Beta interferons in clinically isolated syndromes: a meta-analysis
Melo A, Rodrigues B, Bar-Or A

CRD summary
The review concluded that beta-interferon reduced the risk of conversion to clinically defined multiple sclerosis in patients with clinically isolated syndromes, but few data were available to assess side effects. Due to major limitations in the review process, the conclusions should be regarded with caution.

Authors' objectives
To determine the safety and efficacy of beta-interferon (β-INF) on the occurrence of relapses in patients with a first clinical event suggestive of multiple sclerosis (MS).

Searching
MEDLINE, The Cochrane Library and BIREME were searched for relevant studies; search terms were reported. Reference lists of retrieved studies were searched.

Study selection
Eligible studies were double-blind, placebo-controlled randomised clinical trials (RCTs) that assessed the risk of conversion from clinically isolated syndrome (CIS) to clinically definite MS (CDMS).

In the included studies, participants ranged in age from 18 to 50 years. Patients were allowed to use steroid treatment at the time of the initial attack. Patients were followed for at least two years. β-INF treatments included interferon beta-1a and interferon beta-1b.

Two reviewers independently performed study selection; it was not reported how disagreements were resolved.

Assessment of study quality
Studies were evaluated for validity by two independent reviewers using the Jadad method.

The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted on the cumulative probability of conversion from CIS into CDMS. Only dichotomous data presented as (or allowing transformation into) mean and standard deviation were analysed.

The authors did not state how data were extracted, how many reviewers performed the data extraction or how disagreements were resolved.

Methods of synthesis
Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a fixed effects meta-analysis. Heterogeneity was assessed with the $X^2$ test and the $I^2$ quantity.

Results of the review
Three RCTs (n=1,159) were included. Sample sizes ranged from 308 to 468 participants. No validity assessments of the included studies were reported.

β-INF significantly decreased the risk of conversion to CDMS (OR 0.51, 95% CI 0.42 to 0.63). No statistically significant heterogeneity was detected. Side effects were not fully evaluated by meta-analysis.
Authors' conclusions
Early treatment with beta-interferon reduced the risk of conversion to clinically defined multiple sclerosis in patients with clinically isolated syndromes.

CRD commentary
The review addressed a clear research question, but specific inclusion criteria for participants, interventions and duration of follow up were not clearly reported. Several relevant sources were searched to identify potential studies, but no attempts were made to find unpublished data and it was not stated whether language restrictions applied, so language and publication bias could not be ruled out. Independent study selection and validity assessment were performed, but it did not appear that these assessments were used in sensitivity analyses or to guide interpretation of the results of the review. It was not stated whether duplicate data extraction was undertaken, so reviewer error and bias may have been introduced into the review process. The authors stated that only dichotomous data, presented as mean and standard deviation, were analysed but do not specify the cutoffs for transformation of the data for the outcome of interest, cumulative probability of conversion from CIS into CDMS. The authors also reported the results of another outcome, time to delay of conversion of CIS to CDMS in days (expressed as continuous data), contrary to their assertion that only dichotomous data were analysed. No statistical heterogeneity was found in the analyses. For the outcome cumulative probability of conversion from CIS into CDMS, the authors presented a subgroup analysis of interferon beta-1a, another subgroup analysis of β-INF overall and combined both subgroups to calculate an overall summary of estimate, thus they double counted two trials that were included in both subgroups. However, individual results from the included studies all indicated a significant benefit of β-INF when compared to placebo, which supported the authors’ conclusions. Due to limitations in the review process, lack of reporting of validity assessments and double counting of some trials in the statistical analyses, the authors’ conclusions should be regarded with caution and their reliability is uncertain.

Implications of the review for practice and research
Practice: The authors stated that it was important to establish the optimal dose of β-INF and define a therapeutic window. They suggested that the results of these trials may not be applicable to patients in different populations.

Research: The authors stated that further studies were required to clarify whether, in subgroups of patients with neutralising antibodies that may develop during the course of treatment, the risk of conversion from CIS to CDMS was higher.

Funding
Not stated.

Bibliographic details

PubMedID
18392405

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Demyelinating Diseases /drug therapy; Double-Blind Method; Humans; Immunologic Factors /adverse effects /therapeutic use; Interferon-beta /adverse effects /therapeutic use; Magnetic Resonance Imaging; Middle Aged; Multiple Sclerosis /prevention & control; Randomized Controlled Trials as Topic; Recurrence; Syndrome

AccessionNumber
12008106673

Date bibliographic record published
03/02/2009

**Date abstract record published**
13/01/2010

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.