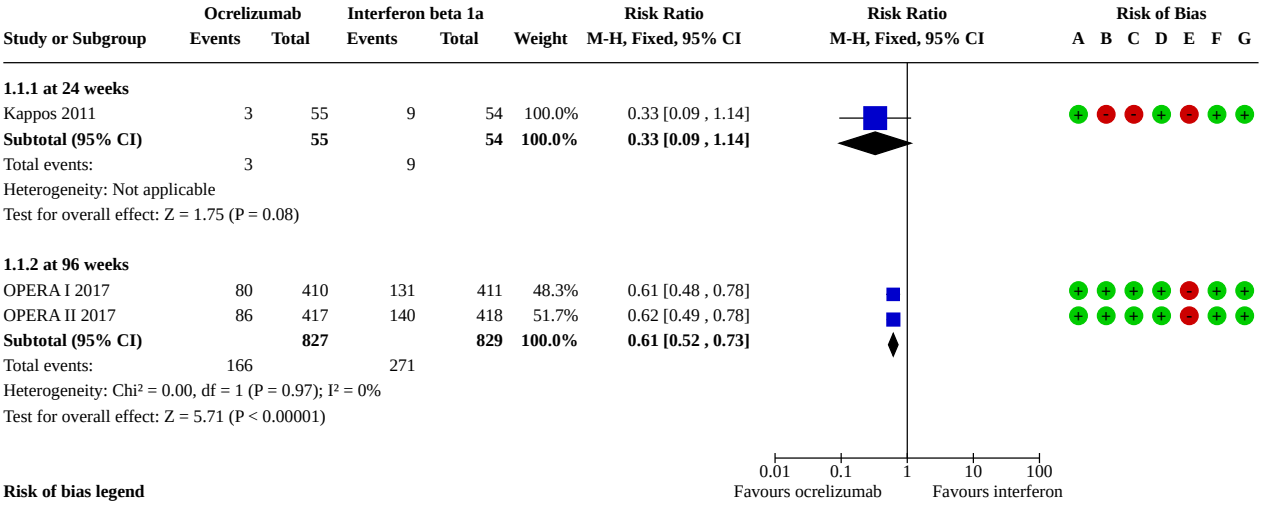
DATA AND ANALYSES

Comparison 1. Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Number of participants experiencing at least one relapse by the end of the study	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 at 24 weeks	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.09, 1.14]
1.1.2 at 96 weeks	2	1656	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.52, 0.73]
1.2 Number of participants experiencing disability progression by the end of the study	2	1656	Hazard Ratio (IV, Fixed, 95% CI)	0.60 [0.43, 0.84]
1.3 Number of participants with any adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 at 24 weeks	1	109	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.81, 1.53]
1.3.2 at 96 weeks	2	1651	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.04]
1.4 Number of participants with any serious adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 at 24 weeks	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.05, 5.26]
1.4.2 at 96 weeks	2	1651	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.11]
1.5 Number of participants experiencing treatment discontinuation caused by adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 at 24 weeks	1	109	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [0.18, 21.02]
1.5.2 at 96 weeks	2	1651	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.37, 0.91]
1.6 Change in SF-36 physical-component summary score from baseline to the end of the study	2	1656	Mean Difference (IV, Fixed, 95% CI)	0.93 [0.02, 1.83]
1.7 Number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging (MRI) by the end of the study	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 at 24 weeks	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.25, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.2 at 96 weeks	2	1656	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.22, 0.35]
1.8 Number of participants with new or newly enlarged T2-hyperintense lesions on MRI by the end of the study	2	1656	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.57, 0.69]
1.9 Mean percentage change in brain volume from week 24 to the end of the study	2	1656	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.05, 0.23]

Analysis 1.1. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 1: Number of participants experiencing at least one relapse by the end of the study

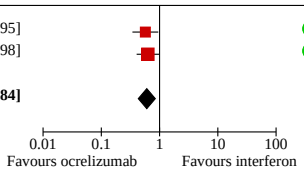


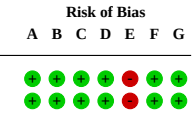
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 1.2. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 2: Number of participants experiencing disability progression by the end of the study

Study or Subgroup	log[Hazard Ratio]	SE	Ocrelizumab Total	Interferon beta 1a Total	Weight	Hazard Ratio IV, Fixed, 95% CI
OPERA I 2017	-0.5621	0.2606	410	411	43.1%	0.57 [0.34 , 0.95]
OPERA II 2017	-0.462	0.2267	417	418	56.9%	0.63 [0.40 , 0.98]
Total (95% CI)			**827**	**829**	**100.0%**	**0.60 [0.43 , 0.84]**

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.95 (P = 0.003)
Test for subgroup differences: Not applicable

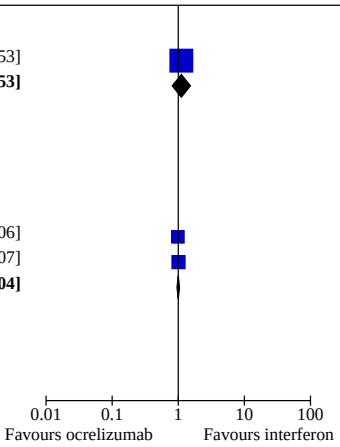


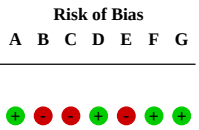


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 1.3. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 3: Number of participants with any adverse events

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Interferon beta 1a Events	Interferon beta 1a Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 at 24 weeks						
Kappos 2011	34	55	30	54	100.0%	1.11 [0.81 , 1.53]
Subtotal (95% CI)		**55**		**54**	**100.0%**	**1.11 [0.81 , 1.53]**
Total events:	34		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.3.2 at 96 weeks						
OPERA I 2017	327	408	331	409	48.1%	0.99 [0.93 , 1.06]
OPERA II 2017	360	417	357	417	51.9%	1.01 [0.95 , 1.07]
Subtotal (95% CI)		**825**		**826**	**100.0%**	**1.00 [0.96 , 1.04]**
Total events:	687		688			
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						

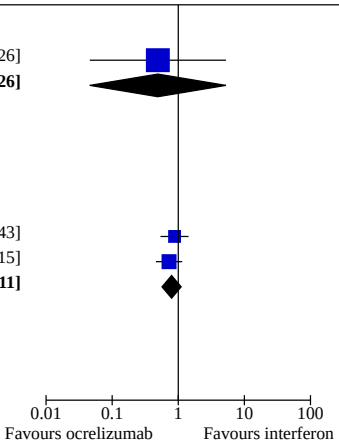


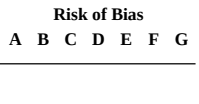


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 1.4. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 4: Number of participants with any serious adverse events

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Interferon beta 1a Events	Interferon beta 1a Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 at 24 weeks						
Kappos 2011	1	55	2	54	100.0%	0.49 [0.05 , 5.26]
Subtotal (95% CI)		**55**		**54**	**100.0%**	**0.49 [0.05 , 5.26]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
1.4.2 at 96 weeks						
OPERA I 2017	28	408	32	409	44.4%	0.88 [0.54 , 1.43]
OPERA II 2017	29	417	40	417	55.6%	0.72 [0.46 , 1.15]
Subtotal (95% CI)		**825**		**826**	**100.0%**	**0.79 [0.57 , 1.11]**
Total events:	57		72			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.36 (P = 0.17)						

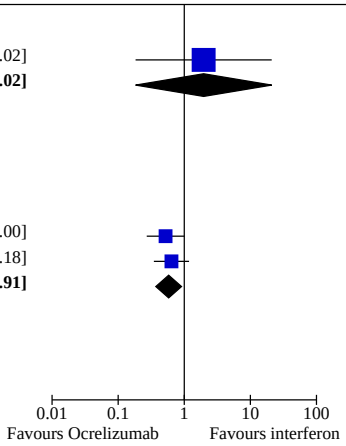


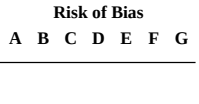


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 1.5. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 5: Number of participants experiencing treatment discontinuation caused by adverse events

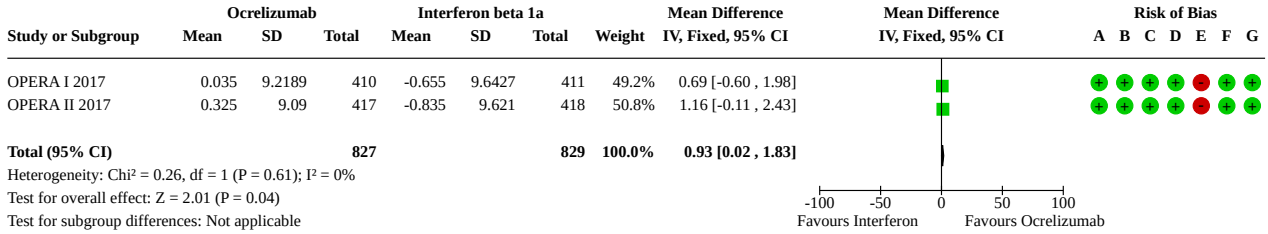
Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Interferon beta 1a Events	Interferon beta 1a Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 at 24 weeks						
Kappos 2011	2	55	1	54	100.0%	1.96 [0.18 , 21.02]
Subtotal (95% CI)		**55**		**54**	**100.0%**	**1.96 [0.18 , 21.02]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
1.5.2 at 96 weeks						
OPERA I 2017	13	408	25	409	50.0%	0.52 [0.27 , 1.00]
OPERA II 2017	16	417	25	417	50.0%	0.64 [0.35 , 1.18]
Subtotal (95% CI)		**825**		**826**	**100.0%**	**0.58 [0.37 , 0.91]**
Total events:	29		50			
Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 2.38 (P = 0.02)						





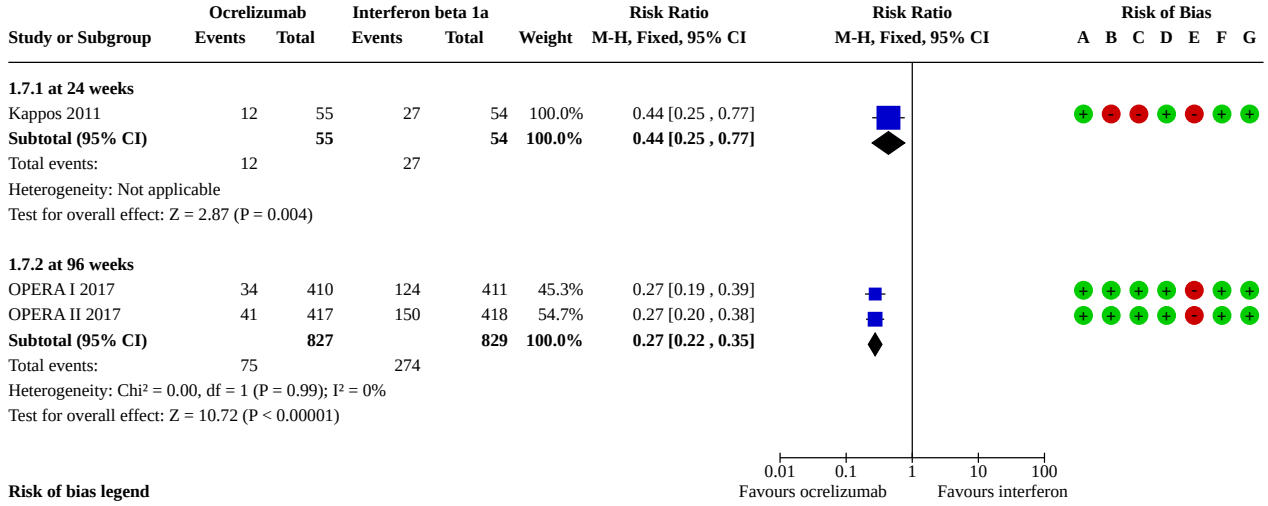
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 1.6. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 6: Change in SF-36 physical-component summary score from baseline to the end of the study



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

Analysis 1.7. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 7: Number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging (MRI) by the end of the study

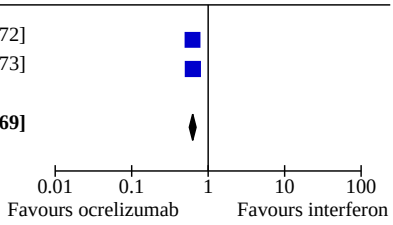


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 1.8. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 8: Number of participants with new or newly enlarged T2-hyperintense lesions on MRI by the end of the study

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Interferon beta 1a Events	Interferon beta 1a Total	Weight	Risk Ratio M-H, Fixed, 95% CI
OPERA I 2017	157	410	252	411	49.3%	0.62 [0.54 , 0.72]
OPERA II 2017	163	417	259	418	50.7%	0.63 [0.55 , 0.73]
Total (95% CI)		**827**		**829**	**100.0%**	**0.63 [0.57 , 0.69]**
Total events:	320		511			

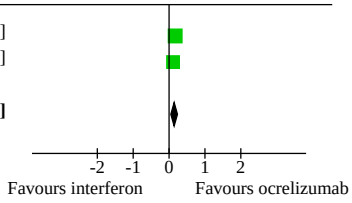
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 9.02 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Ocrelizumab versus interferon beta-1a for relapsing-remitting multiple sclerosis, Outcome 9: Mean percentage change in brain volume from week 24 to the end of the study

Study or Subgroup	ocrelizumab Mean	ocrelizumab SD	ocrelizumab Total	Interferon beta 1a Mean	Interferon beta 1a SD	Interferon beta 1a Total	Weight	Mean Difference IV, Fixed, 95% CI
OPERA I 2017	-0.57	0.927	410	-0.74	0.9282	411	52.8%	0.17 [0.04 , 0.30]
OPERA II 2017	-0.64	0.935	417	-0.75	1.0401	418	47.2%	0.11 [-0.02 , 0.24]
Total (95% CI)			**827**			**829**	**100.0%**	**0.14 [0.05 , 0.23]**

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.01 (P = 0.003)
Test for subgroup differences: Not applicable



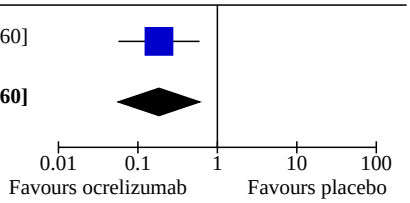
Comparison 2. Ocrelizumab versus placebo for relapsing-remitting multiple sclerosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number of participants experiencing at least one relapse by the end of the study	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.06, 0.60]
2.2 Number of participants with any adverse events	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.15]
2.3 Number of participants with any serious adverse events	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.05, 5.26]
2.4 Number of participants experiencing treatment discontinuation caused by adverse events	1	109	Risk Ratio (M-H, Fixed, 95% CI)	4.91 [0.24, 99.97]
2.5 Number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging by the end of the study	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.20, 0.58]

Analysis 2.1. Comparison 2: Ocrelizumab versus placebo for relapsing-remitting multiple sclerosis, Outcome 1: Number of participants experiencing at least one relapse by the end of the study

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kappos 2011	3	55	16	54	100.0%	0.18 [0.06 , 0.60]
Total (95% CI)		**55**		**54**	**100.0%**	**0.18 [0.06 , 0.60]**
Total events:	3		16			

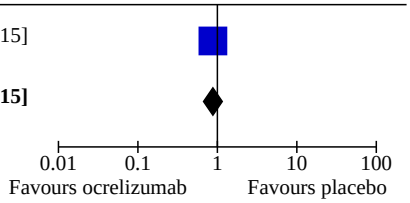
Heterogeneity: Not applicable
Test for overall effect: Z = 2.82 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Ocrelizumab versus placebo for relapsing-remitting multiple sclerosis, Outcome 2: Number of participants with any adverse events

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kappos 2011	34	55	38	54	100.0%	0.88 [0.67 , 1.15]
Total (95% CI)		**55**		**54**	**100.0%**	**0.88 [0.67 , 1.15]**
Total events:	34		38			

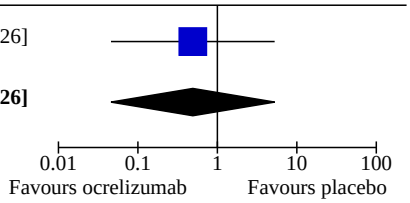
Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Ocrelizumab versus placebo for relapsing-remitting multiple sclerosis, Outcome 3: Number of participants with any serious adverse events

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kappos 2011	1	55	2	54	100.0%	0.49 [0.05 , 5.26]
Total (95% CI)		**55**		**54**	**100.0%**	**0.49 [0.05 , 5.26]**
Total events:	1		2			

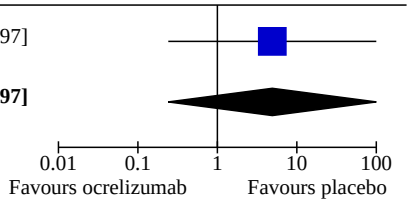
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Ocrelizumab versus placebo for relapsing-remitting multiple sclerosis, Outcome 4: Number of participants experiencing treatment discontinuation caused by adverse events

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kappos 2011	2	55	0	54	100.0%	4.91 [0.24 , 99.97]
Total (95% CI)		**55**		**54**	**100.0%**	**4.91 [0.24 , 99.97]**
Total events:	2		0			

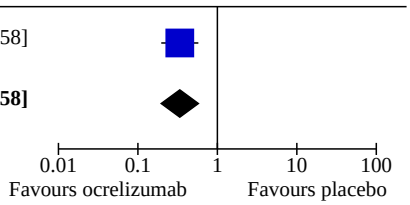
Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Ocrelizumab versus placebo for relapsing-remitting multiple sclerosis, Outcome 5: Number of participants with gadolinium-enhancing T1 lesions on magnetic resonance imaging by the end of the study

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kappos 2011	12	55	35	54	100.0%	0.34 [0.20 , 0.58]
Total (95% CI)		**55**		**54**	**100.0%**	**0.34 [0.20 , 0.58]**
Total events:	12		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.97 (P < 0.0001)
Test for subgroup differences: Not applicable



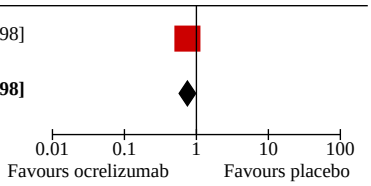
Comparison 3. Ocrelizumab versus placebo for primary progressive multiple sclerosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Number of participants experiencing disability progression by the end of the study	1	731	Hazard Ratio (IV, Fixed, 95% CI)	0.75 [0.58, 0.98]
3.2 Number of participants with any adverse events	1	725	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [1.01, 1.11]
3.3 Number of participants with any serious adverse events	1	725	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.68, 1.23]
3.4 Number of participants experiencing treatment discontinuation caused by adverse events	1	725	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.55, 2.75]
3.5 Change in SF-36 Physical Component Summary score from baseline to the end of the study	1	732	Mean Difference (IV, Fixed, 95% CI)	0.38 [-1.04, 1.80]
3.6 Mean percentage change in brain volume from week 24 to the end of the study	1	732	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.01, 0.37]

Analysis 3.1. Comparison 3: Ocrelizumab versus placebo for primary progressive multiple sclerosis, Outcome 1: Number of participants experiencing disability progression by the end of the study

Study or Subgroup	log[Hazard Ratio]	SE	Ocrelizumab Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
ORATORIO 2017	-0.2877	0.1347	487	244	100.0%	0.75 [0.58 , 0.98]
Total (95% CI)			**487**	**244**	**100.0%**	**0.75 [0.58 , 0.98]**

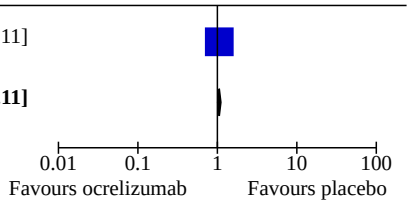
Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Ocrelizumab versus placebo for primary progressive multiple sclerosis, Outcome 2: Number of participants with any adverse events

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ORATORIO 2017	462	486	215	239	100.0%	1.06 [1.01 , 1.11]
Total (95% CI)		**486**		**239**	**100.0%**	**1.06 [1.01 , 1.11]**
Total events:	462		215			

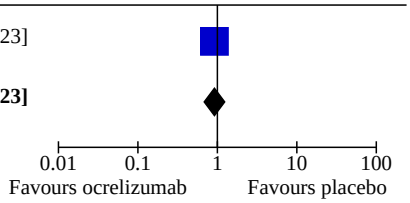
Heterogeneity: Not applicable
Test for overall effect: Z = 2.30 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Ocrelizumab versus placebo for primary progressive multiple sclerosis, Outcome 3: Number of participants with any serious adverse events

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ORATORIO 2017	99	486	53	239	100.0%	0.92 [0.68 , 1.23]
Total (95% CI)		**486**		**239**	**100.0%**	**0.92 [0.68 , 1.23]**
Total events:	99		53			

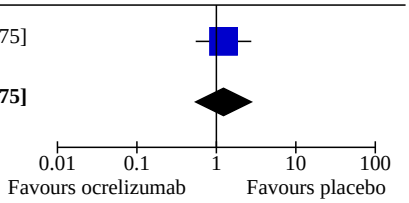
Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Ocrelizumab versus placebo for primary progressive multiple sclerosis, Outcome 4: Number of participants experiencing treatment discontinuation caused by adverse events

Study or Subgroup	Ocrelizumab Events	Ocrelizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ORATORIO 2017	20	486	8	239	100.0%	1.23 [0.55 , 2.75]
Total (95% CI)		**486**		**239**	**100.0%**	**1.23 [0.55 , 2.75]**
Total events:	20		8			

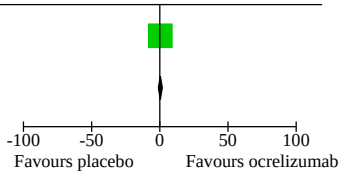
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Ocrelizumab versus placebo for primary progressive multiple sclerosis, Outcome 5: Change in SF-36 Physical Component Summary score from baseline to the end of the study

Study or Subgroup	Ocrelizumab Mean	Ocrelizumab SD	Ocrelizumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
ORATORIO 2017	-0.73	9.2729	488	-1.11	9.2729	244	100.0%	0.38 [-1.04 , 1.80]
Total (95% CI)			**488**			**244**	**100.0%**	**0.38 [-1.04 , 1.80]**

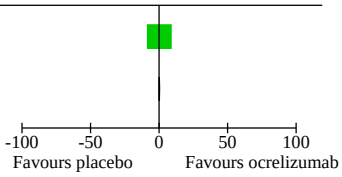
Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Ocrelizumab versus placebo for primary progressive multiple sclerosis, Outcome 6: Mean percentage change in brain volume from week 24 to the end of the study

Study or Subgroup	Ocrelizumab Mean	Ocrelizumab SD	Ocrelizumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
ORATORIO 2017	-0.9	1.1243	488	-1.09	1.1499	244	100.0%	0.19 [0.01 , 0.37]
Total (95% CI)			**488**			**244**	**100.0%**	**0.19 [0.01 , 0.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL (the Cochrane Library) search strategy

CENTRAL (the Cochrane Library) was searched on 8 October 2021 (2021 Issue 9).

#1 MeSH descriptor Multiple Sclerosis, this term only

#2 MeSH descriptor Multiple Sclerosis, Chronic Progressive, this term only

#3 MeSH descriptor Multiple Sclerosis, Relapsing-Remitting, this term only

#4 MeSH descriptor Myelitis, Transverse explode trees 3, 5 and 7

#5 MeSH descriptor Optic Neuritis explode all trees

#6 MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only

#7 MeSH descriptor Demyelinating Autoimmune Diseases, CNS, this term only

#8 "multiple sclerosis":ti,ab,kw

#9 ("neuromyelitis optica" or "optic neuritis"):ti,ab,kw

#10 ("devic disease" or "demyelinating disease" or (adem) or "demyelinating disorder" or "clinically isolated syndrome"):ti,ab,kw

#11 ("transverse myelitis" or "acute disseminated encephalomyelitis" or (encephalomyelitis)):ti,ab,kw

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 ocrelizumab OR ocrevus OR ("R 1594") OR R-1594 OR RG-1594 OR ("PR 070769") OR PR070769 OR PR-070769

#14 #12 AND #13

Appendix 2. MEDLINE (PubMed) search strategy

MEDLINE (PubMed) was searched on 8 October 2021.

#1 "Multiple Sclerosis"[Mesh:noexp]

#2 "Multiple Sclerosis, Chronic Progressive"[Mesh]

#3 "Multiple Sclerosis, Relapsing-Remitting"[Mesh]

#4 "Demyelinating Diseases"[Mesh:noexp]

#5 "Optic Neuritis"[Mesh]

#6 "Demyelinating Autoimmune Diseases, CNS"[Mesh:noexp]

#7 "Encephalomyelitis, Acute Disseminated"[Mesh]

#8 "Myelitis, Transverse"[Mesh]

#9 "multiple sclerosis"[Title/Abstract] OR "neuromyelitis optica"[Title/Abstract] OR "optic neuritis"[Title/Abstract] OR "devic disease"[Title/Abstract] OR "demyelinating disease"[Title/Abstract] OR adem[Title/Abstract] OR "demyelinating disorder"[Title/Abstract] OR "clinically isolated syndrome"[Title/Abstract] OR "transverse myelitis"[Title/Abstract] OR "acute disseminated encephalomyelitis"[Title/Abstract] OR "encephalomyelitis"[Title/Abstract]

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 ("ocrelizumab" [Supplementary Concept]) OR (ocrevus) OR (R 1594) OR (R1594) OR (R-1594) OR (RG-1594) OR (PR 070769) OR (PR070769) OR (PR-070769)

#12 randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]

#13 #10 AND #11 AND #12

Appendix 3. Embase search strategy

Embase was searched on 8 October 2021.

#1 'multiple sclerosis'/exp

#2 'demyelinating disease'/de

#3 'optic neuritis'/exp

#4 'acute disseminated encephalomyelitis'/exp

#5 'myelooptic neuropathy'/exp

#6 'myelitis'/de

#7 'multiple sclerosis':ab,ti OR 'optic neurities':ab,ti OR 'neuromyelitis optica':ab,ti OR encephalomyelitis:ab,ti OR 'clinically isolated syndrome':ab,ti OR 'transverse myelitis':ab,ti OR 'devic disease':ab,ti OR 'demyelinating disease':ab,ti OR 'demyelinating disorder':ab,ti OR 'acute disseminated encephalomyelitis':ab,ti OR adem:ab,ti

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 'ocrelizumab'/exp OR ocrevus OR 'r 1594' OR 'r1594' OR 'r-1594' OR 'rg-1594' OR 'pr 070769' OR 'pr070769' OR 'pr-070769'

#10 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'controlled clinical trial'/de OR 'randomized controlled trial'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover:ab,ti OR 'clinical trial'/exp OR (cross:ab,ti AND over:ab,ti) OR placebo:ab,ti OR 'double blind':ab,ti OR 'single blind':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti

#11 #8 AND #9 AND #10

Appendix 4. ClinicalTrials.gov search strategy

ClinicalTrials.gov was searched on 8 October 2021.

#1 "multiple sclerosis"

#2 "ocrelizumab" OR "ocrevus" OR "R 1594" OR "R-1594" OR "RG-1594" OR "PR 070769" OR "PR070769" OR "PR-070769"

#3 #1 AND #2 AND (Interventional Studies (Clinical Trials) [Filter])

Appendix 5. ICTRP search strategy

ICTRP was searched on 8 October 2021.

#1 "multiple sclerosis"

#2 "ocrelizumab" OR "ocrevus" OR "R 1594" OR "R-1594" OR "RG-1594" OR "PR 070769" OR "PR070769" OR "PR-070769"

#3 #1 AND #2

HISTORY

Protocol first published: Issue 1, 2019

CONTRIBUTIONS OF AUTHORS

ML, JZ drafted the review.

JZ, YZ developed the search strategy.

ML, JZ, JL selected relevant articles for inclusion.

ML, JZ, JL extracted the data from included studies.

ML, JZ, YZ assessed the risk of bias in included studies.

ML, JZ entered data to Review Manager 5.

ML, JZ carried out the analysis.

ML, JZ, SS interpreted the results.

ML, JZ will update the review.

ML, JZ contributed equally to the review and share first authorship.

All review authors read and approved the completed review.

DECLARATIONS OF INTEREST

ML: none.

JZ: none.

YZ: none.

CY: none.

JL: none.

SS: none.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane centre, China

  the Handbook Study Group from the Chinese Cochrane centre for methodological support

External sources

- No sources of support supplied, China

  No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from the published protocol (Lin 2019).

1. We replaced 'the number of participants experiencing disability worsening for at least 12 weeks' with 'the number of participants experiencing disability progression for at least 24 weeks' in the primary outcomes, because the latter is more commonly used in clinical trials and Cochrane systematic reviews (Uitdehaag 2018).
2. We added 'the number of participants experiencing treatment discontinuation caused by adverse events' in the harms outcomes, because it reflects tolerability which is very important.
3. We reported the number of participants experiencing any adverse event separately from the number of participants experiencing any serious adverse event, and defined serious adverse events as any adverse event that, at any dose, fulfilled at least one of the following criteria: was fatal; was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; was medically significant or required intervention to prevent one or other of the outcomes listed above.
4. We added 'change in quality of life at one year and after, or at the end of the study. The following scales were accepted: 36-item Short-Form Health Survey (SF-36) scores, Multiple Sclerosis Quality of Life (MSQoL-54) questionnaire scores, Multiple Sclerosis Quality of Life Inventory (MSQLI), or Functional Assessment of Multiple Sclerosis (FAMS)' in the secondary outcomes, because quality of life is an important outcome in clinical trials (Uitdehaag 2018).
5. Intervention considered changed from 'ocrelizumab at low (600 mg) or high (2000 mg) dose' to 'ocrelizumab alone or associated with other medications at the approved dose of 600 mg for any course duration' in Review draft in 'types of intervention', because ocrelizumab at high (2000 mg) dose was not approved, and it was only evaluated in a short-term phase 2 trial but not in long-term phase 3 trials.
6. We added two potential subgroups: different co-interventions and different types of interferon beta-1a in 'Subgroup analysis and investigation of heterogeneity' section. We planned the subgroup analyses at the protocol stage but did not perform them due to lack of sufficient data.
7. The number of participants experiencing disability progression at 24 weeks is a time-to-event outcome, we used hazard ratio to calculate the data.
8. We planned the following outcomes for the summary of findings tables at the protocol stage: number of participants experiencing at least one relapse, number of participants experiencing disability progression, number of participants with any serious adverse events. We added the following outcomes at the review stage: number of participants with any adverse event, number of participants experiencing treatment discontinuation caused by adverse events, number of participants with gadolinium-enhancing T1 lesions on MRI, number of participants with new or enlarging T2-hyperintense lesions on MRI.
9. In the summary of findings tables, we included trials with a follow-up period longer than 12 months. Trials with a follow-up period shorter than 12 months were not included in the tables. In this review, there are two time points: 24 weeks or 96 weeks. 96-week time point is more important for decision makers, thus, we presented outcomes of 96-week time point.
10. We planned to search CENTRAL, MEDLINE, Embase, CINAHL, LILACS, PEDro, WHO ICTRP, and Clinicaltrials.gov at the protocol stage. We searched the main three databases and two trials registers, CINAHL, LILACS and PEDro were not searched at the review stage.
11. One of the co-authors of the protocol could no longer contribute to the review (CY), and one new co-authors (YZ) contributed to the review instead.
12. Author JL added to sections 'Selection of studies' and 'Data extraction and management'.

13.Author JZ and YZ added to section 'Assessment of risk of bias in included studies'.
14.ML and JZ contributed equally to the review and share first authorship.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized; Gadolinium [therapeutic use]; Interferon beta-1a [adverse effects]; *Multiple Sclerosis [drug therapy]; *Multiple Sclerosis, Relapsing-Remitting [drug therapy]; Recurrence

MeSH check words

Adult; Humans