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Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, Yang X

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[Intervention Review]

alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis

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ABSTRACT

Background

Alemtuzumab is a humanised monoclonal antibody that alters the circulating lymphocyte pool, causing prolonged lymphopenia, thus remoulding the immune repertoire that accompanies homeostatic lymphocyte reconstitution. It has been proved more effective than interferon (IFN) 1a for the treatment of relapsing-remitting multiple sclerosis (RRMS).

Objectives

To compare the efficacy, tolerability and safety of alemtuzumab versus interferon beta 1a in the treatment of people with RRMS to prevent disease activity.

Search methods

We searched the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group Trials Register (1 February 2017) which, among other sources, contains records from CENTRAL, MEDLINE, Embase, CINAHL, LILACS, PEDRO and the trial registry databases Clinical Trials.gov and WHO International Clinical Trials Registry Platform for all prospectively registered and ongoing trials.

Selection criteria

All double-blind, randomised, controlled trials comparing intravenous alemtuzumab (12 mg per day or 24 mg per day on five consecutive days during the first month and on three consecutive days at months 12, 24, 36) versus subcutaneous IFN beta 1a (Rebif), 22 µg or 44 µg three times per week, or IFN beta 1a (Avonex) by intramuscular injection 30 µg once a week, in people of any gender and age with RRMS.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included three trials involving 1694 participants. All trials compared alemtuzumab 12 mg per day or 24 mg per day versus IFN beta 1a for treating RRMS. In CAMMS223, participants received either subcutaneous IFN beta 1a 44 µg three times per week or annual intravenous cycles of alemtuzumab (at a dose of 12 mg per day or 24 mg per day) for 36 months. In CARE-MS I and CARE-MS II, participants received subcutaneous IFN beta 1a 44 µg three times per week or annual intravenous cycles of alemtuzumab 12 mg per day for 24 months. All three studies were at risk of performance bias and attrition bias, one study was 'unclear' risk in selection bias.

alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis (Review)

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Compared with interferon beta 1a, alemtuzumab given at a dose of 12 mg per day probably reduces the risk of relapse (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.52 to 0.70, moderate quality evidence), may reduce the risk of worsening disability (RR 0.60, 95% CI 0.45 to 0.79, low quality evidence) and the risk of developing new T2 lesions on magnetic resonance imaging (RR 0.75, 95% CI 0.61 to 0.93, low quality evidence) after 24 and 36 months' follow-up. Mean Expanded Disability Status Scale (EDSS) scores may be similar between the treatment regimens (mean difference (MD) -0.35, 95% CI -0.73 to 0.03, low quality evidence).

At a dose of 24 mg per day alemtuzumab may reduce relapse (RR 0.38, 95% CI 0.23 to 0.62, low quality evidence), worsening disability (RR 0.42, 95% CI 0.21 to 0.84, low quality evidence). The effects on EDSS scores when compared with interferon beta 1a at three years are uncertain due to the very low quality of evidence (MD -0.83, 95% CI -1.17 to -0.49).

All three trials reported adverse events and serious adverse events. The risk of experiencing an adverse event in either alemtuzumab 12 mg or interferon groups may be similar (RR 1.03, 95% CI 0.98 to 1.08, low quality evidence). The risk of serious adverse events is probably similar between treatments (RR 1.03, 95% CI 0.82 to 1.29, moderate quality evidence). The risk of any adverse event may be similar between alemtuzumab 24 mg and interferon (RR 1.02, 95% CI 0.96 to 1.08, low quality evidence). The risk of serious adverse events is probably similar between treatments (RR 0.95, 95% CI 0.70 to 1.31, moderate quality evidence).

Authors' conclusions

Annual intravenous cycles of alemtuzumab at a dose of 12 mg per day probably reduces the proportion of participants who experience relapse, may reduce the proportion of participants who experience disability worsening and development of new T2 lesions on MRI over 2 to 3 years in comparison with subcutaneous IFN beta-1a 44 µg three times per week. Annual intravenous cycles of alemtuzumab at a dose of 24 mg per day may reduce the proportion of participants who experience relapse and disability worsening over 3 years in comparison with subcutaneous IFN beta-1a 44 µg three times per week. An average reduction of 0.8 EDSS units with alemtuzumab compared with interferon beta-1a was observed at a dose of 24 mg per day in one study.

The rates of adverse events were similarly high for both treatments. The most frequently reported adverse events for both treatments were infusion-associated reactions, infections and autoimmune events. The use of alemtuzumab requires careful monitoring so that potentially serious adverse events can be treated early and effectively.

PLAIN LANGUAGE SUMMARY

Alemtuzumab, a humanised monoclonal antibody, as possible alternative therapy to interferon beta 1a in people with RRMS

Background

Multiple sclerosis is a progressive disease of the central nervous system where the person's own body destroys the coating that protects nerves. The disease may go into remission (where the symptoms reduce or stop) and then relapse (where the symptoms return). This is called relapsing-remitting multiple sclerosis (RRMS). Medicines called monoclonal antibodies (such as alemtuzumab) could be a possible alternative immunotherapy (treatment to stimulate the immune system) to interferon beta treatment (one of the usual treatments) in people with RRMS. In this review, we aimed to compare the benefits, side effects and safety of alemtuzumab versus interferon beta 1a in the treatment of people with RRMS.

Study characteristics

We searched medical databases and found three studies involving 1694 participants (CAMMS223, CARE-MS I and CARE-MS II). CAMMS223 involved people with previously untreated, early RRMS. Participants received either subcutaneous (under the skin) interferon beta 1a (at a dose of 44 µg) three times per week or annual intravenous (into a vein) courses of alemtuzumab (at a dose of either 12 mg per day or 24 mg per day) for 36 months. CARE-MS I enrolled adults aged 18 to 50 years with previously untreated RRMS. Participants received annual intravenous courses of alemtuzumab 12 mg per day or subcutaneous interferon beta 1a 44 µg three times per week for 24 months. CARE-MS II enrolled adults aged 18 to 55 years with RRMS and at least one relapse while on interferon beta or glatiramer (another medicine that alters the immune response) treatment. Participants received subcutaneous interferon beta 1a 44 µg three times per week, annual intravenous courses of alemtuzumab 12 mg per day or annual intravenous courses of alemtuzumab 24 mg per day for 24 months. The evidence is current to 1 February 2017.

Key results

The review of trials found that, compared with subcutaneous interferon beta 1a three times per week, annual intravenous cycles of alemtuzumab probably reduces the proportion of participants who experience relapse, may reduce the proportion of participants who experience disability worsening and development of new T2 lesions on MRI. In one study, alemtuzumab 24 mg leads to slightly better EDSS scores when compared with interferon beta 1a.

The rates of adverse events were similarly high for both treatments. The most frequently reported adverse events for both treatments were infusion-associated reactions, infections and autoimmune events. The use of alemtuzumab requires careful monitoring so that potentially serious adverse events can be treated early and effectively.

Quality of the evidence

The quality of the body of evidence obtained for each outcome is mainly low except for the number of participants experiencing at least one relapse for which the quality of evidence was moderate.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Alemtuzumab 12 mg compared to interferon beta 1a for relapsing-remitting multiple sclerosis

alemtuzumab12 mg compared to interferon beta 1a for relapsing-remitting multiple sclerosis

Patient or population: patients with relapsing-remitting multiple sclerosis

Settings:

Intervention: alemtuzumab 12 mg

Comparison: interferon beta 1a

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Interferon beta 1a	alemtuzumab12 mg				
Number of participants experiencing at least one relapse Follow-up: 24-36 months	448 per 1000	269 per 1000 (233 to 314)	RR 0.6 (0.52 to 0.70)	1414 (3 studies)	⊕⊕⊕⊖ moderate ¹	
Number of participants whose disability worsened Follow-up: 24-36 months	168 per 1000	101 per 1000 (76 to 133)	RR 0.6 (0.45 to 0.79)	1414 (3 studies)	⊕⊕⊖⊖ low ^{1,2}	
Number of participants with at least one adverse event Follow-up: 24-36 months	948 per 1000	976 per 1000 (929 to 1000)	RR 1.03 (0.98 to 1.08)	1415 (3 studies)	⊕⊕⊖⊖ low ^{1,3}	
Number of participants with serious adverse events Follow-up: 24-36 months	192 per 1000	197 per 1000 (157 to 247)	RR 1.03 (0.82 to 1.29)	1415 (3 studies)	⊕⊕⊕⊖ moderate ¹	
Mean Expanded Disability Status Scale score change from baseline Follow-up: 24-36 months	The mean EDSS score in the control groups ranged from -0.14 to 0.38	Mean EDSS score in the intervention groups was 0.35 lower (0.73 lower to 0.03 higher)		1414 (3 studies)	⊕⊕⊖⊖ low ^{1,4}	
Number of participants with new T2-hyperintense lesions on magnetic resonance imaging Follow-up: 24 months	630 per 1000	472 per 1000 (384 to 585)	RR 0.75 (0.61 to 0.93)	1125 (2 studies)	⊕⊕⊖⊖ low ^{1,5}	

Number of participants experiencing treatment discontinuation caused by adverse events

Follow-up: 24-36 months

76 per 1000

25 per 1000
(14 to 43)

RR 0.33
(0.19 to 0.56)

1414
(3 studies)

⊕⊕⊕⊕
low^{1,6}

*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).
The assumed risk in the comparison group is the median control group risk across studies.

CI: Confidence interval; RR: Risk ratio.

GRADE Working Group grades of evidence

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

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

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

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level due to study limitation (blinding of participants and personnel could not be well performed).

² Downgraded for one level due to inconsistency ($I^2 = 66\%$)

³ Downgraded for one level due to inconsistency ($I^2 = 85\%$)

⁴ Downgraded one level due to inconsistency (high heterogeneity, $I^2 = 88\%$)

⁵ Downgraded one level due to inconsistency (high heterogeneity, $I^2 = 73\%$).

⁶ Downgraded one level due to imprecision (low number of events).

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

alemtuzumab24 mg compared to interferon beta 1a for relapsing-remitting multiple sclerosis

Patient or population: patients with relapsing-remitting multiple sclerosis

Settings:

Intervention: alemtuzumab 24 mg

Comparison: interferon beta 1a

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Interferon beta 1a	alemtuzumab24 mg				
Number of participants experiencing at least one relapse Follow-up: 36 months	405 per 1000	154 per 1000 (93 to 251)	RR 0.38 (0.23 to 0.62)	221 (1 study)	⊕⊕⊕⊕ low ^{1,2}	Single study estimate

Number of participants whose disability worsened Follow-up: 36 months	216 per 1000	91 per 1000 (45 to 182)	RR 0.42 (0.21 to 0.84)	221 (1 study)	⊕⊕○○ low ^{1,2}	Single study estimate
Number of participants with at least one adverse event Follow-up: 24-36 months	964 per 1000	984 per 1000 (926 to 1000)	RR 1.02 (0.96 to 1.08)	578 (2 studies)	⊕⊕○○ low ^{1,3}	
Number of participants with serious adverse events Follow-up: 24-36 months	220 per 1000	209 per 1000 (154 to 288)	RR 0.95 (0.7 to 1.31)	578 (2 studies)	⊕⊕⊕○ moderate ¹	
Mean Expanded Disability Status Scale score change from baseline Follow-up: 36 months	Mean EDSS score in the control group was 0.38 higher	Mean EDSS score in the intervention group was 0.45 lower		221 (1 study)	⊕○○○ very low ^{1,4}	Single study estimate
Number of participants experiencing treatment discontinuation caused by adverse events Follow-up: 24-36 months	89 per 1000	30 per 1000 (9 to 14)	RR 0.34 (0.10 to 1.16)	593 (2 studies)	⊕○○○ very low ^{1,2,3}	

*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).
The assumed risk in the comparison group is the median control group risk across studies.

CI: Confidence interval; RR: Risk ratio.

GRADE Working Group grades of evidence

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

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

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

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level due to study limitation (blinding of participants and personnel could not be well performed).

² Downgraded one level due to imprecision (low number of events).

³ Downgraded one level due to inconsistency (high heterogeneity, $I^2 = 86\%$).

⁴ Imprecision (-2): In view of the low number of participants and the wide confidence intervals, we downgraded by two points.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system which is characterised by disseminated inflammatory demyelination. It mainly affects young adults, and leads to disability (Montalban 2010). It has high prevalence in western Europe and North America (more than 100 people per 100,000 population); lower prevalence in central and eastern Europe, the Balkans, Australia and New Zealand (50 per 100,000); and lowest prevalence in Asia, the Middle East, Africa and South America (about 10 to 20 per 100,000) (Koch-Henriksen 2010). Women have approximately a two-fold increased risk of developing MS than men. After the first attack, known as clinically isolated syndromes, which refers to a first episode of largely reversible neurological dysfunction with features suggestive of MS, 51% of people develop MS within six years (Chard 2011; Miller 2012). Most people with MS have a relapsing-remitting course, but after 10 years over half of people with MS convert to a secondary progressive phase which is characterised by continuing deterioration without remission (Weinshenker 1989).

Magnetic resonance imaging (MRI) provides a reflection of the underlying pathology. The MRI measures of disease activity (enhancing demyelinating lesions) and severity (T2-T1-weighted lesion burden) are used to monitor the natural evolution of the disease and treatment effects. They have been integrated with clinical data into diagnostic criteria for MS (McDonald 2001; Polman 2005; Polman 2011).

Considering the autoimmune pathogenesis of the disease, the mainstay of treatment is immunomodulatory therapy with interferon (IFN) beta and glatiramer acetate (GA), which are the current standard first-line treatments for MS. They reduce relapse frequency by about 30% (Brown 2013). Natalizumab, and more recently, fingolimod, have been introduced for people with highly active disease; they are more efficacious but have a more problematic safety profile than IFN and GA (Brown 2013; Pucci 2011).

The social costs associated with MS are high because of its long duration, the early loss of productivity, the need for assistance in activities of daily living, and the use of immunomodulatory treatments and multi-disciplinary health care (Koutsouraki 2010).

Description of the intervention

IFN beta 1a is a lyophilised glycoprotein produced in mammalian cells using the natural human gene sequence. Two preparations are licensed for the treatment of MS: 30 µg once a week administered by intramuscular injection (Avonex) and 22 µg or 44 µg administered three times a week by subcutaneous injections (Rebif). Their efficacy on disease activity is partial (Brown 2013). IFN therapy has been associated with a high frequency of treatment-related adverse events, mainly influenza-like reactions and injection site reactions; most people treated with IFN have leukopenia, lymphopenia, thrombocytopenia and increased plasma hepatic enzymes (Rice 2001). These data suggest the need for alternative MS treatments with less invasive routes of administration and new modes of action to expand the current treatment repertoire, increase patient satisfaction and adherence, and thereby improve efficacy.

alemtuzumab is a humanised monoclonal antibody (mAb), approved by the US Food and Drug Administration (FDA) for the treatment of B-cell chronic lymphocytic leukaemia (FDA 2000). It binds to CD52, a 12-amino acid cell surface protein (Hale 2001) that is expressed at high levels on T cells and B cells, and at lower levels on monocytes, macrophages and eosinophils. Cells of the innate immune system are unaffected (Coles 2013). alemtuzumab alters the circulating lymphocyte pool (Cuker 2011), causing prolonged lymphopenia (Thompson 2010). The therapeutic effect of alemtuzumab is mediated by the remoulding of the immune repertoire that accompanies homeostatic lymphocyte reconstitution (Coles 2013). Recovery of B and T lymphocytes to the lower limit of normal after a single course of alemtuzumab takes eight months (B lymphocytes) and three years (T lymphocytes) (Hill-Cawthorne 2012). alemtuzumab is given as an intravenous infusion of 12 mg/day on five consecutive days during the first month (first cycle) and on three consecutive days at months 12 (second cycle) and 24 (third cycle).

For people with secondary progressive MS, alemtuzumab significantly reduces the mean relapse rate and the risk of new MRI lesions. However, the person's disability continues to deteriorate as their cerebral atrophy progresses. For people with relapsing-remitting MS (RRMS), unlike the progressive cohort, mean disability scores decrease after alemtuzumab (Coles 2013). In a unique programme of drug development in MS, alemtuzumab has been compared in one phase II trial and two phase III trials with the active comparator IFN beta 1a. In these trials, alemtuzumab was more effective in suppressing relapses compared to IFN beta 1a. Indeed, alemtuzumab treatment led to an improvement in disability and a reduction in cerebral atrophy (Coles 2013).

However, alemtuzumab use was associated with an increased occurrence of autoimmune disorders, such as immune thrombocytopenia, thyroid disease and antglomerular basement membrane disease (Cuker 2011). Moreover, in 2005, three people with MS developed severe idiopathic thrombocytopenic purpura while participating in a clinical study of alemtuzumab (Campath) (FDA 2005). One of these people died.

How the intervention might work

The pathology of MS suggests an autoimmune aetiology and includes infiltration of T cells, B cells and macrophages in active MS brain lesions (Ode 2012). alemtuzumab causes rapid and prolonged lymphocyte depletion, finally resulting in immunosuppression and decreased central nervous system immunosurveillance (Bielekova 2010). After alemtuzumab therapy, the consequent homeostatic reconstitution leads to a radically reformed lymphocyte pool with a relative increase in regulatory T cells and expansion of autoreactive T cells (Coles 2013). In theory, these repertoire changes induced by alemtuzumab may improve long-term efficacy, but it could also underlie development of antibody-mediated autoimmune complications (Bielekova 2010).

Studies have demonstrated the efficacy of IFN beta 1a in people with RRMS (Panitch 2002; PRISMS 1998; Schwid 2007), and it has been commonly used in clinical practice. The mechanism of action of these therapeutic agents remains undefined. Several modes of action have been proposed, including: inhibition of T-cell activation and proliferation; apoptosis of autoreactive T cells; induction of regulatory T cells; inhibition of leukocyte migration across the blood-brain barrier; cytokine modulation and potential antiviral

activity. Endogenously produced IFN in the injured brain is also now believed to contribute to mediation of anti-inflammatory and regenerative effects (Dhib-Jalbut 2002; Dhib-Jalbut 2010).

Why it is important to do this review

mAbs have gained relevance in the treatment of MS. Trials demonstrated that alemtuzumab is more effective than IFN beta 1a, significantly reducing the relapse rate, risk for sustained accumulation of disability and mean Expanded Disability Status Scale (EDSS) score at month 36 after treatment. However, 30% of people develop autoimmunity (Thompson 2010). Marketing authorisation for alemtuzumab has been filed, and whilst trial data suggest that its efficacy outperforms both licensed drugs and others in development, there is a significant risk of adverse events, such as infusion-associated reactions, mild-to-moderate infections and autoimmunity (Ali 2013; Coles 2013). While the European Medicines Agency (EMA) has already approved it for RRMS (EMA 2013), it has not been approved by the FDA (FDA 2013; Thompson 2013).

A systematic review is warranted to assess the efficacy, tolerability and safety profile of alemtuzumab versus IFN beta 1a.

OBJECTIVES

To compare the benefit, tolerability and safety of alemtuzumab versus IFN beta 1a in the treatment of people with RRMS to prevent disease activity.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind, randomised, controlled trials (RCTs). We excluded uncontrolled, non-randomised and quasi-randomised trials.

Types of participants

We included participants of any gender and age with RRMS fulfilling Poser criteria (Poser 1983), or original or revised McDonald criteria (McDonald 2001; Polman 2005; Polman 2011). We excluded participants with: a progressive disease course; previous immunosuppressive, investigational or monoclonal antibody therapy and clinically significant autoimmune disorder other than MS.

Types of interventions

Experimental intervention: intravenous alemtuzumab 12 mg per day or 24 mg per day on five consecutive days during the first month and on three consecutive days at months 12 and 24.

Control intervention: subcutaneous IFN beta 1a (Rebif) 22 µg or 44 µg three times per week or intramuscular IFN beta 1a (Avonex) 30 µg once a week.

Types of outcome measures

Primary outcomes

Benefit:

- number of participants experiencing at least one relapse at 24 and 36 months. Relapse was defined as new or worsening pre-

existing neurological symptoms, without fever, that lasted for 48 hours or more and that were accompanied by a change in Functional Score on Kurtzke's EDSS scale assessed by the examining physician. One or more of the following changes compared with baseline was required for relapse confirmation: an increase in total EDSS by 0.5 points; an increase of at least 1 point in two functional-systems scores, or of at least 2 points in one functional-system score. Other less stringent criteria were accepted.

- number of participants whose disability worsened at 24 and 36 months, defined as an increase of at least 1.5 points on the EDSS scale for participants with a baseline score of 0, of at least 1.0 point for participants with a baseline score of 1.0 or more, and of at least 0.5 point for participants with a baseline score of 5.5 or more, sustained for six months (Kurtzke 1983).

Safety:

- number of participants with at least one adverse event, including serious adverse events.

Secondary outcomes

- mean EDSS score change from baseline at 24 and 36 months.
- number of participants with new T2-hyperintense lesions on MRI at 24 and 36 months.
- number of participants experiencing treatment discontinuation caused by adverse events.

Search methods for identification of studies

We conducted a systematic search without language restrictions to identify all relevant published and unpublished RCTs.

Electronic searches

The Information Specialist searched the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group Trials Register, which, among other sources, contains trials from:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 1);
- MEDLINE (PubMed) (1966 to 1 February 2017);
- Embase (Embase.com) (1974 to 1 February 2017);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) (1981 to 1 February 2017);
- Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to 1 February 2017);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch).

The keywords for this review are listed in [Appendix 1](#).

Information on the Trials Register or the Review Group and details of the search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group [module](#).

In addition, the review authors searched the following three Chinese databases using the search terms (duofaxingyinghua) AND (alundankang) AND (β-ganraosu):

- China Biological Medicine Database (CBM-disc) (1979 to 1 February 2017);
- Chinese National Knowledge Infrastructure Database (CNKI) (1979 to 1 February 2017);
- VIP Chinese Science and Technique Journals Database (1979 to 1 February 2017).

Searching other resources

In addition, we used the following methods.

- We screened reference lists of relevant review articles and primary studies found.
- We contacted experts in the field to identify further published or unpublished trials.
- we handsearched congress reports and conference proceedings (from 1994 to 1 February 2017) from the most important neurological associations and MS Societies (e.g. American Academy of Neurology, American Neurological Association, American Committee for Treatment and Research in MS, the European Committee for Treatment and Research in MS) and contact pharmaceutical companies.

Data collection and analysis

Selection of studies

Three review authors (JZ, YX, JL) independently screened titles and abstracts of the citations retrieved by the literature search. We selected the full text of potentially relevant studies for further assessment. We independently evaluated the eligibility of these studies on the basis of information available in the published data. Any disagreement regarding inclusion was resolved by discussion among all review authors.

We collated multiple reports of the same study, so that each study rather than each report, was the unit of interest in the review.

Data extraction and management

Three review authors (JZ, YX, JL) independently extracted the following data.

- Participants: diagnostic criteria, number in each group, age, gender, baseline comparability between groups, length of follow-up, withdrawals or losses to follow-up.
- Methods: study design; randomisation method; allocation concealment method; blinding methods of participants, personnel and outcome assessors.
- Interventions: details of alemtuzumab and IFN beta 1a, such as administration method, dosage and duration, treatment period, cointervention(s).
- Outcomes: primary and secondary outcomes.
- Other: country and setting, publication year, sources of funding, intention-to-treat (ITT) analysis.

Any disagreements were resolved by discussion among all the review authors.

Assessment of risk of bias in included studies

Two review authors (JZ, JL) independently assessed the risk of bias of the included studies using the checklist recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins

2011a). We assessed the risk of bias according the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. Each domain was classified as 'low', 'high' or 'unclear' risk of bias (Higgins 2011b). For each entry, the judgement ('low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias) was followed by a text box for a description of the design, conduct or observations that supported the judgement. There was no disagreement in assessing the risk of bias among the review authors. The final results were recorded in Review Manager 5 (RevMan 2014).

Measures of treatment effect

Data were managed according to the ITT principle. For each outcome, we calculated a summarised estimate of treatment effect (with 95% confidence interval (CI)) for each comparison. For dichotomous outcomes (e.g. relapses, disease progression), we used risk ratios (RR) and for continuous data (e.g. EDSS score), we used mean differences (MD).

Unit of analysis issues

Cluster and cross-over trials have not been carried out to evaluate alemtuzumab treatments for MS. We combined outcome data for participants who had relapses at 24 and 36 months and disability worsening at 24 and 36 months. When studies had multiple arms, we did not combine arms, and compared relevant arms separately in different analyses, to avoid double counting.

Dealing with missing data

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

Assessment of heterogeneity

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

We evaluated statistical heterogeneity among included studies using a Chi² test with an alpha of 0.1, and with the I² test. A P value of less than 0.1 and an I² statistic more than 50% was an indication of substantial statistical heterogeneity (Higgins 2011a); we examined potential sources of clinical and methodological heterogeneity.

Assessment of reporting biases

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

Data synthesis

We used Review Manager 5 software to conduct formal meta-analysis (RevMan 2014). The selection of a fixed-effect or random-effects model was mainly based on the results of the Chi² test and I² statistic for heterogeneity (Higgins 2011a). If the I² statistic indicated substantial statistical heterogeneity, we explored potential causes of heterogeneity first, to determine whether a subgroup analyses was needed. If the substantial heterogeneity still could not be explained, we adopted a random-effects model. If the I² statistic indicated no significant statistical heterogeneity, we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroups analyses.

- Different dosages of alemtuzumab versus IFN beta 1a.
- Different duration of treatment.
- Different cointerventions.
- Different types of IFN beta 1a.

However, because of the limited number of studies, we could not perform all the analyses.

Sensitivity analysis

We planned to perform the following sensitivity analyses.

- Excluding studies at high risk of bias (i.e. non-random sequence generation and inadequate allocation concealment, lack of blinded outcome assessor, lack of blinded participants/personnel, or a combination of these).
- Using a random-effects model if a fixed-effect model was used previously.

However, because of the limited number of studies, we could not perform all the analyses.

Summary of Findings

We presented the main results of the review in two 'Summary of findings' (SoF) tables, one reporting data for alemtuzumab 12 mg and one for alemtuzumab 24 mg, according to recommendations described in Chapter 11 of the *Cochrane Handbook for Systematic*

Reviews of Interventions (version 5.1.0) ([Schünemann 2011](#)). We provided estimates from the pairwise meta-analysis based on the methodology developed from the GRADE Working Group ([GRADE Working Group 2004](#)). We included an overall grading of the evidence for seven patient-important outcomes:

- Number of participants experiencing at least one relapse
- Number of participants whose disability worsened
- Number of participants with at least one adverse events
- Number of participants with serious adverse events
- Mean Expanded Disability Status Scale score change from baseline
- Number of participants with new T2-hyperintense lesions on magnetic resonance imaging
- Number of participants experiencing treatment discontinuation caused by adverse events

We graded the quality of evidence for each outcome considering study limitations, indirectness, inconsistency, imprecision of effect estimates, and risk of reporting bias, assigning four levels of quality of evidence: high, moderate, low, and very low.

RESULTS

Description of studies

Results of the search

The search strategies retrieved 316 references. After screening of titles and abstracts, we obtained 19 full papers (three studies) and assessed them for eligibility ([Figure 1](#)).

Figure 1. Study flow diagram.

Included studies

We included three studies involving 1694 participants in the review. All three studies were multicentric RCTs comparing alemtuzumab versus IFN beta 1a in the treatment of people with RRMS. [CAMMS223 2008](#) and [CARE-MS II](#) are three-arm trials. We did not merge multi-arm trials involving alemtuzumab at different doses compared to Interferon Beta treatment and presented separate data for each arm.

[CAMMS223 2008](#) involved participants with previously untreated, early RRMS. Participants received either subcutaneous IFN beta 1a 44 µg three times per week or annual intravenous cycles of alemtuzumab at either 12 mg per day or 24 mg per day.

[CARE-MS I](#) enrolled adults aged 18 to 50 years with previously untreated RRMS. Participants received annual intravenous cycles of alemtuzumab 12 mg per day or subcutaneous IFN beta 1a 44 µg three times per week.

[CARE-MS II](#) enrolled adults aged 18 to 55 years with RRMS and at least one relapse on IFN beta or glatiramer. Participants received subcutaneous IFN beta 1a 44 µg three times per week, annual intravenous cycles of alemtuzumab 12 mg per day or annual intravenous cycles of alemtuzumab 24 mg per day. The 24 mg per day group was discontinued to aid recruitment, data were included for safety assessments, but data for benefit outcomes were not provided.

Excluded studies

We excluded none of the potentially eligible studies.

Risk of bias in included studies

The risk of bias summaries are provided in [Figure 2](#) and [Figure 3](#).

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CAMMS223 2008	+	?	-	+	-	+	+
CARE-MS I	+	+	-	+	-	+	+
CARE-MS II	+	+	-	+	-	+	+

Allocation

All three included trials were reported as randomised; [CAMMS223 2008](#) used the Pocock and Simon minimisation algorithm, while [CARE-MS I](#) and [CARE-MS II](#) used an interactive voice response system. Thus, the three studies were at low risk of bias for random sequence generation.

For allocation concealment, [CARE-MS I](#) and [CARE-MS II](#) used an interactive voice response system, thus we assessed them at low risk of bias. [CAMMS223 2008](#) did not mention allocation concealment, thus, we assessed it at unclear risk of bias.

Blinding

We considered all studies at high risk of bias of performance bias (participants and personnel) because both drugs (intervention and comparator) had adverse effects that precluded masking.

Incomplete outcome data

All three trials provided sufficient details about the number of, and the reasons for, dropout. In [CAMMS223 2008](#), the dropout rate was unbalanced between the alemtuzumab group (17%) and the IFN beta 1a group (41%), therefore, we classified the trial at high risk. In [CARE-MS I](#), the percentage of dropout was unbalanced between alemtuzumab group (6%) and IFN beta 1a group (16%), therefore, we classified the trial at high risk of incomplete outcome data bias. In [CARE-MS II](#), the percentage of dropout was unbalanced between alemtuzumab group (2.1%) and IFN beta 1a group (12.6%), therefore, we classified the trial at high risk of incomplete outcome data bias.

Selective reporting

All three trials were at low risk of reporting bias as they reported all specified primary and secondary outcomes.

Other potential sources of bias

We did not find any other potential source of bias.

Effects of interventions

See: [Summary of findings for the main comparison Alemtuzumab 12 mg compared to interferon beta 1a for relapsing-remitting multiple sclerosis](#); [Summary of findings 2 Alemtuzumab 24 mg compared to interferon beta 1a for relapsing-remitting multiple sclerosis](#)

Primary outcomes

Number of participants experiencing at least one relapse at 24 and 36 months

All three trials assessed the number of participants experiencing at least one relapse at 24 and 36 months ([CAMMS223 2008](#); [CARE-MS I](#); [CARE-MS II](#)). [CAMMS223 2008](#) reported alemtuzumab 12/24 mg versus IFN beta 1a at 36 months. [CARE-MS I](#) and [CARE-MS II](#) reported alemtuzumab 12 mg versus IFN beta 1a at 24 months. In the alemtuzumab 12 mg comparison, there was significant difference in favour of alemtuzumab at 24 months (RR 0.62, 95% CI 0.53 to 0.72), 36 months (RR 0.53, 95% CI 0.35 to 0.80) and overall (RR 0.60, 95% CI 0.52 to 0.70). There was no significant heterogeneity ($I^2 = 9\%$), so we applied the fixed-effect model was applied ([Analysis 1.1](#)). Only one trial reported alemtuzumab 24 mg versus IFN beta 1a at 36 months ([CAMMS223 2008](#)). There was a significant difference in favour of alemtuzumab (RR 0.38, 95% CI 0.23 to 0.62) (see [Analysis 1.2](#)).

Number of participants whose disease progressed at 24 and 36 months

All three trials assessed the number of participants who experienced disease progression at 24 and 36 months ([CAMMS223 2008](#); [CARE-MS I](#); [CARE-MS II](#)).

[CAMMS223 2008](#) reported alemtuzumab 12/24 mg versus IFN beta 1a at 36 months; [CARE-MS I](#) and [CARE-MS II](#) reported alemtuzumab 12 mg versus IFN beta 1a at 24 months. In the alemtuzumab 12 mg comparison, there was significant difference in favour of alemtuzumab at 24 months (RR 0.68, 95% CI 0.50 to 0.92), 36 months (RR 0.33, 95% CI 0.16 to 0.70) and overall (RR 0.60, 95% CI 0.45 to 0.79). There was no significant heterogeneity ($I^2 = 37\%$), therefore, we applied the fixed-effect model ([Analysis 2.1](#)). One trial reported alemtuzumab 24 mg versus IFN beta 1a ([CAMMS223 2008](#)). There was significant difference in favour of alemtuzumab at 36 months (RR 0.42, 95% CI 0.21 to 0.84) ([Analysis 2.2](#)).

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

All three trials reported adverse events and serious adverse events ([CAMMS223 2008](#); [CARE-MS I](#); [CARE-MS II](#)).

[CAMMS223 2008](#) reported alemtuzumab 12/24 mg versus IFN beta 1a at 36 months; [CARE-MS I](#) reported alemtuzumab 12 mg versus IFN beta 1a at 24 months; and [CARE-MS II](#) reported alemtuzumab 12/24 mg versus IFN beta 1a at 24 months.

In the alemtuzumab 12 mg group, 897/919 (98%) participants experienced any adverse event and in the IFN beta 1a group, 470/496 (95%) participants experienced any adverse events (RR 1.03, 95% CI 0.98 to 1.08) ([Analysis 3.1](#)). In the alemtuzumab 12 mg group, 178/919 (19.3%) participants experienced serious adverse

events and in the IFN beta 1a group, 95/496 (19.2%) participants experienced serious adverse events (RR 1.03, 95% CI 0.82 to 1.29) ([Analysis 4.1](#)).

In the alemtuzumab 24 mg group, 266/269 (99%) participants experienced any adverse event and in the IFN beta 1a group, 298/309 (96%) participants experienced any adverse events (RR 1.02, 95% CI 0.96 to 1.08) ([Analysis 3.2](#)). In the alemtuzumab 24 mg group, 57/269 (21.2%) participants experienced serious adverse events and in the IFN beta 1a group, 68/309 (22.0%) participants experienced serious adverse events (RR 0.95, 95% CI 0.70 to 1.31) ([Analysis 4.2](#)).

Secondary outcomes

Mean EDSS score change from baseline at 24 and 36 months

All three trials reported mean EDSS score change from baseline at 24 and 36 months ([CAMMS223 2008](#); [CARE-MS I](#); [CARE-MS II](#)).

[CAMMS223 2008](#) reported alemtuzumab 12/24 mg versus IFN beta 1a at 36 months. [CARE-MS I](#) and [CARE-MS II](#) reported alemtuzumab 12 mg versus IFN beta 1a at 24 months. Evidence for an effect of decreased disability worsening, as measured by the Expanded Disability Status Scale (EDSS) with alemtuzumab 12 mg compared with IFN beta 1a at 24 months in two studies, was imprecise and with high level of statistical heterogeneity (MD -0.20, 95% CI -0.60 to 0.20; $I^2 = 88\%$; [Analysis 5.1.1](#)). EDSS was reported by [CAMMS223 2008](#) that found significant difference in favour of alemtuzumab 12 mg compared to IFB beta 1a at 36 months of treatment (MD -0.70, 95% CI -1.04 to -0.36; [Analysis 5.1.2](#)). The pooled result did not favour alemtuzumab 12 mg compared to IFN beta 1a (MD -0.35, 95% CI -0.73 to 0.03; [Analysis 5.1](#); [Summary of findings for the main comparison](#)). One trial comparing alemtuzumab 24 mg versus IFN beta 1a ([CAMMS223 2008](#)) found significant difference in favour of alemtuzumab at 36 months but with a wide confidence interval (MD -0.83, 95% CI -1.17 to -0.49; [Analysis 5.2](#)).

Number of participants with new T2-hyperintense lesions on magnetic resonance imaging at 24 and 36 months

Two trials reported the number of participants with new T2-hyperintense lesions on MRI at 24 and 36 months ([CARE-MS I](#); [CARE-MS II](#)). There was significant difference in developing new T2 lesions on MRI favouring alemtuzumab 12 mg at 24 months (RR 0.75, 95% CI 0.61 to 0.93) ([Analysis 6.1](#)). There was significant heterogeneity ($I^2 = 73\%$), so we applied the random-effects model).

Number of participants experiencing treatment discontinuation caused by adverse events

All three trials reported the number of participants experiencing treatment discontinuation caused by adverse events ([CAMMS223 2008](#); [CARE-MS I](#); [CARE-MS II](#)). In the alemtuzumab 12 mg comparison, there was a significant difference in favour of alemtuzumab at 24 and 36 months (RR 0.33, 95% CI 0.19 to 0.56). There was no significant heterogeneity ($P = 0.50$, $I^2 = 0$), so we applied the fixed-effect model ([Analysis 7.1](#)). In the alemtuzumab 24 mg comparison, there was no significant difference in two groups (RR 0.34, 95% CI 0.10 to 1.16). There was significant heterogeneity ($P = 0.14$, $I^2 = 55\%$), so we applied the random-effect model ([Analysis 7.2](#)).

DISCUSSION

Summary of main results

Alemtuzumab was more effective than IFN beta 1a for the treatment of RRMS. This systematic review compared the benefit, tolerability and safety of alemtuzumab versus IFN beta 1a in the treatment of people with RRMS. Three RCTs involving 1694 participants contributed to the final analysis. In [CAMMS223 2008](#), participants received either subcutaneous IFN beta 1a 44 µg three times per week or annual intravenous cycles of alemtuzumab at 12 mg per day or 24 mg per day for 36 months. In [CARE-MS I](#) and [CARE-MS II](#), participants received subcutaneous IFN beta 1a 44 µg three times per week or annual intravenous cycles of alemtuzumab 12 mg per day for 24 months. All three studies were at risk of performance bias and attrition bias, one study was 'unclear' risk in selection bias. In the alemtuzumab 12 mg comparison, the results showed statistically significant differences favouring alemtuzumab in reducing relapses, preventing disease progression and developing new T2 lesions on MRI after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score. In the alemtuzumab 24 mg comparison, the results showed statistically significant differences favouring alemtuzumab in reducing relapses, preventing disease progression and the changes of EDSS score after 36 months' follow-up. The rates of adverse events were similarly high for both treatments, although the risk of discontinuations related to adverse effects was lower with alemtuzumab. However, considering that alemtuzumab is administered once per year, this could have an effect on the observation of adverse events.

Overall completeness and applicability of evidence

The review's aim was to compare the benefit, tolerability and safety of alemtuzumab versus interferon beta 1a in the treatment of people with RRMS to prevent disease activity. We included three studies involving 1694 participants. All three RCTs compared alemtuzumab versus subcutaneous interferon beta-1a in participants with RRMS. alemtuzumab was given intravenously 12 mg per day or 24 mg per day on five consecutive days during the first month and on three consecutive days at months 12 and 24, while IFN beta 1a was given 44 µg subcutaneously three times weekly after dose titration. All three studies reported benefit as clinical relapses, disability worsening and changes of EDSS score. In addition, [CARE-MS I](#) and [CARE-MS II](#) reported participants with new T2-hyperintense lesions on MRI. There is low- to moderate-quality evidence that annual intravenous cycles of alemtuzumab at a dose of 12 mg per day or 24 mg per day probably reduces the proportion of participants who experience relapse, and may reduce disability worsening and development of new T2 lesions on MRI over 2 to 3 years in comparison with subcutaneous IFN beta-1a 44 µg three times per week. An average reduction of 0.8 EDSS units with alemtuzumab compared with interferon beta-1a was observed at a dose of 24 mg per day in one study. All three trials reported adverse events and serious adverse events. The rates of adverse events were similarly high for both treatments, although the risk of discontinuations related to adverse effects was lower with alemtuzumab. In our view, this review has reliably compared the benefit, tolerability and safety of alemtuzumab versus interferon beta 1a.

Quality of the evidence

As presented in [Summary of findings for the main comparison](#) and [Summary of findings 2](#), the quality of the body of evidence obtained for each outcome ranged from very low to moderate. All three studies were at high risk of performance bias and attrition bias, one study was 'unclear' risk in selection bias. There were a low number of events and a high heterogeneity in some outcomes.

Potential biases in the review process

An extensive and comprehensive search was undertaken to limit bias in the review process, however a low number of studies were retrieved.

There were no potential biases from the review authors in the review process. In the development of this review, three review authors independently read and screened trials retrieved for inclusion, independently completed data extraction and assessed the quality of included trials to minimize potential biases. No conflict of interests were found in relation to the review authors of this review.

The limitations of this review include:

- no assessment of publication bias through funnel plot analysis because there were only 3 studies.
- the lack of some outcome data in the included RCTs, for example, the data for benefit outcomes of alemtuzumab at a dose of 24 mg per day were not provided.

Agreements and disagreements with other studies or reviews

One systematic review included three studies in a qualitative synthesis and evaluated the effectiveness of alemtuzumab in the treatment of MS ([Riera 2016](#)). The same studies were eligible for meta-analyses in our current systematic review. There are subtle distinctions between the two reviews in the methods of meta-analysis, but overall, our review achieved similar conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

Annual intravenous cycles of alemtuzumab at a dose of 12 mg per day probably reduces the proportion of participants who experience relapse, may reduce the proportion of participants who experience disability worsening and development of new T2 lesions on MRI over 2 to 3 years in comparison with subcutaneous IFN beta-1a 44 µg three times per week. Annual intravenous cycles of alemtuzumab at a dose of 24 mg per day may reduce the proportion of participants who experience relapse and disability worsening over 3 years in comparison with subcutaneous IFN beta-1a 44 µg three times per week. An average reduction of 0.8 EDSS units with alemtuzumab compared with interferon beta-1a was observed at a dose of 24 mg per day in one study.

The rates of adverse events were similarly high for both treatments. The most frequently reported adverse events for both treatments were infusion-associated reactions, infections and autoimmune events. The use of alemtuzumab requires careful monitoring so that potentially serious adverse events can be treated early and effectively.

Implications for research

Future well-designed randomised, double-blind, controlled trials with larger sample sizes either for mono or combination therapy with alemtuzumab in RRMS are needed. Health-related quality of life outcome should be addressed for such a disabling disease in future research.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

CAMMS223 2008

Methods	Phase II, multicentre, randomised, blinded trial comparing 2 doses of alemtuzumab with subcutaneous interferon beta-1a.
Participants	<p>Date of randomisation: December 2002 to July 2004.</p> <p>Number of participation randomised: 334.</p> <p>Number of centres: 49 centres in Europe and the US.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • diagnosis of RRMS (McDonald criteria) with an onset of symptoms 36 months or less before screening; • ≥ 2 clinical episodes during the previous 2 years; • EDSS score ≤ 3, which ranges from 0 to 10, with higher scores indicating greater disability; • ≥ 1 enhancing lesions as seen on ≥ 1 of up to 4-monthly MRI cranial scans. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • previous disease-modifying treatments;

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CAMMS223 2008 (Continued)

- history of clinically significant autoimmunity;
- presence of serum antithyrotropin-receptor antibodies.

Interventions	<p>alemtuzumab: 12 mg per day or 24 mg per day by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24.</p> <p>Interferon beta-1a: 44 µg subcutaneously 3 times weekly after dose escalation.</p>
Outcomes	<p>Primary outcomes: time to sustained accumulation of disability and rate of relapse.</p> <p>Secondary outcomes: proportion of participants who did not have a relapse, changes in lesion burden (seen on T2-weighted MRI) and brain volume (measured by Losseff method on T1-weighted MRI).</p>
Funding source	Supported by Genzyme and Bayer Schering Pharma.
Notes	In September 2005, alemtuzumab therapy was suspended after immune thrombocytopenic purpura developed in 3 people, 1 of whom died. Treatment with interferon beta 1a continued throughout the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomly assigned in a 1:1:1 ratio to receive alemtuzumab (at a dose of either 12 mg per day or 24 mg per day) or interferon beta-1a with the use of the Pocock and Simon minimization algorithm to balance the study groups with regard to age (<30 years or ≥30 years), sex, and baseline EDSS score (<2.0 or ≥2.0)."
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Both study drugs had adverse events that precluded masking of participants and treating clinicians to treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	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. The effectiveness of blinding was assessed at the end-of-study visit. Safety was assessed quarterly by the treating neurologist, who was aware of study-group assignment. MRI scans were performed annually and interpreted by a neuroradiologist at Perceptive Informatics who was unaware of assignments to study groups." "We used a rater who was unaware of treatment assignments for efficacy outcomes, as advocated by the American Academy of Neurology, and confirmed successful maintenance of blinding throughout the study." "At the end of the study review, 90% and 91% of raters remained unaware of assignments to the group receiving interferon beta-1a and the group receiving alemtuzumab, respectively."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "More patients 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 patients receiving interferon beta-1a completed the 36-month study, as compared with 83% of patients receiving alemtuzumab."
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Low risk	None

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CARE-MS I

Methods	Phase III, multicentre, randomised, rater-masked, controlled trial.
Participants	<p>Date of randomisation: 7 September 2007 to 17 April 2009.</p> <p>Number of participation randomised: 581.</p> <p>Number of centres: 101 academic medical centres and clinical practices in 16 countries.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> aged 18-50 years; RRMS fulfilling the 2005 McDonald criteria; disease duration ≤ 5 years; ≥ 2 relapses in the previous 2 years and ≥ 1 in the previous year; EDSS score ≤ 3.0; cranial abnormalities on MRI attributable to multiple sclerosis. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> progressive disease course; previous multiple sclerosis disease therapy (apart from corticosteroids); previous immunosuppressive, investigational or monoclonal antibody therapy; clinically significant autoimmunity other than multiple sclerosis.
Interventions	<p>alemtuzumab: 12 mg per day by intravenous infusion on 5 days at baseline and 3 days at 12 months.</p> <p>Interferon beta 1a: 44 μg subcutaneously 3 times per week after dose titration.</p>
Outcomes	<p>Primary endpoints: relapse rate and time to 6 month sustained accumulation of disability.</p> <p>Secondary endpoints: proportion of participants who were relapse-free, change in EDSS, percentage change in T2-hyperintense lesion volume and change in MSFC.</p> <p>Safety endpoints: monthly questionnaire follow-up of participants, blood counts, serum creatinine, urinalysis, microscopy monthly (every 3 months in participants in the interferon beta 1a group), and thyroid function tests every 3 months.</p>
Funding source	Funded by Genzyme (Sanofi) and Bayer Schering Pharma.
Notes	

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 in a 2:1 ratio to receive alemtuzumab (12 mg per day), infused intravenously on 5 days at baseline and 3 days at 12 months, or interferon beta 1a (44 μ g) given subcutaneously three-times per week after dose titration."
Allocation concealment (selection bias)	Low risk	Quote: "We randomly allocated patients using an interactive voice response system."
Blinding of participants and personnel (performance bias) All outcomes	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 clini-

CARE-MS I (Continued)

		cal data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists."
Blinking of outcome assessment (detection bias) All outcomes	Low risk	Quote: "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 5172 (>99%) of 5193 EDSS assessments. Only 15 (3%) of 563 patients had one or more assessments done by an unmasked rater. Sensitivity analyses, including exclusion of unmasked assessments, supported the absence of effect of rater unmasking on study results (appendix)."
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>A higher number (31 of 195; 16%) of participants in interferon group did not complete the study than participants in the alemtuzumab group (24 of 386, 6%).</p> <p>There was a trial profile.</p> <p>IFN group: 8 participants did not receive drug (7 withdrew consent, 1 unknown); 14 participants (5 adverse event, 2 lack of efficacy, 1 physician decision, 1 pregnancy, 5 withdrew consent) discontinued the study after receiving study drug; 9 participants (2 physician decision, 4 withdrew consent, 1 lost to follow-up, 1 death, 1 unknown) discontinued study drug but continued in the study.</p> <p>Alemtuzumab group: 10 participants (1 adverse reaction, 8 withdrew consent, 1 unknown) did not receive drug; 9 (2 physician decision, 4 withdrew consent, 1 lost to follow-up, 1 death, 1 unknown) discontinued the study after receiving study drug; 5 (4 adverse event, 1 lack of efficacy) discontinued study drug but continued in the study.</p>
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Low risk	None

CARE-MS II

Methods	Phase III, multicentre, randomised, rater-masked, controlled trial.
Participants	<p>Date of randomisation: 20 October 2007 to 18 September 2009.</p> <p>Number of participation randomised: 840.</p> <p>Number of centres: 194 academic medical centres and clinical practices in 23 countries.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> aged 18-55 years; RRMS fulfilling 2005 McDonald diagnostic criteria; disease duration ≤ 10 years; ≥ 2 attacks in previous 2 years with ≥ 1 in previous year; ≥ 1 relapse while on interferon beta or glatiramer after ≥ 6 months of treatment; EDSS score ≤ 5.0; cranial and spinal MRI lesions fulfilling protocol-defined criteria. <p>Exclusion criteria:</p>

CARE-MS II (Continued)

- progressive forms of multiple sclerosis;
- previous cytotoxic drug use or investigational therapy treatment within the previous 6 months with natalizumab, methotrexate, azathioprine or ciclosporin;
- history of clinically significant autoimmunity other than multiple sclerosis.

Interventions	<p>alemtuzumab: 12 mg per day or 24 mg per day by intravenous infusion for 5 days at baseline and 3 days at 12 months.</p> <p>Interferon beta 1a: 44 µg subcutaneously 3 times per week after dose titration.</p>
Outcomes	<p>Primary endpoints: relapse rate and time to 6-month sustained accumulation of disability.</p> <p>Secondary endpoints: proportion of participants who were relapse-free, changes in EDSS, T2 lesion volume and MSFC.</p> <p>Safety endpoints: monthly questionnaire follow-up of participants, blood counts, serum creatinine, urinalysis with microscopy monthly (every 3 months in participants in the interferon beta 1a group) and thyroid function tests every 3 months.</p>
Funding source	Funded by Genzyme (Sanofi) and Bayer Schering Pharma.
Notes	

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."
Allocation concealment (selection bias)	Low risk	Quote: "We randomly allocated patients with an interactive voice response system."
Blinding of participants and personnel (performance bias) All outcomes	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."
Blinding of outcome assessment (detection bias) All outcomes	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) 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 analyses, sensitivity studies showed these unmasked data had no effect on outcomes (appendix)."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "More patients randomly allocated to interferon beta 1a than alemtuzumab discontinued the trial before treatment (29 [13%] of 231 patients for interferon beta 1a vs 13 [2%] of 609 patients for alemtuzumab) and after starting treatment (27 [12%] of 202 vs 16 [3%] of 596)."
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Low risk	None

EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; MSFC: multiple sclerosis functional composite; RRMS: relapsing-remitting multiple sclerosis.

DATA AND ANALYSES

Comparison 1. Number of participants experiencing at least one relapse at 24 and 36 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alemtuzumab 12 mg vs interferon beta 1a	3	1414	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.52, 0.70]
1.1 At 24 months	2	1191	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.53, 0.72]
1.2 At 36 months	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.35, 0.80]
2 Alemtuzumab 24 mg vs interferon beta 1a	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.23, 0.62]
2.1 At 36 months	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.23, 0.62]

Analysis 1.1. Comparison 1 Number of participants experiencing at least one relapse at 24 and 36 months, Outcome 1 Alemtuzumab 12 mg vs interferon beta 1a.

Analysis 1.2. Comparison 1 Number of participants experiencing at least one relapse at 24 and 36 months, Outcome 2 Alemtuzumab 24 mg vs interferon beta 1a.

Comparison 2. Number of participants whose disease progressed at 24 and 36 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alemtuzumab 12 mg vs interferon beta 1a	3	1414	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.45, 0.79]
1.1 At 24 months	2	1191	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.50, 0.92]
1.2 At 36 months	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.16, 0.70]
2 Alemtuzumab 24 mg vs interferon beta 1a	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.21, 0.84]
2.1 At 36 months	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.21, 0.84]

Analysis 2.1. Comparison 2 Number of participants whose disease progressed at 24 and 36 months, Outcome 1 Alemtuzumab 12 mg vs interferon beta 1a.

Analysis 2.2. Comparison 2 Number of participants whose disease progressed at 24 and 36 months, Outcome 2 Alemtuzumab 24 mg vs interferon beta 1a.

Comparison 3. Number of participants with at least one adverse event at 24 and 36 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alemtuzumab 12 mg vs interferon beta 1a	3	1415	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.08]
1.1 At 24 months	2	1200	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.01, 1.07]
1.2 At 36 months	1	215	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.98, 1.02]
2 Alemtuzumab 24 mg vs interferon beta 1a	2	578	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 At 24 months	1	363	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.01, 1.08]
2.2 At 36 months	1	215	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.97, 1.02]

Analysis 3.1. Comparison 3 Number of participants with at least one adverse event at 24 and 36 months, Outcome 1 Alemtuzumab 12 mg vs interferon beta 1a.

Analysis 3.2. Comparison 3 Number of participants with at least one adverse event at 24 and 36 months, Outcome 2 Alemtuzumab 24 mg vs interferon beta 1a.

Comparison 4. Number of participants with severe adverse events at 24 and 36 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alemtuzumab 12 mg vs interferon beta 1a	3	1415	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.29]
1.1 At 24 months	2	1200	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.34]
1.2 At 36 months	1	215	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.63]
2 Alemtuzumab 24 mg vs interferon beta 1a	2	578	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.31]
2.1 At 24 months	1	363	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.56, 1.30]
2.2 At 36 months	1	215	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.69, 1.80]

Analysis 4.1. Comparison 4 Number of participants with severe adverse events at 24 and 36 months, Outcome 1 Alemtuzumab 12 mg vs interferon beta 1a.

Analysis 4.2. Comparison 4 Number of participants with severe adverse events at 24 and 36 months, Outcome 2 Alemtuzumab 24 mg vs interferon beta 1a.

Comparison 5. Mean Expanded Disability Status Scale score change from baseline at 24 and 36 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alemtuzumab 12 mg vs interferon beta 1a	3	1414	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.73, 0.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 At 24 months	2	1191	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.60, 0.20]
1.2 At 36 months	1	223	Mean Difference (IV, Random, 95% CI)	-0.7 [-1.04, -0.36]
2 Alemtuzumab 24 mg vs interferon beta 1a	1	221	Mean Difference (IV, Random, 95% CI)	-0.83 [-1.17, -0.49]
2.1 At 36 months	1	221	Mean Difference (IV, Random, 95% CI)	-0.83 [-1.17, -0.49]

Analysis 5.1. Comparison 5 Mean Expanded Disability Status Scale score change from baseline at 24 and 36 months, Outcome 1 Alemtuzumab 12 mg vs interferon beta 1a.

Analysis 5.2. Comparison 5 Mean Expanded Disability Status Scale score change from baseline at 24 and 36 months, Outcome 2 Alemtuzumab 24 mg vs interferon beta 1a.

Comparison 6. Number of participants with new T2-hyperintense lesions on magnetic resonance imaging at 24 and 36 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alemtuzumab 12 mg vs interferon beta 1a	2	1125	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.61, 0.93]
1.1 At 24 months	2	1125	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.61, 0.93]

Analysis 6.1. Comparison 6 Number of participants with new T2-hyperintense lesions on magnetic resonance imaging at 24 and 36 months, Outcome 1 Alemtuzumab 12 mg vs interferon beta 1a.

Comparison 7. Number of participants experiencing treatment discontinuation caused by adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alemtuzumab 12 mg vs interferon beta 1a	3	1414	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.19, 0.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 At 24 months	2	1191	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.20, 0.66]
1.2 At 36 months	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.78]
2 Alemtuzumab 24 mg vs interferon beta 1a	2	593	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.10, 1.16]
2.1 At 24 months	1	372	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.23, 1.33]
2.2 At 36 months	1	221	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.67]

Analysis 7.1. Comparison 7 Number of participants experiencing treatment discontinuation caused by adverse events, Outcome 1 Alemtuzumab 12 mg vs interferon beta 1a.

Analysis 7.2. Comparison 7 Number of participants experiencing treatment discontinuation caused by adverse events, Outcome 2 Alemtuzumab 24 mg vs interferon beta 1a.

APPENDICES

Appendix 1. Keywords for English databases

{interferon beta-1a} OR {Avonex} OR {Biogen brand of Interferon beta 1a} OR {Rebif} OR {Serono brand of interferon beta 1a} OR {Betaseron}

AND

{alemtuzumab} OR {Campath 1G} OR {Campath-1G} OR {Campath-1-G} OR {Campath 1M} OR {Campath-1M} OR {MabCampath} OR {Schering brand of alemtuzumab} OR {Campath} OR {Berlex brand of alemtuzumab} OR {Campath 1H} OR {monoclonal antibody Campath-1H} OR {Campath-1H} OR {monoclonal antibod*} OR {Antibodies, Monoclonal}

AND

{relapsing remitting multiple sclerosis} OR {relapsing-remitting multiple sclerosis} OR {remitting-relapsing multiple sclerosis} OR {remitting relapsing multiple sclerosis}

Appendix 2. Keywords for Chinese databases

#1 复发缓解型多发性硬化

#2 β干扰素

#3 β-干扰素

#4 干扰素-β

#5 人成纤维细胞干扰素

#6 阿仑单抗

#7 坎帕斯

#8 #2 OR #3 OR #4 OR #5

#9 #6 OR #7

#10 #1 AND #8 AND #9

WHAT'S NEW

Date	Event	Description
16 April 2018	Amended	The text of the review has been amended throughout. New 'Summary of findings' tables have been incorporated.

CONTRIBUTIONS OF AUTHORS

JZ, YX, SS drafted the review.

JZ, YX, SS developed the search strategy.

JZ, YX, JL selected relevant articles for inclusion.

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

JZ, JL assessed the risk of bias in included studies.

YZ, YX entered data to Review Manager 5.

JZ, YX, XY carried out the analysis.

JZ, YZ interpreted the results.

JZ, YZ will update the review.

All review authors read and approved the completed review.

DECLARATIONS OF INTEREST

JZ: none.

SS: none.

YZ: none.

JL: none.

YX: none.

LM: none.

XY: none.

SOURCES OF SUPPORT

Internal sources

- Department of Neurology, the Second Affiliated Hospital, Guangxi Medical University, China.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

One of the coauthors of the protocol could no longer contribute to the review (Meng L), and two new coauthors (Luo J, Zhang Y) contributed to the review instead.

We planned the following subgroup analyses at the protocol stage but did not perform them due to lack of included studies: different cointerventions, different types of IFN beta 1a.

INDEX TERMS

Medical Subject Headings (MeSH)

Adjuvants, Immunologic [*administration & dosage] [adverse effects]; Alemtuzumab [*administration & dosage] [adverse effects]; Disease Progression; Drug Administration Schedule; Interferon beta-1a [*administration & dosage] [adverse effects]; Multiple Sclerosis, Relapsing-Remitting [*drug therapy]; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Humans