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[Intervention Review]

Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis

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ABSTRACT

Background

Different therapeutic strategies are available for the treatment of people with relapsing-remitting multiple sclerosis (RRMS), including immunomodulators, immunosuppressants and biologics. Although there is consensus that these therapies reduce the frequency of relapses, their relative benefit in delaying new relapses or disability worsening remains unclear due to the limited number of direct comparison trials.

Objectives

To compare the benefit and acceptability of interferon beta-1b, interferon beta-1a (Avonex, Rebif), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine and immunoglobulins for the treatment of people with RRMS and to provide a ranking of these treatments according to their benefit and acceptability, defined as the proportion of participants who withdrew due to any adverse event.

Search methods

We searched the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group Trials Register, which contains trials from CENTRAL (2014, Issue 9), MEDLINE (1966 to 2014), EMBASE (1974 to 2014), CINAHL (1981 to 2014), LILACS (1982 to 2014), clinicaltrials.gov and the WHO trials registry, and US Food and Drug Administration (FDA) reports. We ran the most recent search in September 2014.

Selection criteria

Randomised controlled trials (RCTs) that studied one or more of the 15 treatments as monotherapy, compared to placebo or to another active agent, for use in adults with RRMS.

Data collection and analysis

Two authors independently identified studies from the search results and performed data extraction. We performed data synthesis by pairwise meta-analysis and network meta-analysis. We assessed the quality of the body of evidence for outcomes within the network meta-analysis according to GRADE, as very low, low, moderate or high.

Main results

We included 39 studies in this review, in which 25,113 participants were randomised. The majority of the included trials were short-term studies, with a median duration of 24 months. Twenty-four (60%) were placebo-controlled and 15 (40%) were head-to-head studies.

Network meta-analysis showed that, in terms of a protective effect against the recurrence of relapses in RRMS during the first 24 months of treatment, alemtuzumab, mitoxantrone, natalizumab, and fingolimod outperformed other drugs. The most effective drug was alemtuzumab (risk ratio (RR) versus placebo 0.46, 95% confidence interval (CI) 0.38 to 0.55; surface under the cumulative ranking curve (SUCRA) 96%; moderate quality evidence), followed by mitoxantrone (RR 0.47, 95% CI 0.27 to 0.81; SUCRA 92%; very low quality evidence), natalizumab (RR 0.56, 95% CI 0.47 to 0.66; SUCRA 88%; high quality evidence), and fingolimod (RR 0.72, 95% CI 0.64 to 0.81; SUCRA 71%; moderate quality evidence).

Disability worsening was based on a surrogate marker, defined as irreversible worsening confirmed at three-month follow-up, measured during the first 24 months in the majority of included studies. Both direct and indirect comparisons revealed that the most effective treatments were mitoxantrone (RR versus placebo 0.20, 95% CI 0.05 to 0.84; SUCRA 96%; low quality evidence), alemtuzumab (RR 0.35, 95% CI 0.26 to 0.48; SUCRA 94%; low quality evidence), and natalizumab (RR 0.64, 95% CI 0.49 to 0.85; SUCRA 74%; moderate quality evidence).

Almost all of the agents included in this review were associated with a higher proportion of participants who withdrew due to any adverse event compared to placebo. Based on the network meta-analysis methodology, the corresponding RR estimates versus placebo over the first 24 months of follow-up were: mitoxantrone 9.92 (95% CI 0.54 to 168.84), fingolimod 1.69 (95% CI 1.32 to 2.17), natalizumab 1.53 (95% CI 0.93 to 2.53), and alemtuzumab 0.72 (95% CI 0.32 to 1.61).

Information on serious adverse events (SAEs) was scanty, characterised by heterogeneous results and based on a very low number of events observed during the short-term duration of the trials included in this review.

Authors' conclusions

Conservative interpretation of these results is warranted, since most of the included treatments have been evaluated in few trials. The GRADE approach recommends providing implications for practice based on moderate to high quality evidence. Our review shows that alemtuzumab, natalizumab, and fingolimod are the best choices for preventing clinical relapses in people with RRMS, but this evidence is limited to the first 24 months of follow-up. For the prevention of disability worsening in the short term (24 months), only natalizumab shows a beneficial effect on the basis of moderate quality evidence (all of the other estimates were based on low to very low quality evidence). Currently, therefore, insufficient evidence is available to evaluate treatments for the prevention of irreversible disability worsening.

There are two additional major concerns that have to be considered. First, the benefit of all of these treatments beyond two years is uncertain and this is a relevant issue for a disease with a duration of 30 to 40 years. Second, short-term trials provide scanty and poorly reported safety data and do not provide useful evidence in order to obtain a reliable risk profile of treatments. In order to provide long-term information on the safety of the treatments included in this review, it will be necessary also to evaluate non-randomised studies and post-marketing reports released from the regulatory agencies. Finally, more than 70% of the studies included in this review were sponsored by pharmaceutical companies and this may have influenced the results.

There are three needs that the research agenda should address. First, randomised trials of direct comparisons between active agents would be useful, avoiding further placebo-controlled studies. Second, follow-up of the original trial cohorts should be mandatory. Third, more studies are needed to assess the medium and long-term benefit and safety of immunotherapies and the comparative safety of different agents.

PLAIN LANGUAGE SUMMARY

Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis

Background

Different therapeutic strategies are available for the treatment of people with relapsing-remitting multiple sclerosis (RRMS), including immunomodulators, immunosuppressants, and biologics. Although there is consensus that these therapies may reduce the frequency of relapses, their relative benefit (effectiveness compared to each other) in delaying new relapses or disability worsening remains unclear due to the limited number of direct comparison studies (i.e. studies comparing two or more active agents with each other).

Objectives

We aimed to assess and rank the benefit from and the extent of adverse events associated with 15 drugs, i.e. interferon beta-1b, interferon beta-1a (Avonex, Rebif), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine, and immunoglobulins.

Study characteristics

We included 39 studies up to September 2014 in this review, comprising a total of 25,113 participants suffering from RRMS. The majority of the included studies were short-term, with a median duration of 24 months.

Key results and quality of the evidence

For preventing relapses, alemtuzumab, natalizumab, and fingolimod are more effective than the other drugs, based on moderate to high quality evidence.

For preventing irreversible disability worsening, insufficient evidence is currently available.

Almost all of the agents included in this review were associated with a higher proportion of participants who withdrew due to any adverse event compared to placebo.

It is worth noting the following:

- The benefit of all of these treatments beyond two years is uncertain and this is a very relevant issue for people with a lifelong disease such as multiple sclerosis, who will possibly need long-term treatments.

- Safety data from these short-term studies are scanty, poorly reported and cannot provide enough evidence for us to obtain a reliable risk profile of the treatments included in this review.

- Most of the included studies were sponsored by pharmaceutical companies and this is a known potential source of bias.