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Alemtuzumab for multiple sclerosis (Review)

Riera R, Torloni MR, Martimbianco ALC, Pacheco RL

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[Intervention Review]

Alemtuzumab for multiple sclerosis

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ABSTRACT

Background

Multiple sclerosis (MS) is an autoimmune, T-cell-dependent, inflammatory, demyelinating disease of the central nervous system, with an unpredictable course. Current MS therapies focus on treating and preventing exacerbations, and avoiding the progression of disability. At present, there is no treatment that is capable of safely and effectively reaching these objectives. Clinical trials suggest that alemtuzumab, a humanized monoclonal antibody, could be a promising option for MS.

Objectives

To evaluate the benefits and harms of alemtuzumab alone or associated with other treatments in people with any form of MS.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 21 June 2022.

Selection criteria

We included randomized controlled trials (RCTs) in adults with any subtype of MS comparing alemtuzumab alone or associated with other medications versus placebo; another active drug; or alemtuzumab in another dose, regimen, or duration.

Data collection and analysis

We used standard Cochrane methods. Our co-primary outcomes were 1. relapse-free survival, 2. sustained disease progression, and 3. number of participants experiencing at least one adverse event. Our secondary outcomes were 4. participants free of clinical disability, 5. quality of life, 6. change in disability, 7. fatigue, 8. new or enlarging lesions on resonance imaging, and 9. dropouts. We used GRADE to assess certainty of evidence for each outcome.

Main results

We included three RCTs (1713 participants) comparing intravenous alemtuzumab versus subcutaneous interferon beta-1a for relapsing–remitting MS. Participants were treatment-naive (two studies) or had experienced at least one relapse after interferon or glatiramer (one study). Alemtuzumab was given at doses of 12 mg/day or 24 mg/day for five days at months 0 and 12, or 24 mg/day for three days at months 12 and 24. Participants in the interferon beta-1a group received 44 µg three times weekly.

Alemtuzumab 12 mg: 1. may improve relapse-free survival at 36 months (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.18 to 0.53; 1 study, 221 participants; low-certainty evidence); 2. may improve sustained disease progression-free survival at 36 months (HR 0.25, 95% CI

0.11 to 0.56; 1 study, 223 participants; low-certainty evidence); 3. may make little to no difference on the proportion of participants with at least one adverse event at 36 months (risk ratio [RR] 1.00, 95% CI 0.98 to 1.02; 1 study, 224 participants; low-certainty evidence), although the proportion of participants with at least one adverse event was high with both drugs; 4. may slightly reduce disability at 36 months (mean difference [MD] −0.70, 95% CI −1.04 to −0.36; 1 study, 223 participants; low-certainty evidence). The evidence is very uncertain regarding the risk of dropouts at 36 months (RR 0.81, 95% CI 0.57 to 1.14; 1 study, 224 participants; very low-certainty evidence).

Alemtuzumab 24 mg: 1. may improve relapse-free survival at 36 months (HR 0.21, 95% CI 0.11 to 0.40; 1 study, 221 participants; low-certainty evidence); 2. may improve sustained disease progression-free survival at 36 months (HR 0.33, 95% CI 0.16 to 0.69; 1 study, 221 participants; low-certainty evidence); 3. may make little to no difference on the proportion of participants with at least one adverse event at 36 months (RR 0.99, 95% CI 0.97 to 1.02; 1 study, 215 participants; low-certainty evidence), although the proportion of participants with at least one adverse event was high with both drugs; 4. may slightly reduce disability at 36 months (MD −0.83, 95% CI −1.16 to −0.50; 1 study, 221 participants; low-certainty evidence); 5. may reduce the risk of dropouts at 36 months (RR 0.08, 95% CI 0.01 to 0.57; 1 study, 215 participants; low-certainty evidence).

For quality of life, fatigue, and participants free of clinical disease activity, the studies either did not consider these outcomes or they used different measuring tools to those planned in this review.

Authors' conclusions

Compared with interferon beta-1a, alemtuzumab may improve relapse-free survival and sustained disease progression-free survival, and make little to no difference on the proportion of participants with at least one adverse event for people with relapsing–remitting MS at 36 months. The certainty of the evidence for these results was very low to low.

PLAIN LANGUAGE SUMMARY

Alemtuzumab for multiple sclerosis

Key messages

– Alemtuzumab may reduce the risk of relapse and disease progression when compared to subcutaneous interferon beta-1a in people with relapsing–remitting MS, a type of MS where you have worsened symptoms (relapses) followed by a recovery period (remitting).

– Future well-designed studies are needed to assess patient-related outcomes such as quality of life and fatigue.

What is the issue?

Multiple sclerosis (MS) is a chronic disease of the nervous system that affects young and middle-aged adults. Repeated damage to the myelin sheaths (the membranes that cover and protect nerves) and other parts of the nerves can lead to serious disability. MS may be related to problems in the immune system. Alemtuzumab is a biological medicine (a type of antibody), which has already been used for other diseases.

What did we want to find out?

We aimed to investigate the benefits and unwanted effects (called adverse events) of alemtuzumab used alone or associated with other treatments for people with any form of MS. We wanted to find out if alemtuzumab was better compared to other available treatments for people with MS.

What did we do?

We searched for studies that investigated alemtuzumab for people with any form of MS. We searched the literature up to October 2020. We analyzed and compared the results of the included studies and assessed how much confidence we had in the available evidence.

What did we find?

We found three studies (including 1713 participants) that fulfilled the review selection criteria. All studies compared intravenous (injected into a vein) alemtuzumab versus subcutaneous (injected under the skin) interferon beta-1a for people with relapsing–remitting MS. Two studies (called CARE-MS I and CAMMS223) were treating the participants for their MS the first time (treatment-naive). The third study (CARE-MS II) included participants with at least one relapse while being treated with interferon beta or glatiramer acetate for at least six months.

Main results

The review of these studies found that, compared to subcutaneous interferon beta-1a, alemtuzumab may reduce the risk of relapse and disease progression (worsening of the MS) in people with relapsing–remitting MS, and make little to no difference in the proportion of participants with at least one adverse event (but both medicines had a high proportion of participants with at least one adverse event). There is a lack of information about the effects of alemtuzumab on other outcomes such as quality of life and fatigue.

What are the limitations of the evidence?

Our confidence in the effects of alemtuzumab, compared to interferon beta-1a, for the main outcomes ranges from low to very low. This means that there is a high probability that future studies could change our conclusions.

How up to date is the evidence?

The evidence is up to date to June 2022.

Summary of findings 1. Alemtuzumab 12 mg compared to interferon beta-1a for multiple sclerosis

Alemtuzumab 12 mg compared to interferon beta-1a for multiple sclerosis

Patient or population: adults with relapsing–remitting multiple sclerosis
Settings: outpatients
Intervention: alemtuzumab 12 mg
Comparison: interferon beta-1a

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Interferon beta-1a	Alemtuzumab 12 mg				
Relapse-free survival Follow-up: 36 months	**10 per 100**[a]	**49 per 100** (30 to 66)	**HR 0.31** (0.18 to 0.53)	221 (1 study)	⊕⊕⊖⊖ **Low**[b]	Alemtuzumab may increase relapse-free survival at 36 months.
Sustained disease progression-free survival Follow-up: 36 months	**75 per 100**[a]	**93 per 100** (85 to 97)	**HR 0.25** (0.11 to 0.56)	223 (1 study)	⊕⊕⊖⊖ **Low**[b]	Alemtuzumab may increase sustained disease progression-free survival at 36 months.
Adverse events, including serious events Assessed by: number of participants with ≥ 1 event Follow-up: 36 months	**100 per 100**	**100 per 100** (98 to 100)	**RR 1.00** (0.98 to 1.02)	224 (1 study)	⊕⊕⊖⊖ **Low**[c]	Alemtuzumab may result in little to no difference in the proportion of participants with ≥ 1 adverse event at 36 months.
Change in disability Assessed by: EDSS Follow-up: 36 months	The mean EDSS score in the control group was 0.38	The mean change in EDSS in the intervention groups was **0.70 lower** (1.04 lower to 0.36 lower)	—	223 (1 study)	⊕⊕⊖⊖ **Low**[b]	Alemtuzumab may result in a slight reduction in disability at 36 months.

New or enlarging T2-hyperintense lesions Assessed by: number of participants with new or enlarging T2-hyperintense lesions Follow-up: 36 months	—	—	—	—	—	—
Dropouts Assessed by: number of participants who dropped out Follow-up: 36 months	**41 per 100**	**33 per 100** (23 to 46)	**RR 0.81** (0.57 to 1.14)	224 (1 study)	⊕⊖⊖⊖ **Very low**[c,d]	We are very uncertain about the effects of alemtuzumab for dropouts at 36 months.

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; **EDSS:** Expanded Disability Status Scale; **HR:** hazard ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a] Control group risk was derived from Kaplan-Meier curves from the included study (CAMMS223).
[b] Risk of bias. Participants and personnel were not blinded and this outcome could have been affected by this. There was high risk of attrition bias. Downgraded two levels.
[c] Risk of bias. Participants and personnel were not blinded and this is a patient-reported outcome. There was high risk of attrition bias. Downgraded two levels.
[d] Imprecision. Wide CI, including null effect, and both clinical benefit and harm.

Summary of findings 2. Alemtuzumab 24 mg compared to interferon beta-1a for multiple sclerosis

Alemtuzumab 24 mg compared to interferon beta-1a for multiple sclerosis

Patient or population: adults with multiple sclerosis
Settings: outpatients
Intervention: alemtuzumab 24 mg
Comparison: interferon beta-1a

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	Interferon beta-1a	Alemtuzumab 24 mg				
Relapse-free survival Follow-up: 36 months	**10 per 100**[a]	**62 per 100** (40 to 78)	**HR 0.21** (0.11 to 0.40)	221 (1 study)	⊕⊕⊖⊖ **Low**[b]	Alemtuzumab may increase relapse-free survival at 36 months.
Sustained disease progression-free survival Follow-up: 36 months	**75 per 100**[a]	**91 per 100** (82 to 96)	**HR 0.33** (0.16 to 0.69)	221 (1 study)	⊕⊕⊖⊖ **Low**[b]	Alemtuzumab may increase sustained disease progression-free survival at 36 months.
Adverse events, including serious adverse events Assessed by: number of participants with ≥ 1 event Follow-up: 36 months	**95 per 100**	**94 per 100** (92 to 96)	**RR 0.99** (0.97 to 1.02)	215 (1 study)	⊕⊕⊖⊖ **Low**[c]	Alemtuzumab may result in little to no difference in the proportion of participants with ≥ 1 adverse event at 36 months.
Change in disability Assessed by: EDSS Follow-up: 36 months	The mean EDSS score in the control group was 0.38	The mean change in EDSS in the intervention group was **0.83 lower** (1.16 lower to 0.50 lower)	__	221 (1 study)	⊕⊕⊖⊖ **Low**[b]	Alemtuzumab may result in a slight reduction in disability at 36 months.
New or enlarging T2-hyperintense lesions Follow-up: 36 months	—	—	—	—	—	—
Dropouts Follow-up: 36 months	**12 per 100**	**1 per 100** (0 to 7)	**RR 0.08** (0.01 to 0.57)	215 (1 study)	⊕⊕⊖⊖ **Low**[c]	Alemtuzumab may result in a reduction of dropouts at 36 months.

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; **EDSS:** Expanded Disability Status Scale; **HR:** hazard ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

[a] Control group risk was derived from Kaplan-Meier curves from the included study (CAMMS223).
[b] Participants and personnel were not blinded and this outcome could have been affected by this. There was high risk of attrition bias. Downgraded two levels.
[c] Risk of bias. Participants and personnel were not blinded and this is a patient-reported outcome. There was high risk of attrition bias. Downgraded two levels.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease of the central nervous system (brain and spinal cord), the causes of which remain unknown (Coles 1999a; Gray 2004). It is the most common cause of non-traumatic neurological disability in young adults (Noseworthy 2000). Almost two million people in the world are affected by this condition, which can substantially impair quality of life and is associated with high costs for patients, their families, and society in general (Multiple Sclerosis International Federation 2010).

Four types of MS have been identified: relapsing–remitting (RR), secondary-progressive (SP), primary-progressive (PP), and progressive-relapsing (PR). The disease course is unpredictable; while some individuals are minimally affected, others show rapid progression of the disease, reaching total physical incapacity (Lublin 1996). In the first form, MS is characterized by relapses and remissions (RR), but given time sequelae from relapses may cause increased disability (Hawkins 1999). In some people, the disease is progressive from its onset (PP); others experience periods of progression followed by relapses and remissions (SP) (Lublin 1996). In other cases, MS shows progression from onset but with clear relapses (PR).

Description of the intervention

Therapeutic strategies for MS aim to treat exacerbations, prevent new exacerbations, and avoid progression of disability (Filippini 2013). Current disease-modifying treatments decrease the frequency of relapse and modestly reduce the accumulation of disability (Coles 2006; Rieckmann 2009). Consequently, new agents that effectively control the disease are needed.

Alemtuzumab (Lemtrada, previously known as Campath-1H) is a humanized monoclonal antibody against cell surface CD52, which can be found in a variety of cell populations, including B and T lymphocytes, thymocytes, and monocytes but not in hematologic precursors or plasma cells (Gilleece 1993). However, the exact function of CD52 is still unknown (Xia 1991).

In 2001, alemtuzumab was approved for fludarabine-resistant B-cell chronic lymphocytic leukemia (FDA 2001; Keating 2002). Since that time, it has been used for several other diseases (licensed or off-label use), including immune thrombocytopenic purpura, aplastic anemia, autoimmune hemolytic anemia, vasculitis, hematopoietic stem cell transplants (as a conditioning regimen), and organ transplants (as an induction agent) (Gomez-Almaguer 2012; Lockwood 2003; Waldmann 2005; Weissenbacher 2010).

One study published in 1999, including 36 participants with progressive MS, reported that daily intravenous infusions of alemtuzumab (20 mg over four hours for five days) were associated with a reduction in gadolinium-enhanced magnetic resonance imaging (MRI) lesions and a reduction in relapses, with no clinical improvement in disability (Coles 1999b). Open studies involving participants with RR MS reported that the drug reduced relapse rates and disability (Coles 2006; Hirst 2008).

Alemtuzumab is already approved for MS in the EU (EMA 2013). The US Food and Drug Administration (FDA) approved alemtuzumab for the treatment of people with RR MS who have had an inadequate response to two or more drugs indicated for the treatment of MS (FDA 2014).

The guidelines from the Association of British Neurologists identified alemtuzumab as having the greatest activity in preventing relapses. However, because of safety concerns, the guidelines recommended this drug as a second-line treatment (Scolding 2015).

Alemtuzumab is available for the treatment of MS in 12 mg/1.2 mL single-dose vials (10 mg/mL). The proposed initial dosage for MS is 12 mg daily for five consecutive days (intravenous infusion), followed by a second treatment course of 12 mg daily for three consecutive days. The second treatment course is administered 12 months after the first course. Premedication with corticosteroids is recommended immediately before alemtuzumab and during the first three days of any treatment course (FDA 2014). The overall half-life of the drug is approximately 21 days. Alemtuzumab is available as a liquid to be made up into a solution for infusion (drip) into a vein. An infusion provides 12 mg and lasts around four hours.

Alemtuzumab can produce serious adverse events including other autoimmune syndromes affecting the thyroid and blood cells (thrombocytopenia, hemolytic anemia, pancytopenia) and nephropathies, and it can increase the risk of thyroid cancer (FDA 2014). At five-year follow-up, the cumulative risk of autoimmune disease is approximately 22%, Graves' disease 12%, immune thrombocythemia purpura 3%, and Goodpasture's disease (severe glomerulopathy) 0.4% (Cossburn 2011).

In 2015, the FDA updated a general overview of recommendations (Risk Evaluation and Mitigation Strategy Program) about Lemtrada for patients, pharmacies, and healthcare providers (FDA 2015).

How the intervention might work

Previous research has suggested that alemtuzumab depletes the T- and B-cells that may be responsible for cellular damage, while sparing innate immune cells (Rao 2012). Change in the composition of lymphocytes that accompanies lymphocyte reconstitution has also been reported (Hill-Cawthorne 2012).

Why it is important to do this review

Results of randomized controlled trials (RCTs) of alemtuzumab for MS are promising and a systematic review of all RCTs was warranted to evaluate its effectiveness and safety for MS. Considering the prevalence and the potential clinical impact of MS, we must synthesize and appraise critically all available evidence on interventions proposed for this condition. It is also important to maintain/update the results of this review as many new therapies are in development to treat MS and the results of this review will provide an important piece of evidence for clinical decision-making and clinical practice guideline development.

This is an update of a previously published review (Riera 2016). The review was updated because the search was conducted in 2015 and there was a need to assess if further studies were available. It was also necessary to update the review appraisal methods and wording, as Cochrane methodology has improved over the years.

OBJECTIVES

To evaluate the benefits and harms of alemtuzumab alone or associated with other treatments in people with any form of MS.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel RCTs. We did not consider non-randomized, quasi-randomized, or cross-over trials.

Types of participants

We included adults diagnosed with MS according to the McDonald criteria (McDonald 2001; Polman 2011), or Poser criteria (Poser 1983). We considered participants with any form of MS (RR, PP, SP, or PR) for inclusion. We planned to include studies with only a subset of eligible participants only if separated data were available.

Types of interventions

Experimental intervention: alemtuzumab alone or associated with other medications (that were also given to participants in the comparison group) at any dose and for any course duration.

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

Types of outcome measures

Primary outcomes

- Relapse-free survival. Relapse was defined as newly developed or recently worsened symptoms of neurological dysfunction, lasting longer than 24 hours and objectively confirmed. However, we considered less stringent criteria and assessed these separately.
- Sustained disease progression-free survival, defined as at least 1.0-point increase in the Expanded Disability Status Scale (EDSS) score (Kurtzke 1983) for participants with a baseline score of 5.0 or less or at least 0.5-point increase for participants with a baseline score of 5.5 points or greater confirmed at six months. We considered a 1-point increase in EDSS score confirmed at three months' follow-up as a surrogate outcome measure of progression.
- Adverse events: number of participants with at least one adverse event, including serious adverse events.

We assessed all primary outcomes after 12 and 24 months' follow-up and at the end of the follow-up period.

Secondary outcomes

- Clinical disease activity free: number of participants free of clinical disease activity, defined as no relapses and no sustained accumulation of disability. Sustained accumulation disability was defined as an increase of at least 1.5 points on the EDSS for participants with a baseline score of 0 and of at least 1.0 point for participants with a baseline score of 1.0 or more.
- Quality of life as assessed using the Multiple Sclerosis Quality of Life scale (MSQOL)-54 (Vickrey 1995) or the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Fischer 1999).
- Change in disability as assessed using the EDSS (Kurtzke 1983). We included change in EDSS scores as a secondary outcome instead of a primary outcome because short-term changes in EDSS scores may not be a reliable marker of irreversible change in RR MS (Healy 2013).
- Fatigue as assessed using the Fatigue Severity Scale or the Fatigue Index Scale (Krupp 1989).
- New or enlarging T2-hyperintense lesions: number of participants with new or enlarging T2-hyperintense lesions on MRI (Li 1999).
- Dropouts: number of participants who dropped out.

We assessed all secondary outcomes after 12 and 24 months and at the end of the follow-up period.

Search methods for identification of studies

This is an update of a previously published review (Riera 2016). We conducted an updated search on 21 June 2022 without language restrictions to identify all relevant published RCTs using the optimally sensitive strategy developed by Cochrane for the identification of RCTs.

Electronic searches

The Information Specialist of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group ran a bespoke search on 21 June 2022 of the following sources:

- Cochrane Central Register of Controlled Trials (CENTRAL 2022, Issue 6);
- MEDLINE (PubMed) (1966 to 21 June 2022);
- Embase (Embase.com) (1974 to 21 June 2022);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO host);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- EU Clinical Trials Register (EU-CTR);
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch);
- German Clinical Trials Register (DRKS) (www.drks.de/drks_web/);
- International Standard Randomised Controlled Trial Number (ISRCTN) (www.isrctn.com/).

The search strategies for each database are listed in Appendix 1.

Searching other resources

In addition, we used the following methods.

- We screened the bibliographic references of identified studies to identify additional studies.
- We contacted pharmaceutical companies (Genzyme-Sanofi and Bayer) for information on any unpublished trials.
- We contacted the main authors of studies if data reported in the original articles were incomplete, and we asked experts in this field about additional unpublished or ongoing studies.

Data collection and analysis

Selection of studies

Two review authors (RR and RLP) independently screened the titles and abstracts of all records retrieved by the search in order to identify potentially relevant studies. We retrieved the full-text reports/publications of those deemed eligible for inclusion and two review authors (RR and RLP) independently read the full texts to identify studies that met the selection criteria. The review authors recorded the reasons for exclusion of rejected studies. We resolved disagreements between review authors by discussion until there was consensus with the consultation of a third review author (ALM) if needed. We collated multiple reports of each study so that the study, and not the reports, was the unit of analysis.

Data extraction and management

We used a data collection form to report information on study characteristics and outcome data. Three review authors (RR, RLP, and ALB) extracted the following information from the primary studies included in the review.

- Publication details (i.e. year, country, authors)
- Study design and methods: inclusion/exclusion criteria, randomization method, allocation concealment, blinding
- Setting
- Population data (i.e. age, severity of disease, type of MS)
- Details of intervention (i.e. dose, regimen, duration)
- Outcome measures (including effectiveness and adverse effects)
- Number of dropouts
- Length of follow-up
- Types of data analyses (e.g. intention-to-treat, modified intention-to-treat)
- Any other potential risk of bias

We discussed disagreements until consensus was reached, with the involvement of a third review author (MRT) if needed. One review author (RR) inserted data into Review Manager 5 software (Review Manager 2020). We double-checked that data were entered correctly into the form.

Assessment of risk of bias in included studies

Two review authors (RR and RLP) independently assessed the methodological quality of included studies using the RoB 1 tool and the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A third review author (ALM or MRT) resolved any disagreements. We assessed risk of bias according to the following domains.

- Sequence generation: was the allocation sequence adequately generated?
- Allocation concealment: was allocation adequately concealed?
- Blinding of participants, personnel, and outcome assessors: was knowledge of the allocated interventions adequately prevented during the study?
- Incomplete outcome data: were outcome data adequately assessed and accounted for? (we considered a loss to follow-up rate greater than 15% as high risk).
- Selective outcome reporting: were the reports of the study free of any suggestion of selective outcome reporting?
- Other potential threats to validity: was the study apparently free from other problems that could put it at risk of bias?

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgment in the risk of bias table. We judged the following domains at outcome-level: blinding of participants and personnel, blinding of outcome assessors, and incomplete outcome data.

Measures of treatment effect

For each outcome, we calculated a summarized estimate of treatment effect (with 95% confidence interval [CI]) for each comparison. We reported dichotomous outcomes as risk ratios (RRs). We used the mean difference (MD) for continuous outcomes and the hazard ratio (HR) for time-to-event outcomes.

Unit of analysis issues

The unit of analysis was the individual participant. For studies with multiple treatment groups of the same interventions, but using different doses (alemtuzumab 12 mg or 24 mg), we compared each arm with the common comparator separately. We based our choice on the recommendations of Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

If we had included any cluster-RCTs, we would have calculated the design effect based on intracluster correlation as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Dealing with missing data

In cases where there were missing or unavailable data, we contacted the primary authors for further information (i.e. CAMMS223).

We performed a search for protocols or additional articles related to the included studies (or both). If relevant data were unavailable, we presented and discussed the results in the main text of the review.

Assessment of heterogeneity

We investigated heterogeneity using the Chi^2 test and the I^2 statistic, which indicates the degree of variation across studies that is due to heterogeneity rather than due to chance. We considered an I^2 value greater than 50% as substantial heterogeneity (Higgins 2021). We checked clinical and methodological diversity as potential causes of heterogeneity.

Assessment of reporting biases

Although planned, as it was not possible to pool more than 10 studies, we did not use funnel plots to explore possible publication bias.

Data synthesis

We summarized data using Review Manager 5 software (Review Manager 2020). By default, we used a random-effects model for meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses for all outcomes.

- Treatment duration (12 or 24 months)

- Disease type: RR, PP, SP, or PR
- Disability at baseline (EDSS score 5.0 or less or 5.5 or greater)
- Treatment-naive or previously treated participants

However, we did not carry out subgroup analyses to consider disease type and disability at baseline due to a lack of available data.

Sensitivity analysis

We planned to perform sensitivity analysis for primary outcomes by excluding trials presenting one or more domains at high risk of bias. However, all the studies presented at least one domain at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

We created two summary of findings tables.

- Alemtuzumab 12 mg versus interferon beta-1a
- Alemtuzumab 24 mg versus interferon beta-1a

We considered the following outcomes at 36 months.

- Relapse-free survival
- Sustained disease progression-free survival
- Adverse events, including serious adverse events
- Change in disability (EDSS)
- New or enlarging T2-hyperintense lesions
- Dropouts

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 Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021) using GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade or upgrade the certainty of evidence in the footnotes, and made comments to aid readers' understanding of the review when necessary.

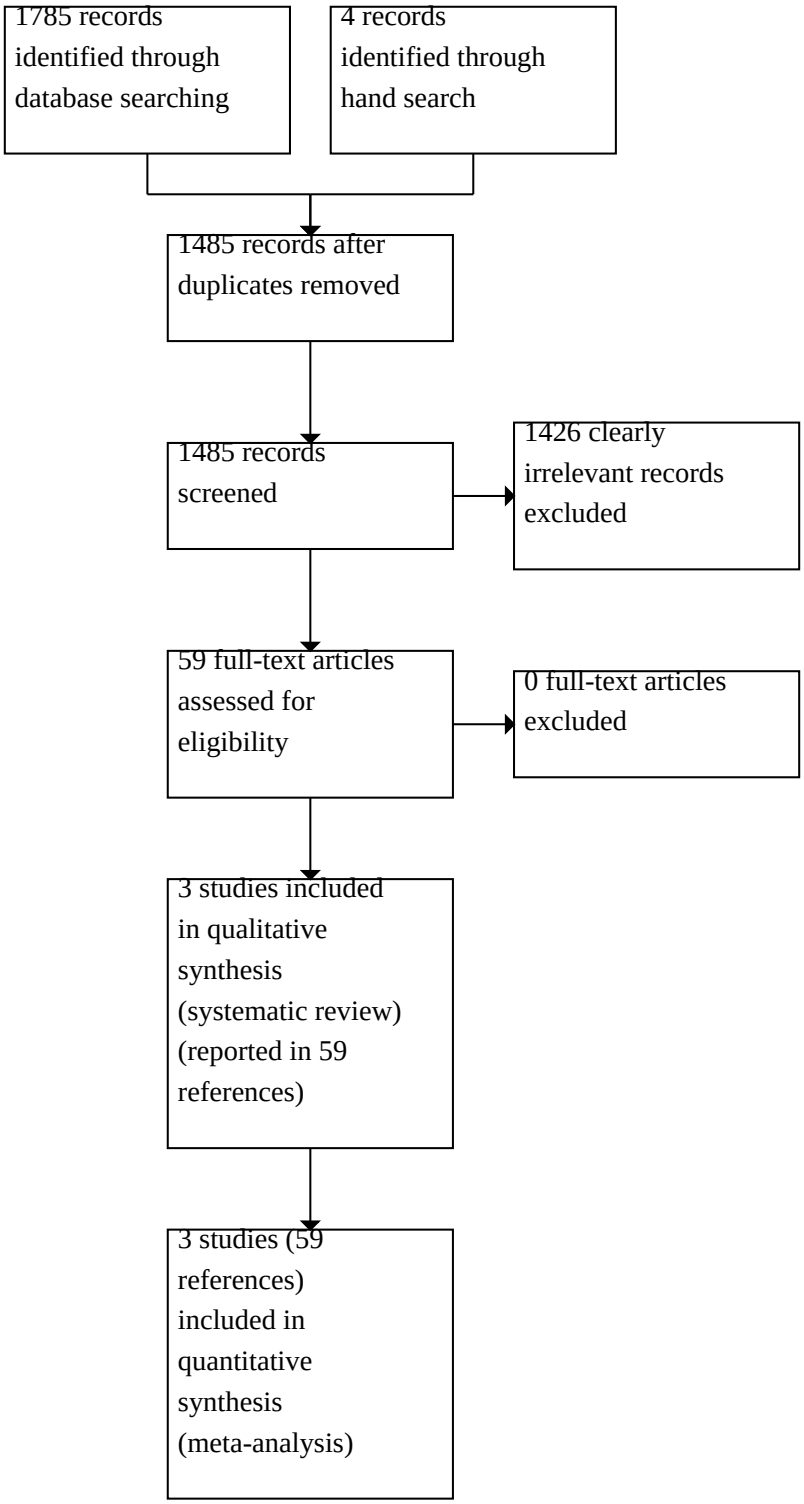
RESULTS

Description of studies

Results of the search

In this update, the search strategy retrieved 1789 references: 181 in CENTRAL, 645 in MEDLINE, 854 in Embase, 17 in CINAHL, 48 in ClinicalTrials.gov, 11 in the WHO International Clinical Trials Registry Platform, 18 in the EU-CTR, three in the ISRCTN registry, eight in DRKS, and four from handsearching. After eliminating 304 duplicates, we screened the titles and abstracts of 1485 references. Of these, we excluded 1426 clearly irrelevant records and considered 59 references as potentially eligible. After reading the full texts, we included these 59 records, which referred to three RCTs. The flow diagram of the process of study identification and selection is presented in Figure 1. In relation to the previous version of this review, this current version included 27 additional references reporting the same three RCTs already included (Riera 2016). There were no new data for the outcomes of interest and review findings remained unchanged. We excluded no studies, no studies are awaiting classification, and there are no ongoing studies.

Figure 1. PRISMA study flow diagram.



Included studies

The three RCTs included 1713 participants (CAMMS223; CARE-MS I; CARE-MS II). All studies were multicenter trials comparing alemtuzumab versus subcutaneous interferon beta-1a for people with RR MS according to the McDonald criteria (McDonald 2001).

Participants were treatment-naive in CARE-MS I and CAMMS223. CARE-MS II included only participants with at least one relapse while being treated with interferon beta or glatiramer for at least six months.

In the CARE-MS I and CARE-MS II studies, the interventions were given for 12 months (CARE-MS I; CARE-MS II); in the CAMMS223 study, the treatment lasted 24 months (CAMMS223). The studies used the following regimens:

- CAMMS223 was a phase II trial: alemtuzumab (either 12 mg/day or 24 mg/day) was given by intravenous infusion on five consecutive days during the first month and on three consecutive days at months 12 and 24.
- CARE-MS I (or CAMMS323) was a phase III trial: alemtuzumab (12 mg/day) was given by intravenous infusion on five consecutive days during the first month and on three consecutive days at month 12.
- CARE-MS II (or CAMMS324) study was a phase III trial: alemtuzumab (either 12 mg/day or 24 mg/day) was given by intravenous infusion on five consecutive days during the first month and on three consecutive days at month 12 (CARE-MS II).

In all studies, the dose of interferon beta-1a was 44 µg given subcutaneously three times weekly after dose titration.

The studies assessed the following outcomes.

- Relapse-free survival: CAMMS223; CARE-MS I; CARE-MS II.
- Sustained disease progression-free survival: CAMMS223; CARE-MS I; CARE-MS II.
- Adverse events: CAMMS223; CARE-MS I; CARE-MS II.
- Change in disability (EDSS): CAMMS223; CARE-MS I; CARE-MS II.
- Quality of life: CARE-MS I; CARE-MS II (but the tools used were not planned in this review).
- New or enlarging T2-hyperintense lesions: CARE-MS I; CARE-MS II.
- Dropouts: CAMMS223; CARE-MS I; CARE-MS II.

None of the studies assessed or reported clinical disease activity free and fatigue using the tools proposed in this review. Details of the three studies are available in the Characteristics of included studies table.

Excluded studies

For the updated search, we did not identify/exclude any ineligible studies at the full-text screening stage.

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' judgments about each risk of bias item for each included study.

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

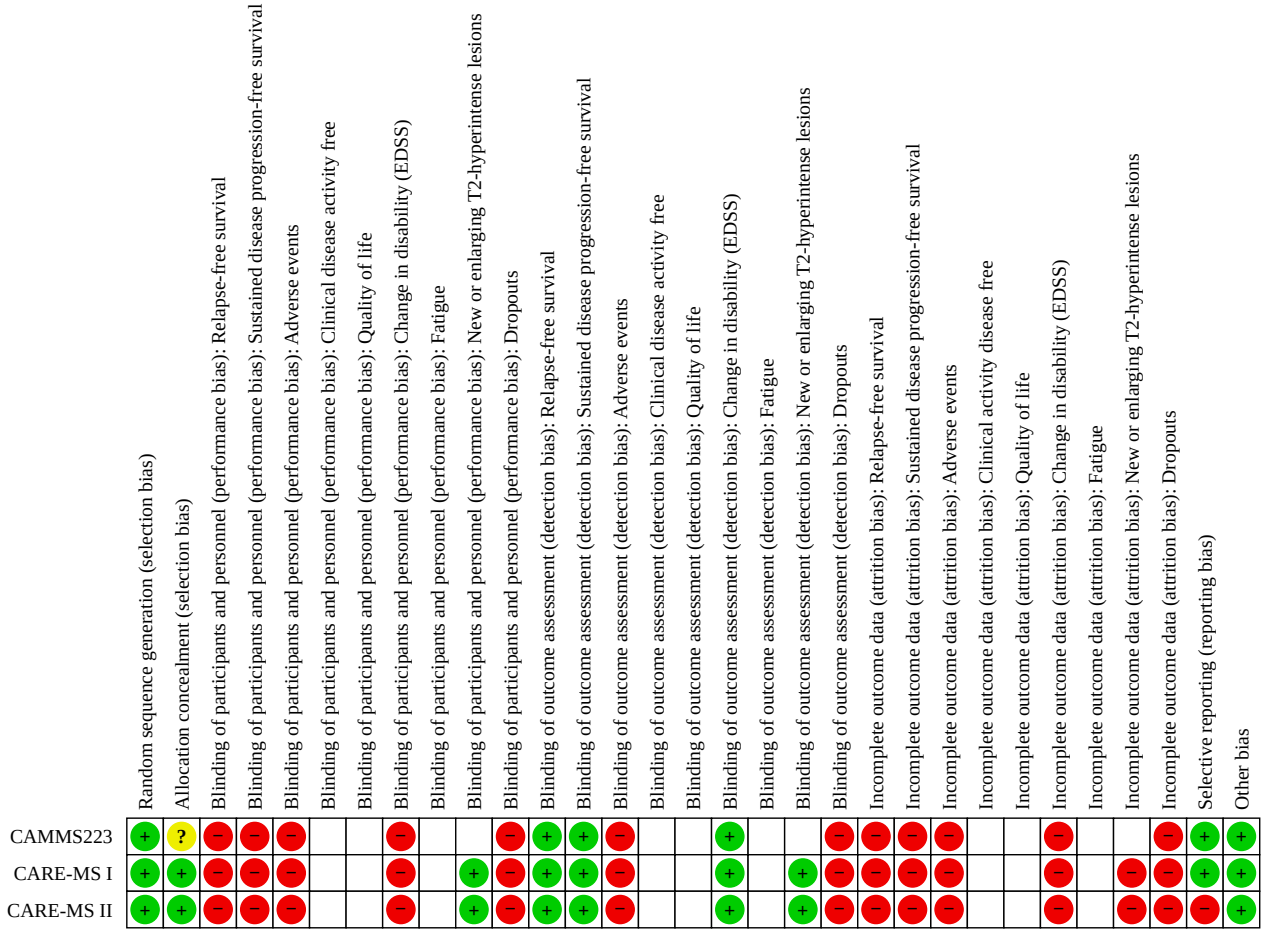


Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Allocation

We classified all studies at low risk of bias for generation of allocation sequence. The methods were reported and were judged to be appropriate.

For allocation concealment, we classified CARE-MS I and CARE-MS II at low risk of bias because they provided an adequate method to ensure allocation concealment. We classified CAMMS223 as presenting an unclear risk of bias because it did not provide sufficient information to allow judgment.

Blinding

We considered all studies at high risk of performance bias for all outcomes, except for new or enlarging T2-hyperintense lesions. The compared interventions had adverse effects that precluded blinding and were administered by different routes. However, it is unlikely that the lack of blinding of participants and personnel could affect the MRI findings.

For detection bias, we classified the studies at the outcome level as follows.

- Relapse-free survival: we judged the three studies at low risk of bias since they reported blinded outcome assessment.
- Sustained disease progression-free survival: we judged the three studies at low risk of bias since the methods were described and seemed appropriate.
- Adverse events: we judged the three studies at high risk of bias since the participants and personnel were unblinded and this is a patient-reported outcome.
- Change in disability (EDSS): we judged the three studies at low risk of bias since they reported blinded outcome assessment.
- New or enlarging T2-hyperintense lesions: we judged CARE-MS I and CARE-MS II at low risk of bias since they reported blinded outcome assessment (CAMMS223 did not assess this outcome).
- Dropouts: we judged the three studies at high risk of bias since the participants and personnel were unblinded and this is a patient-reported outcome.

Incomplete outcome data

We judged all three studies at high risk of bias for all outcomes because the frequency of losses was high and unbalanced between groups (in terms of frequency and reasons for losses).

Selective reporting

We classified CAMMS223 and CARE-MS I at low risk of bias for selective reporting, but we judged CARE-MS II at high risk of bias because efficacy analysis was not reported for alemtuzumab 24 mg.

Other potential sources of bias

There were no other known potential sources of bias in the three studies.

Effects of interventions

See: **Summary of findings 1** Alemtuzumab 12 mg compared to interferon beta-1a for multiple sclerosis; **Summary of findings 2** Alemtuzumab 24 mg compared to interferon beta-1a for multiple sclerosis

Comparison 1: alemtuzumab 12 mg versus subcutaneous interferon beta-1a

See Summary of findings 1.

Primary outcomes

Relapse-free survival

None of the studies provided data for the 12-month analysis.

At 24 months, alemtuzumab may increase relapse-free survival compared to interferon beta-1a (HR 0.50, 95% CI 0.41 to 0.60; 2 studies, 1248 participants; I^2 = 0%; low-certainty evidence, downgraded due to risk of bias; Analysis 1.1) (CARE-MS I; CARE-MS II). In subgroup analyses, this result was consistent when we considered separately treatment-naive (HR 0.45, 95% CI 0.33 to 0.61; 1 study, 581 participants) (CARE-MS I), and previously treated participants (HR 0.53, 95% CI 0.41 to 0.69; 1 study, 667 participants) (CARE-MS II) (test for subgroup differences: Chi^2 = 0.63, df = 1 (P = 0.43); I^2 = 0%; Analysis 1.1).

At 36 months, alemtuzumab may increase relapse-free survival compared to interferon beta-1a (45/110 with alemtuzumab versus 24/111 with interferon beta-1a; HR 0.31, 95% CI 0.18 to 0.53; 1 study, 221 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 1.2) (CAMMS223).

Sustained disease progression-free survival

None of the studies provided data for the 12-month analysis.

At 24 months, alemtuzumab may increase sustained disease progression-free survival compared to interferon beta-1a (HR 0.62, 95% CI 0.44 to 0.87; 2 studies, 1191 participants; low-certainty evidence, downgraded due to risk of bias; I^2 = 0%; Analysis 1.3) (CARE-MS I; CARE-MS II). This finding was similar in the subgroup analysis of previously treated participants (HR 0.58, 95% CI 0.38 to 0.89; 1 study, 628 participants) (CARE-MS II). However, the estimate was very imprecise in the treatment-naive subgroup (HR 0.70, 95% CI 0.40 to 1.22; 563 participants). The test for subgroup interaction was not significant (P = 0.60) (Analysis 1.3).

At 36 months, and considering treatment-naive participants, alemtuzumab may increase the sustained disease progression-free survival compared to interferon beta-1a (HR 0.25, 95% CI 0.11 to 0.56; 1 study, 223 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 1.4) (CAMMS223).

Number of participants with at least one adverse event, including serious adverse events

None of the studies provided data for the 12-month analysis.

At 24 months, alemtuzumab may make little to no difference in the proportion of participants with at least one adverse event compared to interferon beta-1a (800/822 with alemtuzumab versus 400/466 with interferon beta-1a; RR 1.04, 95% CI 1.01 to 1.06; 2 studies, 1248 participants; I^2 = 0%; low-certainty evidence, downgraded due to risk of bias; Analysis 1.5). This result was consistent in subgroup analyses of treatment-naive (HR 1.04, 95% CI 1.00 to 1.09; 1 study, 581 participants) (CARE-MS I) and previously treated participants (HR 1.03, 95% CI 1.00 to 1.07; 1 study, 667 participants) (test for subgroup differences: Chi^2 = 0.08, df = 1, P = 0.78; I^2 = 0%; Analysis 1.5) (CARE-MS II).

At 36 months, alemtuzumab may make little to no difference in the proportion of participants with at least one adverse event compared to interferon beta-1a (113/113 with alemtuzumab versus 111/111 with interferon beta-1a; RR 1.00, 95% CI 0.98 to 1.02; 1 study, 224 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 1.6) (CAMMS223).

At 24 and 36 months, the proportion of participants with at least one adverse event was high with both interventions.

Secondary outcomes

Clinical disease activity free

None of the studies assessed number of participants free of clinical disease activity.

Quality of life

One study assessed quality of life but used tools that were not included in the review protocol (CARE-MS II).

Change in disability

None of the studies provided data for the 12-month analyses.

At 24 months, considering both treatment-naive and previously treated participants (who failed after interferon beta or glatiramer treatment), the evidence was very uncertain about the effects of alemtuzumab on changes in disability (EDSS) compared to interferon beta-1a (MD −0.20, 95% CI −0.60 to 0.20; 2 studies, 1199 participants; I^2 = 88%; very low-certainty evidence, downgraded due to risk of bias and inconsistency; Analysis 1.7) (CARE-MS I; CARE-MS II). This result was consistent in the subgroup analysis involving treatment-naive participants (MD 0, 95% CI −0.19 to 0.19; 1 study, 571 participants) (CARE-MS I). When we analyzed only previously treated participants, alemtuzumab was associated with slightly reduced disability (assessed by EDSS) (MD −0.41, 95% CI −0.62 to −0.20; 1 study, 628 participants) but this difference had limited clinical relevance (CARE-MS II). Test for subgroup interaction was significant (Chi^2 = 8.37, df = 1, P = 0.004; I^2 = 88.1%).

At 36 months, alemtuzumab may result in a slight reduction in disability compared to interferon beta-1a (MD −0.70, 95% CI −1.04 to −0.36; 1 study, 223 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 1.8) (CAMMS223).

Fatigue (Fatigue Severity Scale or the Fatigue Index Scale)

None of the studies assessed fatigue.

New or enlarging T2-hyperintense lesions

None of the studies provided data for the 12- and 36-month analyses.

At 24 months, the evidence is very uncertain about the effects of alemtuzumab in the proportion of participants with new or enlarging T2-hyperintense lesions, considering both treatment-naive and previously treated participants, compared to interferon beta-1a (RR 0.74, 95% CI 0.59 to 0.91; 2 studies, 1238 participants; I^2 = 80%; very low-certainty evidence, downgraded due to risk of bias and inconsistency; Analysis 1.9) (CARE-MS I; CARE-MS II). This result was consistent in subgroup analyses involving treatment-naive (RR 0.82, 95% CI 0.71 to 0.95; 1 study, 581 participants) (CARE-MS I), and previously treated participants (RR 0.66, 95% CI 0.59 to 0.75; 1 study, 657 participants) (CARE-MS II). Test for subgroup interaction was significant (Chi^2 = 5.01, df = 1, P = 0.03; I^2 = 80.1%).

Dropouts

None of the studies provided data for the 12-month analysis.

At 24 months, alemtuzumab may reduce the risk of dropouts compared to interferon beta-1a (RR 0.31, 95% CI 0.22 to 0.44; 2 studies, 1248 participants; I^2 = 29%; low-certainty evidence, downgraded due to risk of bias; Analysis 1.10) (CARE-MS I; CARE-MS II). This result was consistent in subgroup analyses of treatment-naive (RR 0.39, 95% CI 0.24 to 0.65; 1 study, 581 participants) (CARE-MS I) and previously treated participants (RR 0.27, 95% CI 0.19 to 0.39; 1 study, 667 participants) (CARE-MS II). Test for subgroup interaction was not significant (Chi^2 = 1.41, df = 1, P = 0.24; I^2 = 29%).

At 36 months, the evidence is very uncertain about the effects of alemtuzumab on the risk of dropouts compared to interferon beta-1a (RR 0.81, 95% CI 0.57 to 1.14; 1 study, 224 participants; very low-certainty evidence, downgraded due to risk of bias and imprecision; Analysis 1.11) (CAMMS223).

Comparison 2: alemtuzumab 24 mg versus subcutaneous interferon beta-1a

See Summary of findings 2.

Primary outcomes

Relapse-free survival

None of the studies provided data for 12- or 24-month analyses.

At 36 months, alemtuzumab may increase relapse-free survival compared to interferon beta-1a (17/110 with alemtuzumab versus 45/111 with interferon beta-1a; HR 0.21, 95% CI 0.11 to 0.40; 1 study, 221 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 2.1) (CAMMS223).

Sustained disease progression-free survival

None of the studies provided data for the 12- or 24-month analyses.

At 36 months, alemtuzumab may increase sustained disease progression-free survival compared to interferon beta-1a (HR 0.33, 95% CI 0.16 to 0.69; 1 study, 221 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 2.2) (CAMMS223).

Number of participants with at least one adverse event, including serious adverse events

None of the studies provided data for the 12-month analysis.

At 24 months, alemtuzumab may make little to no difference in the proportion of participants with at least one adverse event compared to interferon beta-1a (159/161 with alemtuzumab versus 191/202 with interferon beta-1a; RR 1.04, 95% CI 1.01 to 1.08; 1 study, 363 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 2.3) (CARE-MS II).

At 36 months, alemtuzumab may make little to no difference in the proportion of participants with at least one adverse event compared to interferon beta-1a (107/108 with alemtuzumab versus 107/107 with interferon beta-1a; RR 0.99, 95% CI 0.97 to 1.02; 1 study, 215 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 2.4) (CAMMS223).

At 24 and 36 months, the proportion of participants with at least one adverse event was high with both interventions.

Secondary outcomes

Clinical disease activity free

None of the studies assessed number of participants free of clinical disease activity.

Quality of life

One study assessed quality of life but used a tool that was not included in this review protocol (CARE-MS II).

Change in disability

None of the studies provided data for the 12- or 24-month analyses.

At 36 months, alemtuzumab may result in a slight reduction in disability (assessed by EDSS) compared to interferon beta-1a (MD −0.83, 95% CI −1.16 to −0.50; 1 study, 221 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 2.5) (CAMMS223).

Fatigue (Fatigue Severity Scale or the Fatigue Index Scale)

None of the studies assessed fatigue.

New or enlarging T2-hyperintense lesions

None of the studies assessed new or enlarging T2-hyperintense lesions.

Dropouts

None of the studies provided data for the 12-month analyses.

At 24 months, the evidence is very uncertain for the effects of alemtuzumab on the risk of dropouts compared to interferon beta-1a (6/161 with alemtuzumab versus 15/202 with interferon beta-1a; RR 0.50, 95% CI 0.20 to 1.26; 1 study, 363 participants; very low-certainty evidence, downgraded due to risk of bias and imprecision; Analysis 2.6) (CARE-MS II).

At 36 months, alemtuzumab may result in a reduction on the risk of dropouts compared to interferon beta-1a (1/108 with alemtuzumab versus 13/107 with interferon beta-1a; RR 0.08, 95% CI 0.01 to 0.57; 1 study, 215 participants; low-certainty evidence, downgraded due to risk of bias; Analysis 2.7) (CAMMS223).

DISCUSSION

Summary of main results

This Cochrane Review aimed to assess the benefits and harms of alemtuzumab compared with any other drug treatment for any type of MS.

Based on the results of three RCTs, compared to subcutaneous interferon beta-1a, alemtuzumab 12 mg:

- may improve relapse-free survival at 24 and 36 months;
- may improve sustained disease progression-free survival at 24 and 36 months;
- may make little to no difference in the proportion of participants with at least one adverse event at 24 and 36 months, although the proportion of participants with at least one adverse event was high in both the alemtuzumab 12 mg and the interferon beta-1a groups;
- evidence is very uncertain about the effects of alemtuzumab on change in disability (EDSS) at 24 months; alemtuzumab may result in a slight reduction in disability at 36 months;
- evidence is very uncertain about the effects of alemtuzumab on new or enlarging T2-hyperintense lesions at 24 months;
- may reduce the risk of dropouts at 24 months, but the evidence is very uncertain on the effects of alemtuzumab at 36 months.

Based on the results of two RCTs, compared to subcutaneous interferon beta-1a, alemtuzumab 24 mg:

- may improve relapse-free survival at 36 months;
- may improve sustained disease progression-free survival at 36 months;
- may make little to no difference in the proportion of participants with at least one adverse event at 24 and 36 months; although the proportion of participants with at least one adverse event was high in both the alemtuzumab and the interferon beta-1a groups;
- may slightly reduce disability (EDSS) at 36 months;
- may reduce the risk of dropouts at 36 months, but the evidence is very uncertain on the effects of alemtuzumab at 24 months.

Overall completeness and applicability of evidence

We included three RCTs that compared alemtuzumab 12 mg or 24 mg versus subcutaneous interferon beta-1a 44 µg subcutaneously during 12 or 24 months for participants (naive or previously treated with glatiramer or interferon beta-1a) with RR MS, and a follow-up of up to 36 months for some outcomes. Therefore, the available evidence is valid for these specific comparisons and this subtype of MS, and the implications of extrapolating our findings to different situations are unknown.

Considering the availability and the confidence on the current data, there remains a lack of evidence about the effects of alemtuzumab for other subtypes of MS, when compared to other pharmacologic options and at extended long-term (more than 36 months) use.

Additionally, the following outcomes were not considered or reported by the RCTs: number of participants free of clinical disease activity, quality of life (assessed by the MSQOL or the MSQLI) and fatigue (assessed by the Fatigue Severity Scale or the Fatigue Index Scale).

Some probable reasons for this lack of evidence include 1. outcomes that were initially proposed in the trial protocols but were not available for this review even after contact with study authors; 2. outcomes that were not originally planned at the protocol stage of the included RCTs.

Regarding alemtuzumab doses, although the included RCTs assessed 12 mg and 24 mg, the dose proposed for licensing was 12 mg/day (Genzyme 2013). According to Genzyme, the reasons for this decision were that there was no difference in pharmacodynamic response between 24 mg/day and 12 mg/day dose levels, and the overall frequency of adverse events was higher in the 24 mg/day group, suggesting better tolerability of the 12 mg/day dose. Additionally, the efficacy on imaging outcomes was reduced with the 12 mg/day regimen, suggesting that larger reductions in dose would probably connote impairment in efficacy (Genzyme 2013).

Our preplanned approach to address adverse events of alemtuzumab at the protocol stage could be further improved, as assessing the proportion of participants with at least one adverse event would not completely differentiate serious from non-serious adverse events and would not allow assessment of specific and clinically important events, such as autoimmune diseases, thyroid dysfunctions, blood and lymphatic system disorders, and infections. We thus highlight that the primary safety outcome of this review update should be interpreted with caution. For the future updates of this review, we plan to redefine our types of safety outcomes based on the most up-to-date clinical perspectives.

Quality of the evidence

As presented in Summary of findings 1 and Summary of findings 2, the certainty of the evidence for each outcome ranged from very low to low. The certainty was downgraded mainly due to methodological limitations and, less frequently, due to inconsistency and imprecision as presented below for each outcome.

- Relapse-free survival: certainty downgraded due to methodological limitations (performance and attrition bias) at 24 and 36 months.
- Sustained disease progression-free survival: certainty downgraded due to methodological limitations (performance and attrition bias) at 24 and 36 months.
- Adverse events: certainty downgraded due to methodological limitations (performance, attrition, and detection bias) at 24 and 36 months.
- Change in disability (EDSS): certainty downgraded due to methodological limitations (performance and attrition bias) and inconsistency at 24 months; certainty downgraded due to methodological limitations (performance and attrition bias) at 36 months.
- New or enlarging T2-hyperintense lesions: certainty downgraded due to methodological limitations (performance and attrition bias) and inconsistency at 24 months.
- Dropouts: certainty downgraded due to methodological limitations (performance, attrition, and detection bias) and imprecision at 24 and 36 months.

The risk of bias of the studies was high mainly due to methodological limitations related to the lack of blinding of participants and personnel. The difference in specific adverse events related to alemtuzumab or interferon beta-1a precluded the blinding of participants and personnel, and this circumstance may not be changed in future RCTs.

Potential biases in the review process

To avoid the introduction of bias, throughout the review, we strictly followed all the recommendations on searching, study selection, data collection, and data analysis described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Limitations of this review include: 1. no assessment of publication bias through funnel plot analysis because there were fewer than 10 studies included in the meta-analysis, 2. not all planned subgroup/sensitivity analyses could be conducted due to the low number of studies or limited availability of data, 3. comparison of alemtuzumab versus non-pharmacological option (such as autologous stem cell transplant) were not considered for inclusion; 4. a restricted number of validated tools (Fatigue Severity Scale and the Fatigue Index Scale) were considered for fatigue assessment and none of the studies used them.

Agreements and disagreements with other studies or reviews

During the conduct of the first version of this review, one non-Cochrane systematic review assessing all available treatments for MS was published (CADTH 2013). The review evaluated direct and indirect comparisons between several drugs, including alemtuzumab. The findings were similar to those of our review, including the results of meta-analysis and the risk of bias of the included RCTs.

One Cochrane Review published in 2017 (Zhang 2017), and with a more restricted clinical question, analyzed specifically alemtuzumab versus interferon beta-1a for RR MS, and included the same three RCTs (CAMMS223; CARE-MS I; CARE-MS II). Their results and overall conclusions for this comparison were similar to those of our review.

Another Cochrane Review that performed network meta-analysis considering all immunomodulators and immunosuppressants for RR MS was published in 2015 and included data from the same three RCTs (CAMMS223; CARE-MS I; CARE-MS II) (Tramacere 2015). The review had overall conclusions similar to ours.

AUTHORS' CONCLUSIONS

Implications for practice

For people with relapsing–remitting multiple sclerosis (MS), alemtuzumab 12 mg may present better results than subcutaneous interferon beta-1a at 24 and 36 months for relapse-free survival and sustained disease progression-free survival (low-certainty evidence).

Alemtuzumab 24 mg may present better results for relapse-free survival and sustained disease progression-free survival at 36 months (low-certainty evidence).

As for safety, alemtuzumab 12 mg and 24 mg may make little to no difference on adverse events after 24 and 36 months compared with interferon beta-1a (low-certainty evidence), although the risk of adverse events was high in all groups.

There is a lack of evidence on the number of participants free of clinical disease activity, quality of life, fatigue, and changes in new or enlarging T2-hyperintense lesions on magnetic resonance imaging.

When balancing the potential benefits and harms of this treatment, it is important to consider the risk of other autoimmune syndromes, thyroid disease, and malignancies related to alemtuzumab (FDA 2014). The included follow-up periods were relatively short; considering the chronic nature of MS, there is still a lack of evidence about long-term effects (after 36 months) of alemtuzumab for people with MS.

Implications for research

Due to a lack of available data, further randomized studies are needed to answer the following questions.

- Is alemtuzumab effective for forms of MS other than relapsing–remitting MS?
- Is alemtuzumab more effective than other available treatments (other than interferon beta-1a)?
- Are the observed effects of alemtuzumab sustained after 36 months?
- Are other doses and course durations of alemtuzumab effective for MS?
- What is the rate of individual adverse events related to alemtuzumab (including serious events such as autoimmune diseases and thyroid dysfunctions)?
- Does alemtuzumab improve quality of life, rate of participants free of clinical disease activity, and fatigue?
- Are there very long-term adverse events associated with the use of alemtuzumab in people with MS?

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this review update.

- Sign-off Editor (final editorial decision): Robert Boyle, Imperial College London.
- Managing Editor (provided editorial guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service.
- Editorial Assistant (conducted editorial policy checks, selected peer reviewers, collated peer-reviewer comments, supported editorial team): Sara Hales-Brittain, Cochrane Central Editorial Service.

- Copy Editor (copy editing and production): Anne Lawson, Central Production Service, Cochrane.
- Peer-reviewers (provided comments and recommended an editorial decision): Dennis Bourdette, Department of Neurology, Oregon Health & Science University (clinical/content review); Hans-Peter Hartung, Department of Neurology, Heinrich-Heine-University Düsseldorf, Germany; Brain and Mind Center, University of Sydney, Australia; Department of Neurology, Palacky University Olomouc, Czech Republic (clinical/content review); Ivan Perez-Neri, National Institute of Neurology and Neurosurgery Manuel Velasco Suárez (consumer review), Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review). An additional peer reviewer provided search peer review, but chose not to be publicly acknowledged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

CAMMS223

Study characteristics	
Methods	• CAMMS223 (primary reference) • Multicenter, phase II, randomized controlled trial • 49 centers in Europe and the US • Randomization ratio 1:1:1, stratification to balance the study groups with regard to age (< 30 years or ≥ 30 years), gender and baseline EDSS (< 2.0 or ≥ 2.0) • 334 randomized/333 available for analysis • Treatment duration: 24 months • Follow-up duration: 36 months
Participants	Inclusion criteria • Diagnosis of relapsing–remitting MS based on the McDonald criteria • Onset of symptoms ≤ 36 months before the time of screening; ≥ 2 clinical episodes during the previous 2 years; a score of ≤ 3 on the EDSS, which ranges from 0 to 10, with higher scores indicating greater disability; and ≥ 1 enhancing lesions, as seen on ≥ 1 of ≤ 4 monthly cranial MRI scans. Exclusion criteria • Previous disease-modifying treatments • History of clinically significant autoimmunity • Presence of serum antithyrotropin receptor antibodies
Interventions	Main interventions • Alemtuzumab 12 mg administered IV, once a day for 5 consecutive days at the first month and for 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥ 100×10^6 cells/L) (n = 113/available for analysis = 112) • Alemtuzumab 24 mg administered IV, once a day for 5 consecutive days at the first month and for 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥ 100×10^6 cells/L) (n = 110/available for analysis = 110) Comparator • Interferon beta-1a 44 µg administered subcutaneously 3 times weekly after dose escalation (n = 111/available for analysis = 111) All participants received methylprednisolone 1 g IV for 3 days at baseline and at months 12 and 24, coinciding with infusion cycles as premedication for those receiving alemtuzumab. Some participants also received antihistamines or antipyretics at the investigators' discretion.
Outcomes	Primary outcome measures • Rate of participants with sustained accumulation of disability: assessed according to ordinal EDSS. Sustained accumulation of disability defined as an increase of ≥ 1.5 points for participants with a baseline score of 0 and of ≥ 1.0 point for participants with a baseline score of ≥ 1.0; all scores were confirmed twice during a 3- and 6-month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS aside from relapse. • Rate of relapse: defined as new or worsening symptoms with an objective change in neurologic exam attributable to MS that lasted for ≥ 48 hours, that were present at normal body temperature, and that were preceded by ≥ 30 days of clinical stability. Secondary outcome measures • Proportion of participants who did not have a relapse (proportion of participants with relapse-free survival) • Changes in lesion burden (as seen on T2-weighted MRI) • Brain volume (as measured by the Losseff method on T1-weighted MRI)

CAMMS223 *(Continued)*

- Adverse effects, including:
  - thyroid function and levels of antithyrotropin receptor antibodies and lymphocyte subpopulations measured quarterly at a central laboratory
  - serum-binding antibodies against alemtuzumab measured using a validated enzyme-linked immunosorbent assay at BioAnaLab
  - immune thrombocytopenia by single confirmed platelet count < 50,000/μL without clumping or a platelet count > 50,000 /μL but < 100,000/μL on ≥ 2 consecutive occasions during a period of ≥ 1 month, with normal hemoglobin, neutrophil, and eosinophil counts; an absence of splenomegaly; and a normal peripheral-blood smear (apart from thrombocytopenia)
- Dropouts

All adverse events with onset up to 36 months were reported. In addition, all serious adverse events and autoimmune-associated disorders occurring before 1 March 2008 were listed. A subsequent adverse event of Burkitt's lymphoma not associated with Epstein–Barr virus was also included in this report.

Notes

- The effectiveness of blinding was assessed at the end-of-study visit.
- Participants with an increased level of disability could be discontinued from the study.
- There was no active monitoring for progressive multifocal leukoencephalopathy.
- Preplanned interim analyses were performed when most participants had completed ≥ 1 year and 2 years with a prespecified alpha spending function. Disclosure of these results formed part of safety announcements by the sponsor in September 2005 and 2006. After the interim analyses, $P < 0.016$ was considered statistically significant for the rates of sustained disability and $P < 0.004$ for relapse.
- In September 2005, the data and safety monitoring board recommended suspension of alemtuzumab treatments after receiving reports of 3 cases of immune thrombocytopenic purpura, including 1 death. All safety and efficacy assessments proceeded as planned and participants who were receiving interferon beta-1a continued to receive the drug. At the time of dose suspension, only 2 eligible participants (1%) had not received the second cycle of alemtuzumab at month 12, whereas 155 participants (75%) were precluded from receiving the third cycle of alemtuzumab at month 24.
- More participants discontinued interferon beta-1a than alemtuzumab, principally because of a lack of efficacy and adverse events, so that only 59% of the original group of participants receiving interferon beta-1a completed the 36-month study, as compared with 83% of participants receiving alemtuzumab. At the end-of-study review, 90% of raters remained unaware of assignments to the group receiving interferon beta-1a and 91% to the group receiving alemtuzumab.
- Funding: Genzyme

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible participants were randomly assigned in a 1:1:1 with the use of the Pocock and Simon minimisation algorithm." Comment: the method was described and seemed appropriate.
Allocation concealment (selection bias)	Unclear risk	No information available to allow a judgment.
Blinding of participants and personnel (performance bias) Relapse-free survival	High risk	Quote: "Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per litre). Interferon beta-1a (at a dose of 44 μg) was administered subcutaneously three times weekly after dose escalation." Comment: the interventions were administered by different routes and there was no placebo.

CAMMS223 *(Continued)*

Blinding of participants and personnel (performance bias) Sustained disease progression-free survival	High risk	Quote: "Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per litre). Interferon beta-1a (at a dose of 44 µg) was administered subcutaneously three times weekly after dose escalation." Comment: interventions were administered by different routes and there was no placebo.
Blinding of participants and personnel (performance bias) Adverse events	High risk	Quote: "Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per litre). Interferon beta-1a (at a dose of 44 µg) was administered subcutaneously three times weekly after dose escalation." Comment: interventions were administered by different routes and there was no placebo.
Blinding of participants and personnel (performance bias) Change in disability (EDSS)	High risk	Quote: "Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per litre). Interferon beta-1a (at a dose of 44 µg) was administered subcutaneously three times weekly after dose escalation." Comment: interventions were administered by different routes and there was no placebo.
Blinding of participants and personnel (performance bias) Dropouts	High risk	Quote: "Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per litre). Interferon beta-1a (at a dose of 44 µg) was administered subcutaneously three times weekly after dose escalation." Comment: interventions were administered by different routes and there was no placebo.
Blinding of outcome assessment (detection bias) Relapse-free survival	Low risk	Quote: "EDSS scores were determined quarterly in a blinded fashion by a neurologist who also adjudicated possible relapses. Patients wore clothing that covered injection sites." Comment: outcome assessor was blinded.
Blinding of outcome assessment (detection bias) Sustained disease progression-free survival	Low risk	Quote: "EDSS scores were determined quarterly in a blinded fashion by a neurologist who also adjudicated possible relapses. Patients wore clothing that covered injection sites." Comment: outcome assessor was blinded.
Blinding of outcome assessment (detection bias) Adverse events	High risk	Quote: "Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per litre). Interferon beta-1a (at a dose of 44 µg) was administered subcutaneously three times weekly after dose escalation." Comment: participants were not blinded (comparators were administered by different routes) and this was a participant-reported outcome.
Blinding of outcome assessment (detection bias) Change in disability (EDSS)	Low risk	Quote: "EDSS scores were determined quarterly in a blinded fashion by a neurologist who also adjudicated possible relapses. Patients wore clothing that covered injection sites."

CAMMS223 *(Continued)*

		Comment: outcome assessor was blinded.
Blinding of outcome assessment (detection bias) Dropouts	High risk	Quote: "Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per litre). Interferon beta-1a (at a dose of 44 µg) was administered subcutaneously three times weekly after dose escalation." Comment: participants were not blinded (comparators were administered by different routes) and this was a participant-reported outcome.
Incomplete outcome data (attrition bias) Relapse-free survival	High risk	84 losses (25.1%) and an imbalance among comparison groups: 40% in interferon group, 18.6% in alemtuzumab 12 mg group, and 16.4% in alemtuzumab 24 mg group.
Incomplete outcome data (attrition bias) Sustained disease progression-free survival	High risk	84 losses (25.1%) and an imbalance among comparison groups: 40% in interferon group, 18.6% in alemtuzumab 12 mg group, and 16.4% in alemtuzumab 24 mg group.
Incomplete outcome data (attrition bias) Adverse events	High risk	84 losses (25.1%) and an imbalance among comparison groups: 40% in interferon group, 18.6% in alemtuzumab 12 mg group, and 16.4% in alemtuzumab 24 mg group.
Incomplete outcome data (attrition bias) Change in disability (EDSS)	High risk	84 losses (25.1%) and an imbalance among comparison groups: 40% in interferon group, 18.6% in alemtuzumab 12 mg group, and 16.4% in alemtuzumab 24 mg group.
Incomplete outcome data (attrition bias) Dropouts	High risk	84 losses (25.1%) and an imbalance among comparison groups: 40% in interferon group, 18.6% in alemtuzumab 12 mg group, and 16.4% in alemtuzumab 24 mg group.
Selective reporting (reporting bias)	Low risk	All planned outcomes in the protocol (NCT00050778) were reported.
Other bias	Low risk	No other source of bias identified.

CARE-MS I

Study characteristics	
Methods	• CARE-MS I (primary reference) • Multicenter, phase III, randomized controlled trial • 101 academic medical centers and clinical practices in 16 countries • Randomization ratio 2:1; stratification by site • 581 randomized/563 available for analysis • Treatment duration: 12 months • Follow-up duration: 24 months
Participants	Inclusion criteria • Aged 18–50 years • Diagnosis of relapsing–remitting MS fulfilling the McDonald criteria • Disease duration ≤ 5 years • ≥ 2 relapses in the previous 2 years and ≥ 1 in the previous year

CARE-MS I *(Continued)*

- EDSS 10 scores ≤ 3.0
- Cranial abnormalities on MRI attributable to MS

Exclusion criteria

- Progressive disease course
- Previous MS disease therapy (apart from corticosteroids)
- Previous immunosuppressive, investigational, or monoclonal antibody therapy
- Clinically significant autoimmunity other than MS

Interventions	Main interventions • Alemtuzumab 12 mg administered IV, once a day for 5 consecutive days at baseline and for 3 consecutive days at 12 months (n = 386/available for analysis = 376) After a protocol amendment in January 2009, participants in the alemtuzumab group received oral acyclovir 200 mg twice daily during alemtuzumab infusion and for 28 days thereafter as prophylaxis against herpes infection. Comparator • Interferon beta-1a 44 µg given subcutaneously 3 times weekly after dose titration (n = 195/available for analysis = 187) Participants in both groups received methylprednisolone 1 g/day IV on 3 consecutive days at baseline and month 12. Concomitant treatment with an antipyretic or antihistamine drug was allowed, at the discretion of the treating neurologist.
Outcomes	Primary outcome measures • Relapse rate, defined as new or worsening neurological symptoms attributable to MS, lasting ≥ 48 hours, without pyrexia, after ≥ 30 days of clinical stability, with an objective change on neurological exam assessed by a blinded rater. The relapse adjudication panel decided the status of suspected relapses on the basis of the protocol definition and their blinded review of all data collected by the site, including whether there was an objective change corresponding to current relapse symptoms (1 point on 2 functional system scales or 2 points on 1 functional system scale or increase in the EDSS). • Sustained accumulation of disability, defined as an increase from baseline of ≥ 1 EDSS point (or ≥ 1.5 points if baseline EDSS was 0) confirmed over 6 months. Secondary outcome measures (24 months) • Rate of relapse-free participants • Change in EDSS • Number of participants with new or enlarging T2-hyperintense lesions on MRI • Change in Multiple Sclerosis Functional Composite • Freedom from clinical disease activity, defined as absence both of relapses and sustained accumulation of disability • Freedom from MRI disease activity, defined as absence both of gadolinium-enhancing lesions and new or enlarging T2-hyperintense lesions • Adverse events, actively searched by a monthly questionnaire follow-up of participants, complete blood counts, serum creatinine, urinalysis, and microscopy monthly (every 3 months for participants in the interferon beta-1a group), and thyroid function tests every 3 months
Notes	• Raters completed a questionnaire assessing quality of the blinding at each EDSS assessment • All participants who received ≥ 1 dose of study drug were included in the efficacy and safety analyses according to treatment assignment ('modified ITT analysis') • Funding: Genzyme. The study sponsor was involved in the design and undertaking of the trial, data analysis and interpretation, writing of the manuscript, and the decision to submit the manuscript for publication. Bayer Schering Pharma participated in the design and oversight of the trial. Clinical in-

CARE-MS I *(Continued)*

vestigators collaborated with the sponsor to design and oversee the trial. The sponsor performed the statistical analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We randomly allocated patients using an interactive voice response system." Comment: method was described and seemed appropriate.
Allocation concealment (selection bias)	Low risk	Quote: "We randomly allocated patients using an interactive voice response system." Comment: method was described and seemed appropriate.
Blinding of participants and personnel (performance bias) Relapse-free survival	High risk	Quote: "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo, we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) Sustained disease progression-free survival	High risk	Quote: "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo, we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) Adverse events	High risk	Quote: "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo, we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) Change in disability (EDSS)	High risk	Quote: "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo, we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo, we secured clini-

CARE-MS I *(Continued)*

New or enlarging T2-hyperintense lesions		cal data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) Dropouts	High risk	Quote: "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo, we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) Relapse-free survival	Low risk	Quote: "… we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: outcome assessors were blinded.
Blinding of outcome assessment (detection bias) Sustained disease progression-free survival	Low risk	Quote: "… we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: outcome assessors were blinded.
Blinding of outcome assessment (detection bias) Adverse events	High risk	Quote: "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo, we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: outcome assessors were blinded, but this was a participant-reported outcome.
Blinding of outcome assessment (detection bias) Change in disability (EDSS)	Low risk	Quote: "… we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: outcome assessors were blinded. Comment: outcome assessor could have been unblinded, but this occurred in < 1% of assessments and sensitivity analysis for the results was consistent with the main analysis.
Blinding of outcome assessment (detection bias) New or enlarging T2-hyperintense lesions	Low risk	Quote: "… we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists." Comment: outcome assessors were blinded.
Blinding of outcome assessment (detection bias) Dropouts	High risk	Quote: "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo, we secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists."

CARE-MS I *(Continued)*

		Comment: outcome assessors were blinded, but this was a participant-reported outcome.
Incomplete outcome data (attrition bias) Relapse-free survival	High risk	Quote: "Figure 1: Trial profile," page 1820 (CARE-MS I). Comment: overall, 9.4% (55) of participants were lost-to follow-up: 6.21% in alemtuzumab 12 mg group and 15.9% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) Sustained disease progression-free survival	High risk	Quote: "Figure 1: Trial profile," page 1820. Comment: overall, 9.4% (55) of participants were lost-to follow-up: 6.21% in alemtuzumab 12 mg group and 15.9% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) Adverse events	High risk	Quote: "Figure 1: Trial profile," page 1820. Comment: overall, 9.4% (55) of participants were lost-to follow-up: 6.21% in alemtuzumab 12 mg group and 15.9% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) Change in disability (EDSS)	High risk	Quote: "Figure 1: Trial profile," page 1820. Comment: overall, 9.4% (55) of participants were lost-to follow-up: 6.21% in alemtuzumab 12 mg group and 15.9% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) New or enlarging T2-hyperintense lesions	High risk	Quote: "Figure 1: Trial profile," page 1820. Comment: overall, 9.4% (55) of participants were lost-to follow-up: 6.21% in alemtuzumab 12 mg group and 15.9% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) Dropouts	High risk	Quote: "Figure 1: Trial profile," page 1820. Comment: overall, 9.4% (55) of participants were lost-to follow-up: 6.21% in alemtuzumab 12 mg group and 15.9% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Selective reporting (reporting bias)	Low risk	All planned outcomes in the protocol were reported (NCT00530348).
Other bias	Low risk	No other source of bias was found.

CARE-MS II

Study characteristics	
Methods	• CARE-MS II (primary reference) • Multicenter, phase III, randomized controlled trial • 194 centers worldwide • 840 randomized; 798 available for analysis

CARE-MS II *(Continued)*

- Randomization ratio 1:2:2
- Treatment duration: 12 months
- Follow-up: 24 months

Participants	Inclusion criteria • Aged 18–55 years • Diagnosis of relapsing–remitting MS fulfilling the McDonald diagnostic criteria • Disease duration ≤ 10 years • ≥ 2 relapses in previous 2 years, with ≥ 1 in previous year • ≥ 1 relapse while receiving interferon beta or glatiramer acetate after ≥ 6 months of treatment • EDSS scores ≤ 5.0 • Cranial and spinal MRI lesions fulfilling protocol-defined criteria (MRI scan demonstrating white matter lesions attributable to MS) Exclusion criteria • Previous treatment with alemtuzumab • Previous treatment with any investigational drug (i.e. a medication that was not approved at any dose or for any indication) • Treatment with natalizumab, methotrexate, azathioprine, or cyclosporine in the past 6 months • Previous treatment with mitoxantrone, cyclophosphamide, cladribine, rituximab, or any other immunosuppressive; or cytotoxic therapy (other than steroid treatment) • Any progressive form of MS • Any disability acquired from trauma or another illness that could have interfered with evaluation of disability due to MS • Major systemic disease that could not be treated or adequately controlled by therapy • Active infection or high risk of infection • Autoimmune disorder (other than MS) • Impaired hepatic or renal function • History of malignancy, except basal skin cell carcinoma • Medical, psychiatric, cognitive, or other conditions that compromised the patient's ability to understand the patient information, to give informed consent, to comply with the trial protocol, or to complete the study • Known bleeding disorder • Women of childbearing potential with a positive serum pregnancy test, pregnant, or lactating • Current participation in another clinical study or previous participation in CAMMS323 (NCT00530348) • Previous hypersensitivity reaction to any immunoglobulin product • Known allergy or intolerance to interferon beta, human albumin, or mannitol • Intolerance of pulsed corticosteroids, especially a history of steroid psychosis • Inability to self-administer SC injections or receive SC injections from caregiver • Inability to undergo MRI with gadolinium administration • Unwilling to use a reliable and acceptable birth control method throughout the study period (fertile participants only)
Interventions	Main interventions • Alemtuzumab 12 mg/day IV, once a day for 5 consecutive days at month 0 and 12 mg/day IV, once a day for 3 consecutive days at month 12 (n = 436, available for analysis = 426) • Alemtuzumab 24 mg/day IV, once a day for 5 consecutive days at month 0 and 24 mg/day IV, once a day for 3 consecutive days at month 12 (n = 173, available for analysis = 170) Alemtuzumab administered in 2 annual cycles, once at beginning of study and again 1 year later Comparator

CARE-MS II *(Continued)*

	• Interferon beta-1a (Rebif) 44 µg, 3 times weekly by self-injection SC (n = 231, available for analysis = 202)
Outcomes	Primary outcome measures • Time to sustained accumulation of disability (time frame: 2 years) • Relapse rate defined as new or worsening symptoms with an objective changes in neurologic exam attributable to MS that lasted for ≥ 48 hours, that were present at normal body temperature and that were preceded by ≥ 30 days of clinical stability (time frame: 2 years) Secondary outcome measures • Rate of participants who are relapse-free at year 2 • Change from baseline in EDSS (time frame: 2 years) • Acquisition of disability as measured by change from baseline in Multiple Sclerosis Functional Composite (time frame: 2 years) • Number of participants with new or enlarging T2-hyperintense lesions in MRI • Adverse effects • Quality of life: assessed by Functional Assessment of Multiple Sclerosis (scale 0–176 for total score); Medical Outcomes Study 36-Item Short-Form Survey (SF-36; scale 1–100; healthy population mean = 50; administered annually in the core study); and EuroQol in 5 Dimensions VAS (scale 0–100) Coprimary endpoints were relapse rate and time to 6-month sustained accumulation of disability, comparing alemtuzumab 12 mg and interferon beta-1a in all participants who received ≥ 1 dose of study drug.
Notes	• The 24 mg/day group was discontinued to aid recruitment, but data were included for safety assessments. The decision to close recruitment was made by the Neurology Steering Committee and Genzyme management without review of safety or efficacy data from this study. • Raters completed a questionnaire assessing quality of the blinding at each EDSS assessment. • Funding: Genzyme (Sanofi) and Bayer – Schering Pharma.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We randomly allocated patients with an interactive voice response system in a 2:2:1 scheme to receive alemtuzumab 12 mg per day, alemtuzumab 24 mg per day, or interferon beta 1a." Comments: method was described and seemed appropriate.
Allocation concealment (selection bias)	Low risk	Quote: "We randomly allocated patients with an interactive voice response system in a 2:2:1 scheme to receive alemtuzumab 12 mg per day, alemtuzumab 24 mg per day, or interferon beta 1a." Comments: method was described and seemed appropriate.
Blinding of participants and personnel (performance bias) Relapse-free survival	High risk	Quote: "Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses." Comments: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) Sustained disease progression-free survival	High risk	Quote: "Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses."

CARE-MS II *(Continued)*

		Comments: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) Adverse events	High risk	Quote: "Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses." Comments: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) Change in disability (EDSS)	High risk	Quote: "Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses." Comments: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) New or enlarging T2-hyperintense lesions	Low risk	Quote: "Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses." Comments: participants and personnel were not blinded.
Blinding of participants and personnel (performance bias) Dropouts	High risk	Quote: "Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses." Comments: participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) Relapse-free survival	Low risk	Quote: "Raters were masked to treatment-group assignment." Comment: outcome assessors were blinded.
Blinding of outcome assessment (detection bias) Sustained disease progression-free survival	Low risk	Quote: "Raters were masked to treatment-group assignment." Comment: outcome assessors were blinded.
Blinding of outcome assessment (detection bias) Adverse events	High risk	Quote: "Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses." Comment: outcome assessors were blinded, but this was a participant-reported outcome.
Blinding of outcome assessment (detection bias) Change in disability (EDSS)	Low risk	Quote: "Raters, who were masked to treatment-group assignment, did the EDSS assessments every 3 months and when a relapse was suspected, and the Multiple Sclerosis Functional Composite (MSFC)16 once every 6 months. Raters completed a questionnaire assessing quality of the masking at each EDSS assessment. In the absence of a masked rater, unmasked raters could submit EDSS assessments." "Masking was successful for 5850 (>99%) of 5865 EDSS assessments. Only 12 (2%) of 672 patients had one or more assessments done by an unmasked rater; although included in efficacy analyse." Comment: outcome assessor could be unblinded, but this occurred in only 2% of assessments and sensitivity analysis for the results was consistent with the main analysis.

CARE-MS II *(Continued)*

Blinding of outcome assessment (detection bias) New or enlarging T2-hyperintense lesions	Low risk	Quote: "Raters were masked to treatment-group assignment." Comment: outcome assessors were blinded.
Blinding of outcome assessment (detection bias) Dropouts	High risk	Quote: "Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses." Comment: outcome assessors were blinded, but this was a participant-reported outcome.
Incomplete outcome data (attrition bias) Relapse-free survival	High risk	Quote: "Figure 1: Trial profile," page 1830. Comment: overall, 14.9% (125 participants) were lost-to follow-up: 8.5% in alemtuzumab 12 mg group, 8.7% in alemtuzumab 24 mg group, and 31.6% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) Sustained disease progression-free survival	High risk	Quote: "Figure 1: Trial profile," page 1830. Comment: overall, 14.9% (125 participants) were lost-to follow-up: 8.5% in alemtuzumab 12 mg group, 8.7% in alemtuzumab 24 mg group, and 31.6% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) Adverse events	High risk	Quote: "Figure 1: Trial profile," page 1830. Comment: overall, 14.9% (125 participants) were lost-to follow-up: 8.5% in alemtuzumab 12 mg group, 8.7% in alemtuzumab 24 mg group, and 31.6% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) Change in disability (EDSS)	High risk	Quote: "Figure 1: Trial profile," page 1830. Comment: overall, 14.9% (125 participants) were lost-to follow-up: 8.5% in alemtuzumab 12 mg group, 8.7% in alemtuzumab 24 mg group, and 31.6% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) New or enlarging T2-hyperintense lesions	High risk	Quote: "Figure 1: Trial profile," page 1830. Comment: overall, 14.9% (125 participants) were lost-to follow-up: 8.5% in alemtuzumab 12 mg group, 8.7% in alemtuzumab 24 mg group, and 31.6% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Incomplete outcome data (attrition bias) Dropouts	High risk	Quote: "Figure 1: Trial profile," page 1830. Comment: overall, 14.9% (125 participants) were lost-to follow-up: 8.5% in alemtuzumab 12 mg group, 8.7% in alemtuzumab 24 mg group, and 31.6% in interferon beta-1a group. There was an imbalance between groups with some indications of differences in reasons for losses.
Selective reporting (reporting bias)	High risk	Efficacy analysis was not performed for alemtuzumab 24 mg. The recruitment to this arm was closed early to reduce overall sample size, duration of enrollment period, overall duration of study (ISRCTN70702834).
Other bias	Low risk	No other source of bias identified.

EDSS: Expanded Disability Status Scale; ITT: intention-to-treat; IV: intravenous; MRI: magnetic resonance imaging; MS: multiple sclerosis; n: number; SC: subcutaneous; VAS: Visual Analogue Scale.

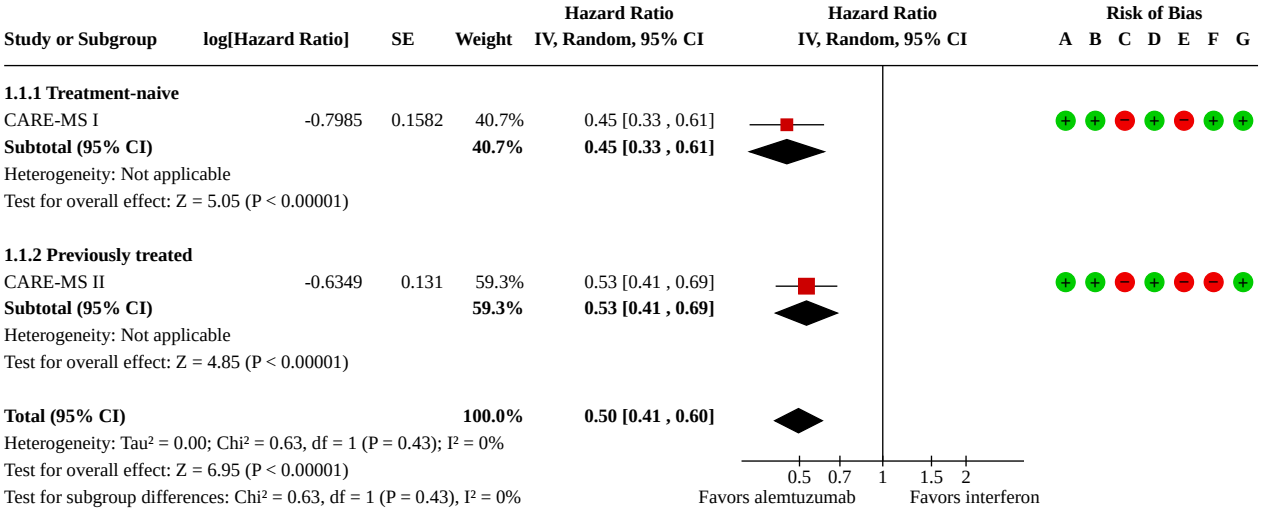
DATA AND ANALYSES

Comparison 1. Alemtuzumab 12 mg versus interferon beta-1a

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Relapse-free survival at 24 months	2		Hazard Ratio (IV, Random, 95% CI)	0.50 [0.41, 0.60]
1.1.1 Treatment-naive	1		Hazard Ratio (IV, Random, 95% CI)	0.45 [0.33, 0.61]
1.1.2 Previously treated	1		Hazard Ratio (IV, Random, 95% CI)	0.53 [0.41, 0.69]
1.2 Relapse-free survival at 36 months	1	221	Hazard Ratio (IV, Random, 95% CI)	0.31 [0.18, 0.53]
1.3 Sustained disease progression-free survival at 24 months	2		Hazard Ratio (IV, Random, 95% CI)	0.62 [0.44, 0.87]
1.3.1 Treatment-naive	1		Hazard Ratio (IV, Random, 95% CI)	0.70 [0.40, 1.22]
1.3.2 Previously treated	1		Hazard Ratio (IV, Random, 95% CI)	0.58 [0.38, 0.89]
1.4 Sustained disease progression-free survival at 36 months	1	223	Hazard Ratio (IV, Random, 95% CI)	0.25 [0.11, 0.56]
1.5 Adverse events, including serious adverse events at 24 months	2	1248	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.01, 1.06]
1.5.1 Treatment-naive	1	581	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.00, 1.09]
1.5.2 Previously treated	1	667	Risk Ratio (M-H, Random, 95% CI)	1.03 [1.00, 1.07]
1.6 Adverse events, including serious adverse events at 36 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7 Change in disability (Expanded Disability Status Scale [EDSS]) at 24 months	2	1199	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.60, 0.20]
1.7.1 Treatment-naive	1	571	Mean Difference (IV, Random, 95% CI)	0.00 [-0.19, 0.19]
1.7.2 Previously treated	1	628	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.62, -0.20]

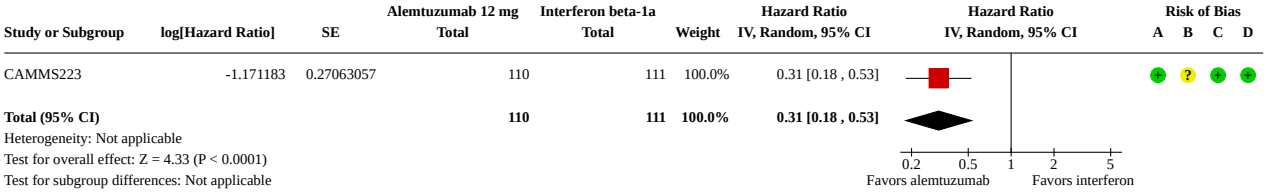
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Change in disability (EDSS) at 36 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.9 New or enlarging T2-hyperintense lesions at 24 months	2	1238	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.59, 0.91]
1.9.1 Treatment-naive	1	581	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.71, 0.95]
1.9.2 Previously treated	1	657	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.59, 0.75]
1.10 Dropouts at 24 months	2	1248	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.22, 0.44]
1.10.1 Treatment-naive	1	581	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.24, 0.65]
1.10.2 Previously treated	1	667	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.19, 0.39]
1.11 Dropouts at 36 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 1: Relapse-free survival at 24 months



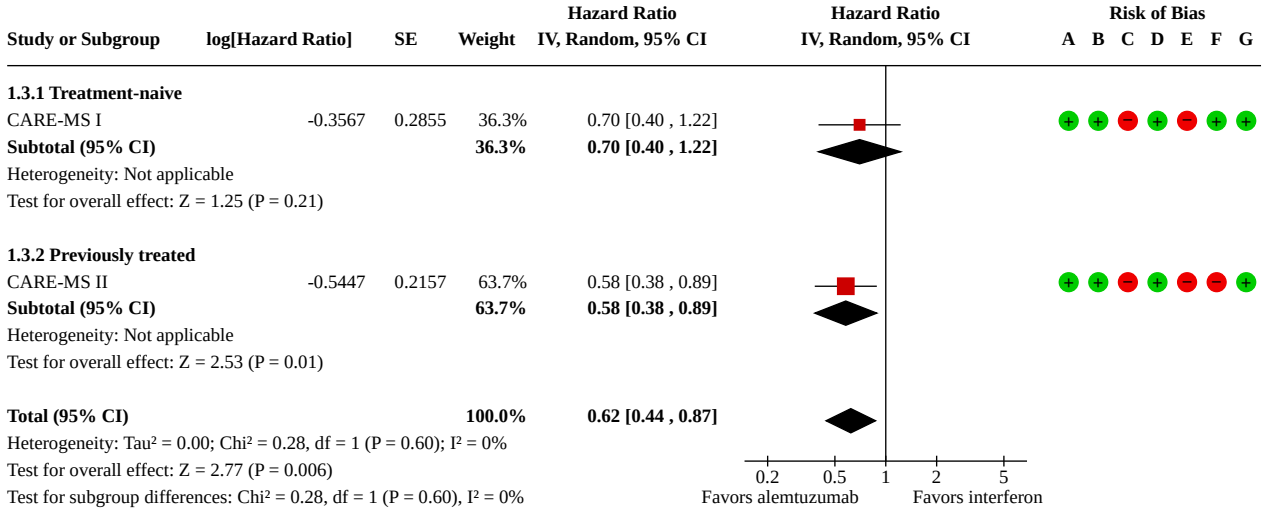
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Relapse-free survival
(D) Blinding of outcome assessment (detection bias): Relapse-free survival
(E) Incomplete outcome data (attrition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

Analysis 1.2. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 2: Relapse-free survival at 36 months



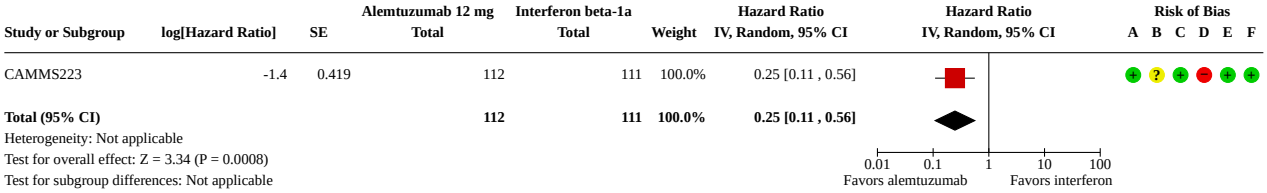
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

Analysis 1.3. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 3: Sustained disease progression-free survival at 24 months



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

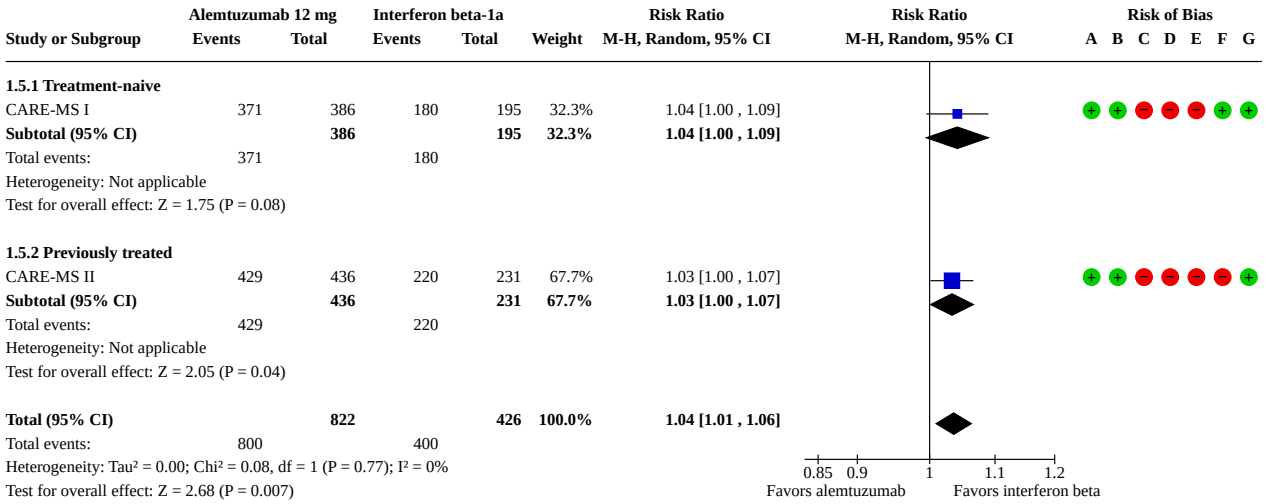
Analysis 1.4. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 4: Sustained disease progression-free survival at 36 months



Heterogeneity: Not applicable
Test for overall effect: Z = 3.34 (P = 0.0008)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Sustained disease progression-free survival
(D) Incomplete outcome data (attrition bias): Sustained disease progression-free survival
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.5. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 5: Adverse events, including serious adverse events at 24 months



Total events: 371 180
Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)

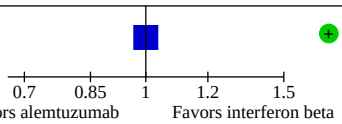
Total events: 429 220
Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)

Total events: 800 400
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%

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

Analysis 1.6. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 6: Adverse events, including serious adverse events at 36 months

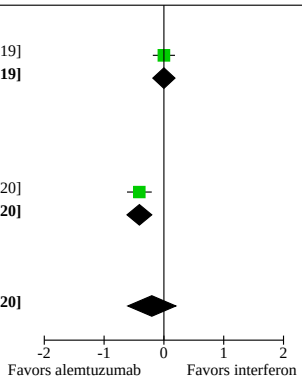
Study or Subgroup	Alemtuzumab 12 mg Events	Total	Interferon beta-1a Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
CAMMS223	113	113	111	111	1.00 [0.98 , 1.02]		+	?	+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

Analysis 1.7. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 7: Change in disability (Expanded Disability Status Scale [EDSS]) at 24 months

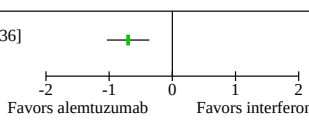
Study or Subgroup	Alemtuzumab 12 mg Mean	SD	Total	Interferon beta-1a Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
1.7.1 Treatment-naive																
CARE-MS I	-0.14	1.0848	376	-0.14	1.062	195	50.7%	0.00 [-0.19 , 0.19]		+	+	−	+	−	+	+
Subtotal (95% CI)			**376**			**195**	**50.7%**	**0.00 [-0.19 , 0.19]**								
Heterogeneity: Not applicable																
Test for overall effect: Z = 0.00 (P = 1.00)																
1.7.2 Previously treated																
CARE-MS II	-0.17	1.2601	426	0.24	1.2253	202	49.3%	-0.41 [-0.62 , -0.20]		+	+	−	+	−	−	+
Subtotal (95% CI)			**426**			**202**	**49.3%**	**-0.41 [-0.62 , -0.20]**								
Heterogeneity: Not applicable																
Test for overall effect: Z = 3.88 (P = 0.0001)																
Total (95% CI)			**802**			**397**	**100.0%**	**-0.20 [-0.60 , 0.20]**								
Heterogeneity: Tau² = 0.07; Chi² = 8.37, df = 1 (P = 0.004); I² = 88%																
Test for overall effect: Z = 0.99 (P = 0.32)																
Test for subgroup differences: Chi² = 8.37, df = 1 (P = 0.004), I² = 88.1%																



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

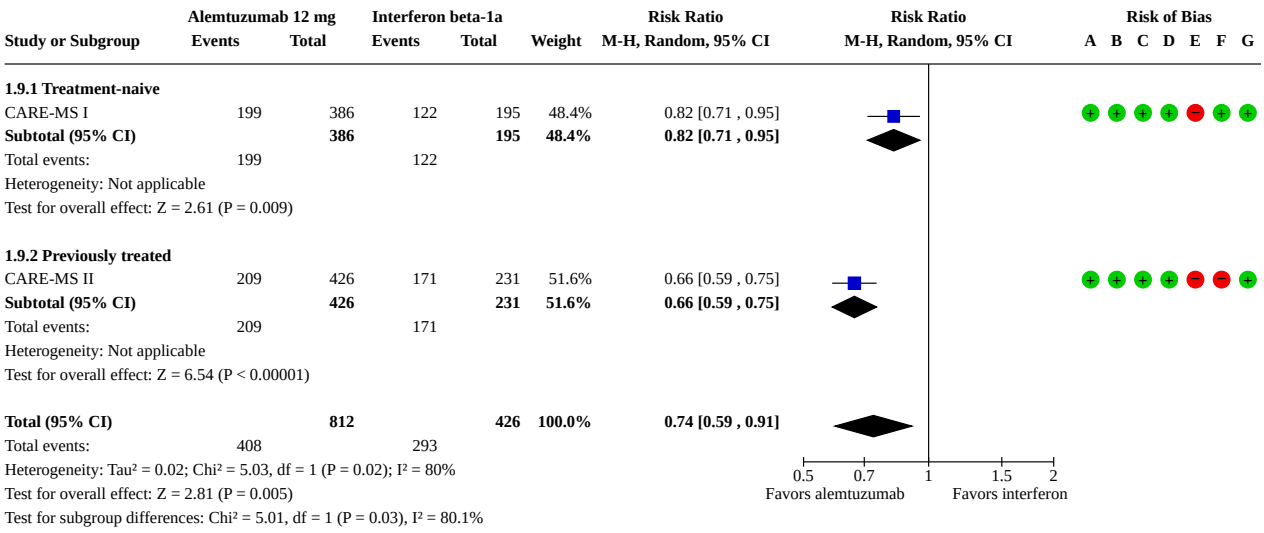
Analysis 1.8. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 8: Change in disability (EDSS) at 36 months

Study or Subgroup	Alemtuzumab 12 mg Mean	SD	Total	Interferon beta-1a Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
CAMMS223	-0.32	1.2284	112	0.38	1.3291	111	-0.70 [-1.04 , -0.36]		+	?	−	+	−	+	+



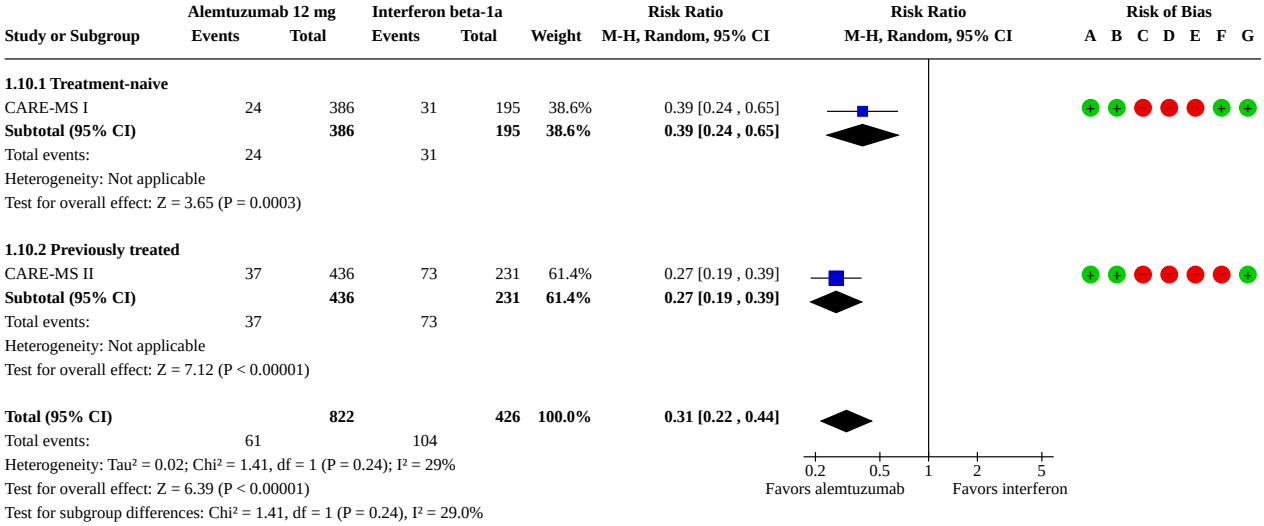
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Change in disability (EDSS)
(D) Blinding of outcome assessment (detection bias): Change in disability (EDSS)
(E) Incomplete outcome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

Analysis 1.9. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 9: New or enlarging T2-hyperintense lesions at 24 months



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): New or enlarging T2-hyperintense lesions
(D) Blinding of outcome assessment (detection bias): New or enlarging T2-hyperintense lesions
(E) Incomplete outcome data (attrition bias): New or enlarging T2-hyperintense lesions
(F) Selective reporting (reporting bias)
(G) Other bias

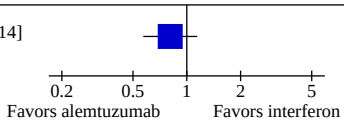
Analysis 1.10. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 10: Dropouts at 24 months



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

Analysis 1.11. Comparison 1: Alemtuzumab 12 mg versus interferon beta-1a, Outcome 11: Dropouts at 36 months

Study or Subgroup	Alemtuzumab 12 mg Events	Alemtuzumab 12 mg Total	Interferon beta-1a Events	Interferon beta-1a Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
CAMMS223	37	113	45	111	0.81 [0.57 , 1.14]	+	?	+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

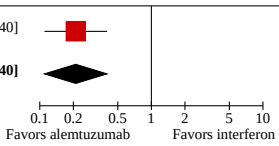
Comparison 2. Alemtuzumab 24 mg versus interferon beta-1a

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Relapse-free survival at 36 months	1	221	Hazard Ratio (IV, Random, 95% CI)	0.21 [0.11, 0.40]
2.2 Sustained disease progression-free survival at 36 months	1	221	Hazard Ratio (IV, Random, 95% CI)	0.33 [0.16, 0.69]
2.3 Adverse events, including serious adverse events at 24 months	1	363	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.01, 1.08]
2.4 Adverse events, including serious adverse events at 36 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.5 Change in disability (Expanded Disability Status Scale) at 36 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.6 Dropouts at 24 months	1	363	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.20, 1.26]
2.7 Dropouts at 36 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2: Alemtuzumab 24 mg versus interferon beta-1a, Outcome 1: Relapse-free survival at 36 months

Study or Subgroup	log[Hazard Ratio]	SE	Alemtuzumab 24 mg Total	Interferon beta-1a Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D
CAMMS223	-1.5606477	0.3293327	110	111	100.0%	0.21 [0.11 , 0.40]	+	?	+	+
Total (95% CI)			**110**	**111**	**100.0%**	**0.21 [0.11 , 0.40]**				

Heterogeneity: Not applicable
Test for overall effect: Z = 4.74 (P < 0.00001)
Test for subgroup differences: Not applicable

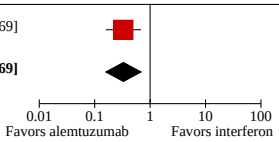


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

Analysis 2.2. Comparison 2: Alemtuzumab 24 mg versus interferon beta-1a, Outcome 2: Sustained disease progression-free survival at 36 months

Study or Subgroup	log[Hazard Ratio]	SE	Alemtuzumab 24 mg Total	Interferon beta-1a Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D
CAMMS223	-1.1086626	0.37283617	110	111	100.0%	0.33 [0.16 , 0.69]		+	?	+	+
Total (95% CI)			**110**	**111**	**100.0%**	**0.33 [0.16 , 0.69]**					

Heterogeneity: Not applicable
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: Not applicable

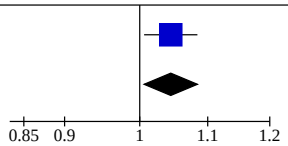


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

Analysis 2.3. Comparison 2: Alemtuzumab 24 mg versus interferon beta-1a, Outcome 3: Adverse events, including serious adverse events at 24 months

Study or Subgroup	Alemtuzumab 24 mg Events	Total	Interferon beta-1a Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
CARE-MS II	159	161	191	202	100.0%	1.04 [1.01 , 1.08]		+	+	−	+
Total (95% CI)		**161**		**202**	**100.0%**	**1.04 [1.01 , 1.08]**					
Total events:	159		191								

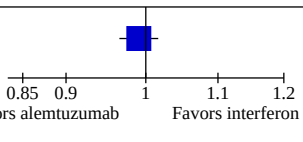
Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

Analysis 2.4. Comparison 2: Alemtuzumab 24 mg versus interferon beta-1a, Outcome 4: Adverse events, including serious adverse events at 36 months

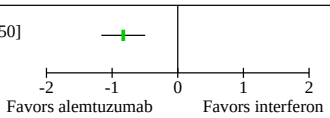
Study or Subgroup	Alemtuzumab 24 mg Events	Total	Interferon beta-1a Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
CAMMS223	107	108	107	107	0.99 [0.97 , 1.02]		+	?	+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

Analysis 2.5. Comparison 2: Alemtuzumab 24 mg versus interferon beta-1a, Outcome 5: Change in disability (Expanded Disability Status Scale) at 36 months

Study or Subgroup	Alemtuzumab 24 mg Mean	SD	Total	Interferon beta-1a Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D
CAMMS223	-0.45	1.21	110	0.38	1.32	111	-0.83 [-1.16 , -0.50]		+	?	+	+

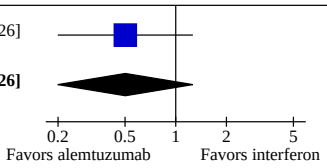


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

Analysis 2.6. Comparison 2: Alemtuzumab 24 mg versus interferon beta-1a, Outcome 6: Dropouts at 24 months

Study or Subgroup	Alemtuzumab 24 mg Events	Total	Interferon beta-1a Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
CARE-MS II	6	161	15	202	100.0%	0.50 [0.20 , 1.26]		+	+	−	+
Total (95% CI)		**161**		**202**	**100.0%**	**0.50 [0.20 , 1.26]**					
Total events:	6		15								

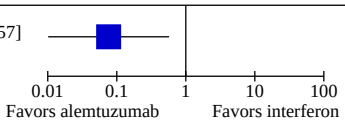
Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

Analysis 2.7. Comparison 2: Alemtuzumab 24 mg versus interferon beta-1a, Outcome 7: Dropouts at 36 months

Study or Subgroup	Alemtuzumab 24 mg Events	Total	Interferon beta-1a Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D
CAMMS223	1	108	13	107	0.08 [0.01 , 0.57]		+	?	+	+



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Multiple Sclerosis] this term only

#2 MeSH descriptor: [Multiple Sclerosis, Relapsing-Remitting] explode all trees

#3 MeSH descriptor: [Demyelinating Diseases] this term only

#4 MeSH descriptor: [Optic Neuritis] explode all trees

#5 MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only

#6 MeSH descriptor: [Encephalomyelitis, Acute Disseminated] explode all trees

#7 MeSH descriptor: [Myelitis, Transverse] explode all trees

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

#9 "neuromyelitis optica":ti,ab,kw

#10 "optic neuritis":ti,ab,kw

#11 "devic disease":ti,ab,kw

#12 "demyelinating disease":ti,ab,kw

#13 adem:ti,ab,kw

#14 "demyelinating disorder":ti,ab,kw

#15 "clinically isolated syndrome":ti,ab,kw

#16 "transverse myelitis":ti,ab,kw

#17 encephalomyelitis:ti,ab,kw

#18 {OR #1-#17}

#19 MeSH descriptor: [Alemtuzumab] explode all trees

#20 (alemtuzumab OR lemtrada OR campath OR mabcambath):ti,ab,kw

#21 #19 OR #20

#22 #18 AND #21

CINAHL

S1 (MH "Multiple Sclerosis")

S2 (MH "Demyelinating Diseases")

S3 (MH "Optic Neuritis")

S4 (MH "Demyelinating Autoimmune Diseases, CNS")

S5 (MH "Encephalomyelitis, Acute Disseminated")

S6 (MH "Myelitis, Transverse")

S7 TI "multiple sclerosis" OR AB "multiple sclerosis"

S8 TI "neuromyelitis optica" OR AB "neuromyelitis optica"

S9 TI "optic neuritis" OR AB "optic neuritis"

S10 TI "devic disease" OR AB "devic disease"

S11 TI "demyelinating disease" OR AB "demyelinating disease"

S12 TI adem OR AB adem

S13 TI "demyelinating disorder" OR AB "demyelinating disorder"

S14 TI "clinically isolated syndrome" OR AB "clinically isolated syndrome"

S15 TI "transverse myelitis" OR AB "transverse myelitis"

S16 TI encephalomyelitis OR AB encephalomyelitis

S17 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16

S18 TI (alemtuzumab OR lemtrada OR campath OR mabcambath) AND AB (alemtuzumab OR lemtrada OR campath OR mabcambath)

S19 S17 AND S18

S20 (MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample OR TI (randomised OR randomized) OR AB (random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR AB (CONTROL W5 GROUP) OR MH (CROSSOVER DESIGN) OR MH (COMPARATIVE STUDIES) OR AB (CLUSTER W3 RCT)) NOT ((MH ANIMALS+ NOT MH HUMAN) OR (MH (ANIMAL STUDIES) NOT MH (HUMAN)) OR (TI (ANIMAL MODEL) NOT MH (HUMAN)))

S21 S19 AND S20

Embase

#1 'multiple sclerosis'/exp

#2 'demyelinating disease'/de

#3 'optic neuritis'/exp

#4 'acute disseminated encephalomyelitis'/exp

#5 'transverse myelitis'/exp

#6 'multiple sclerosis':ab,ti

#7 'neuromyelitis optica':ab,ti

#8 'optic neuritis':ab,ti

#9 'devic disease':ab,ti

#10 'demyelinating disease':ab,ti

#11 adem:ab,ti

#12 'demyelinating disorder':ab,ti

#13 'clinically isolated syndrome':ab,ti

#14 'transverse myelitis':ab,ti

#15 encephalomyelitis:ab,ti

#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15

#17 'alemtuzumab'/exp

#18 alemtuzumab:ab,ti OR lemtrada:ab,ti OR campath:ab,ti OR mabcambath:ab,ti

#19 #17 OR #18

#20 #16 AND #19

#21 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti

#22 #20 AND #21

#23((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)

#24 ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))

#25 #23 OR #24

#26 #22 NOT #25

EU Clinical Trials Register (EU-CTR)

Multiple sclerosis AND alemtuzumab

German Clinical Trials Register (DRKS)

Alemtuzumab AND Health Condition or Problem studied: multiple sclerosis

Clinical trials

Condition or disease: Multiple sclerosis

AND

Other terms: (alemtuzumab OR lemtrada OR campath OR mabcambath)

ISRCTN

Alemtuzumab within condition: Multiple sclerosis

MEDLINE via PubMed

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

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

#3 "Demyelinating Diseases"[Mesh:noexp]

#4 "Optic Neuritis"[Mesh]

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

#6 "Encephalomyelitis, Acute Disseminated"[Mesh]

#7 "Myelitis, Transverse"[Mesh]

#8 "multiple sclerosis"[Title/Abstract]

#9 "neuromyelitis optica"[Title/Abstract]

#10 "optic neuritis"[Title/Abstract]

#11 "devic disease"[Title/Abstract]

#12 "demyelinating disease"[Title/Abstract]

#13 adem[Title/Abstract]

#14 "demyelinating disorder"[Title/Abstract]

#15 "clinically isolated syndrome"[Title/Abstract]

#16 "transverse myelitis"[Title/Abstract]

#17 "encephalomyelitis"[Title/Abstract]

#18 "Multiple Sclerosis"[Mesh:noexp]

#19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20 "Alemtuzumab"[Mesh]

#21 Alemtuzumab[title/abstract] OR Lemtrada[title/abstract] OR Campath[title/abstract] OR MabCambath[title/abstract]

#22 #20 OR #21

#23 #19 AND #22

#24 (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]) NOT (animals [mh] NOT humans [mh])

#25 #23 AND #24

WHO – ICTRP

Condition: Multiple sclerosis

AND

Intervention: (alemtuzumab OR lemtrada OR campath OR mabcambath)

Recruitment status: ALL

WHAT'S NEW

Date	Event	Description
12 April 2023	New search has been performed	Search updated to 21 June 2022.
12 April 2023	New citation required but conclusions have not changed	In this update (searches run on 21 June 2022), we added 24 new references that refer to the three studies already included in the original review published in 2016 (CAMMS223, CARE-I, and CARE-II). There were no new outcome data added and results remained unchanged. We added a summary of findings table for the comparison of alemtuzumab 24 mg versus interferon.

HISTORY

Protocol first published: Issue 7, 2014
Review first published: Issue 4, 2016

CONTRIBUTIONS OF AUTHORS

- ALM was the contact person who coordinated the contributions from coauthors and was responsible for the final draft of the review update.
- RR, RLP, and ALM worked on study selection, data extraction, risk-of-bias assessment, and GRADE assessment.
- RR and RLP performed data analyses.
- RR, RLP, ALM, and MRT wrote the review update.
- RR, RLP, ALM, and MRT responded to the clinical comments of the referees.
- RR, RLP, ALM, and MRT answered the methodologic and statistical questions of the referees.
- RR, RLP, ALM, and MRT will be in charge of further updating.

DECLARATIONS OF INTEREST

ALM: none known.

MRT: none known.

RLP: none known.

RR: none known.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other

None.

External sources

- New Source of support, Other

None.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- One of the coauthors of the protocol, for unforeseen reasons, could no longer collaborate on the review and asked to be excluded from authoring.
- At the protocol stage, we planned the following subgroup analyses for disease type (relapsing–remitting, primary-progressive, secondary-progressive or progressive-relapsing) and disability at baseline (EDSS scores 5.0 or less or 5.5 or greater), but due to lack of sufficient data these additional analyses were not conducted.
- At the protocol stage, we planned to conduct subgroup analyses for different doses and regimens of alemtuzumab (12 mg or 24 mg). However, it would not be clinically reasonable to pool such different schemes as main analyses. So, we maintained separated main analyses for different doses or regimens, rather than as subgroup analyses.
- We did not plan the subgroup analysis taking into account previous treatment (treatment naive versus previously treated participants) at the protocol stage but as it seemed to be clinically relevant, we performed it when there were sufficient data.
- In the protocol, we proposed to assess 'number of participants without relapse' and 'number of progression-free participants' as primary outcomes. However, we found available data only for 'relapse-free survival' and 'sustained disease progression-free survival'. We decided to use both measures in the final review, since they are the opposite of the same measurement and this change would not influence neither the effect of the intervention nor its interpretation.
- In the protocol, we proposed to assess the 'Changes in the number of MRI T2- and T1-weighted lesions after treatment'. However, we discussed among the review authors and peer reviewers whether 'Patients with new or enlarging T2-hyperintense lesions' could be more relevant for decision-making, since it comprises the total area of all MS lesions. Moreover, since this is a dichotomous measure, it could be easier for physicians and consumers to interpret. We considered this outcome sufficiently relevant (even though it is a secondary outcome) to warrant a change in its presentation regardless of the tool/measurement used to assess it. Therefore, we decided to change the way it was measured, leading to the presentation of the existing results.
- We planned the following outcomes for the summary of findings tables at the protocol stage, but we did not include them due to lack of data: 1-point EDSS increase confirmed at three months' follow-up and quality of life. We included the outcome dropout rate in the summary of findings tables.
- In the protocol, we did not predefine the use of the hazard ratio to estimate the effect size of time-to-event outcomes. We added this information in the final version of the review because we used this measure for the outcomes of relapse-free survival and sustained disease progression.

Differences between original review and current update

- The search for this update did not retrieve any new studies, and we included the same three RCTs from the first version of the review. Any changes we performed were related to methodologic advances and new recommendations in Cochrane guidance.
- In this updated version, we added a second summary of findings table with results from the comparison alemtuzumab 24 mg compared to interferon beta-1a. We also added the follow-up 36 months to the original summary of findings table.
- We revised the certainty of evidence appraisal for the comparison alemtuzumab 12 mg compared to interferon beta-1a at 24 months, which led to it being further downgraded for some outcomes. We judged a need to better reflect uncertainties related to the risk of bias and inconsistency in the outcome results. The updated assessment followed the most recent GRADE guidelines, and Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).
- The new GRADE assessment resulted in a downgrade of the certainty of evidence from moderate to low for the outcomes relapse-free survival, sustained disease progression-free survival, and number of participants with at least one adverse event (following further considerations of risk of bias). We downgraded the outcome number of participants with new or enlarging T2-hyperintense lesions from moderate to very low (following further considerations of risk of bias and inconsistency).
- We reworded the certainty of evidence presentation and estimates of results following the most recent guidance from Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

INDEX TERMS

Medical Subject Headings (MeSH)

Alemtuzumab [adverse effects]; Interferon beta-1a [adverse effects]; *Multiple Sclerosis [drug therapy]; *Multiple Sclerosis, Relapsing-Remitting [drug therapy]; Neoplasm Recurrence, Local [drug therapy]

MeSH check words

Adult; Humans