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### ► **To cite this version:**

Irene Tramacere, Gianni Virgili, Vittorio Perduca, Ersilia Lucenteforte, Maria Donata Benedetti, et al.. Adverse effects of immunotherapies for multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews*, 2023, 2023 (11), pp.CD012186. 10.1002/14651858.CD012186.pub2 . hal-04342560v2

**HAL Id: hal-04342560**

**<https://hal.science/hal-04342560v2>**

Submitted on 27 Sep 2024

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Adverse effects of immunotherapies for multiple sclerosis: a network meta-analysis.

*Cochrane Database of Systematic Reviews* 2023, Issue 11. Art. No.: CD012186.

DOI: [10.1002/14651858.CD012186.pub2](https://doi.org/10.1002/14651858.CD012186.pub2).

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**Adverse effects of immunotherapies for multiple sclerosis: a network meta-analysis (Review)**

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[Intervention Review]

# Adverse effects of immunotherapies for multiple sclerosis: a network meta-analysis

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**Editorial group:** Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group.

**Publication status and date:** New, published in Issue 11, 2023.

**Citation:** Tramacere I, Virgili G, Perduca V, Lucenteforte E, Benedetti MD, Capobussi M, Castellini G, Frau S, Gonzalez-Lorenzo M, Featherstone R, Filippini G. Adverse effects of immunotherapies for multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2023, Issue 11. Art. No.: CD012186. DOI: [10.1002/14651858.CD012186.pub2](https://doi.org/10.1002/14651858.CD012186.pub2).

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## ABSTRACT

### Background

Multiple sclerosis (MS) is a chronic disease of the central nervous system that affects mainly young adults (two to three times more frequently in women than in men) and causes significant disability after onset. Although it is accepted that immunotherapies for people with MS decrease disease activity, uncertainty regarding their relative safety remains.

### Objectives

To compare adverse effects of immunotherapies for people with MS or clinically isolated syndrome (CIS), and to rank these treatments according to their relative risks of adverse effects through network meta-analyses (NMAs).

### Search methods

We searched CENTRAL, PubMed, Embase, two other databases and trials registers up to March 2022, together with reference checking and citation searching to identify additional studies.

### Selection criteria

We included participants 18 years of age or older with a diagnosis of MS or CIS, according to any accepted diagnostic criteria, who were included in randomized controlled trials (RCTs) that examined one or more of the agents used in MS or CIS, and compared them versus placebo or another active agent. We excluded RCTs in which a drug regimen was compared with a different regimen of the same drug without another active agent or placebo as a control arm.

## Data collection and analysis

We used standard Cochrane methods for data extraction and pairwise meta-analyses. For NMAs, we used the *netmeta* suite of commands in R to fit random-effects NMAs assuming a common between-study variance. We used the CINEMA platform to GRADE the certainty of the body of evidence in NMAs. We considered a relative risk (RR) of 1.5 as a non-inferiority safety threshold compared to placebo. We assessed the certainty of evidence for primary outcomes within the NMA according to GRADE, as very low, low, moderate or high.

## Main results

This NMA included 123 trials with 57,682 participants.

### Serious adverse events (SAEs)

Reporting of SAEs was available from 84 studies including 5696 (11%) events in 51,833 (89.9%) participants out of 57,682 participants in all studies. Based on the absolute frequency of SAEs, our non-inferiority threshold (up to a 50% increased risk) meant that no more than 1 in 18 additional people would have a SAE compared to placebo.

Low-certainty evidence suggested that three drugs may decrease SAEs compared to placebo (relative risk [RR], 95% confidence interval [CI]): interferon beta-1a (Avonex) (0.78, 0.66 to 0.94); dimethyl fumarate (0.79, 0.67 to 0.93), and glatiramer acetate (0.84, 0.72 to 0.98).

Several drugs met our non-inferiority criterion versus placebo: moderate-certainty evidence for teriflunomide (1.08, 0.88 to 1.31); low-certainty evidence for ocrelizumab (0.85, 0.67 to 1.07), ozanimod (0.88, 0.59 to 1.33), interferon beta-1b (0.94, 0.78 to 1.12), interferon beta-1a (Rebif) (0.96, 0.80 to 1.15), natalizumab (0.97, 0.79 to 1.19), fingolimod (1.05, 0.92 to 1.20) and laquinimod (1.06, 0.83 to 1.34); very low-certainty evidence for daclizumab (0.83, 0.68 to 1.02).

Non-inferiority with placebo was not met due to imprecision for the other drugs: low-certainty evidence for cladribine (1.10, 0.79 to 1.52), siponimod (1.20, 0.95 to 1.51), ofatumumab (1.26, 0.88 to 1.79) and rituximab (1.01, 0.67 to 1.52); very low-certainty evidence for immunoglobulins (1.05, 0.33 to 3.32), diroximel fumarate (1.05, 0.23 to 4.69), peg-interferon beta-1a (1.07, 0.66 to 1.74), alemtuzumab (1.16, 0.85 to 1.60), interferons (1.62, 0.21 to 12.72) and azathioprine (3.62, 0.76 to 17.19).

### Withdrawals due to adverse events

Reporting of withdrawals due to AEs was available from 105 studies (85.4%) including 3537 (6.39%) events in 55,320 (95.9%) patients out of 57,682 patients in all studies. Based on the absolute frequency of withdrawals, our non-inferiority threshold (up to a 50% increased risk) meant that no more than 1 in 31 additional people would withdraw compared to placebo.

No drug reduced withdrawals due to adverse events when compared with placebo.

There was very low-certainty evidence (meaning that estimates are not reliable) that two drugs met our non-inferiority criterion versus placebo, assuming an upper 95% CI RR limit of 1.5: diroximel fumarate (0.38, 0.11 to 1.27) and alemtuzumab (0.63, 0.33 to 1.19).

Non-inferiority with placebo was not met due to imprecision for the following drugs: low-certainty evidence for ofatumumab (1.50, 0.87 to 2.59); very low-certainty evidence for methotrexate (0.94, 0.02 to 46.70), corticosteroids (1.05, 0.16 to 7.14), ozanimod (1.06, 0.58 to 1.93), natalizumab (1.20, 0.77 to 1.85), ocrelizumab (1.32, 0.81 to 2.14), dimethyl fumarate (1.34, 0.96 to 1.86), siponimod (1.63, 0.96 to 2.79), rituximab (1.63, 0.53 to 5.00), cladribine (1.80, 0.89 to 3.62), mitoxantrone (2.11, 0.50 to 8.87), interferons (3.47, 0.95 to 12.72), and cyclophosphamide (3.86, 0.45 to 33.50).

Eleven drugs may have increased withdrawals due to adverse events compared with placebo: low-certainty evidence for teriflunomide (1.37, 1.01 to 1.85), glatiramer acetate (1.76, 1.36 to 2.26), fingolimod (1.79, 1.40 to 2.28), interferon beta-1a (Rebif) (2.15, 1.58 to 2.93), daclizumab (2.19, 1.31 to 3.65) and interferon beta-1b (2.59, 1.87 to 3.77); very low-certainty evidence for laquinimod (1.42, 1.01 to 2.00), interferon beta-1a (Avonex) (1.54, 1.13 to 2.10), immunoglobulins (1.87, 1.01 to 3.45), peg-interferon beta-1a (3.46, 1.44 to 8.33) and azathioprine (6.95, 2.57 to 18.78); however, very low-certainty evidence is unreliable.

Sensitivity analyses including only studies with low attrition bias, drug dose above the group median, or only patients with relapsing remitting MS or CIS, and subgroup analyses by prior disease-modifying treatments did not change these figures.

## Rankings

No drug yielded consistent P scores in the upper quartile of the probability of being better than others for primary and secondary outcomes.

## Authors' conclusions

We found mostly low and very low-certainty evidence that drugs used to treat MS may not increase SAEs, but may increase withdrawals compared with placebo. The results suggest that there is no important difference in the occurrence of SAEs between first- and second-line drugs and between oral, injectable, or infused drugs, compared with placebo.

Our review, along with other work in the literature, confirms poor-quality reporting of adverse events from RCTs of interventions. At the least, future studies should follow the CONSORT recommendations about reporting harm-related issues. To address adverse effects, future systematic reviews should also include non-randomized studies.

## PLAIN LANGUAGE SUMMARY

### What are the risks of therapies for treating multiple sclerosis?

#### Key messages

- Immunotherapies used to treat multiple sclerosis appear not to increase serious health events, compared to sham drugs (placebo).
- Many of these drugs have unwanted effects and, for some of them, more people included in studies dropped out because of side effects compared to sham drugs.
- These results are only partly, or are not, reliable since serious health events are relatively rare in people with multiple sclerosis, meaning that the issue is difficult to study, and serious health events were also not well reported in the studies.

#### What is the condition?

Multiple sclerosis (MS) affects the brain and the spinal cord. MS affects more women than men. In MS, the immune system attacks the sheath that covers our body's nerves and weakens their function. Some people with severe MS may even not be able to use their arms or legs well for some time, but they usually recover. Disability, for example in walking, can arise in some people who have many attacks over the years.

#### How is the condition treated?

Several treatments that modulate the immune system are available that can help speed recovery from attacks and improve the course of the disease.

#### What did we want to find out?

We aimed to investigate the risks of the drugs used to treat MS. We wanted to assess all types of health events that are serious, for example, admissions to hospital, or events that made people stop taking the medication. We also wanted to investigate health events in specific body organs.

#### What did we do?

We searched for studies that investigated drugs aiming to improve the course of MS, compared with other drugs or sham drugs, in people with recurrent episodes of the disease.

#### What did we find?

Serious health events were found in about one in nine people receiving a sham drug during one or two years. The following drugs were found not to increase these events: interferon beta-1a (Avonex), dimethyl fumarate, glatiramer acetate, teriflunomide, ocrelizumab, ozanimod, interferon beta-1b, interferon beta-1a (Rebif), natalizumab, fingolimod, and laquinimod. We cannot tell whether the following drugs cause more serious health events than sham because the studies were small or there were few events (for cladribine, siponimod, ofatumumab, and rituximab). We were very unsure about daclizumab, immunoglobulins, diroximel fumarate, peg-interferon beta-1a, alemtuzumab, interferons and azathioprine because the evidence regarding serious health events was of very poor quality.

Unwanted effects causing people to stop taking the medication were found in one in 16 people receiving a sham drug for one or two years. The following drugs may have increased these dropouts: teriflunomide, glatiramer acetate, fingolimod, interferon beta-1a (Rebif), daclizumab and interferon beta-1b. We cannot tell whether ofatumumab causes more dropouts than sham because the studies were small or there were few events. We are very unsure about diroximel fumarate, alemtuzumab, methotrexate, corticosteroids, ozanimod, natalizumab, ocrelizumab, dimethyl fumarate, siponimod, rituximab, cladribine, mitoxantrone, interferons, cyclophosphamide, laquinimod, interferon beta-1a (Avonex), immunoglobulins, peg-interferon beta-1a and azathioprine because the evidence regarding dropouts was of very poor quality.

#### What are the limitations of the evidence?

Most of the evidence came from studies conducted in ways that may have introduced errors into their results, including the fact that harms were not well reported. Moreover, serious health events and unwanted effects are rare in people with MS and, thus, difficult to study.

#### How up-to-date is the evidence?

This review is up-to-date until March 2022.