Disease-modifying drugs for multiple sclerosis: a rapid and systematic review
Clegg A, Bryant J, Milne R

Authors' objectives
To provide a rapid review of the effectiveness and costs of disease-modifying drugs in multiple sclerosis (MS).

Searching
Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, NHS CRD’s Database of Abstracts of Reviews of Effectiveness (DARE) and NHS Economic Evaluation Database (NHS EED), MEDLINE, EMBASE, PubMed and the National Research Register (NRR) were searched from 1980 to July 1999 (search terms provided). In addition, the bibliographies of related papers were searched and pharmaceutical companies and experts in the field were contacted for additional information about published and unpublished material. No information from companies associated with the manufacture of interferon beta and copolymer I was included in the report. Only English language studies were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and systematic reviews of RCTs were included in the review.

Specific interventions included in the review
Drugs that modify the course of MS, specifically beta interferon, glatiramer (copolymer I), azathioprine, intravenous immunoglobulin, methotrexate, cladribine, mitoxantrone, cyclophosphamide, and other new drugs such as peptides. Various drug regimens were reported in the review. Interventions were compared with each other or placebo.

Participants included in the review
Individuals diagnosed with MS who met the criteria for treatment with disease-modifying drugs.

Outcomes assessed in the review
Relapse rate, disease progression, and side-effects were the primary outcome measures. Other non-patient outcomes, such as magnetic resonance imaging (MRI) findings were extracted if the study did not include any of the primary outcomes. Non-patient outcomes were not extracted if primary outcome measures were used.

How were decisions on the relevance of primary studies made?
Decisions were made by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Assessment of study quality
Study validity was judged using the criteria outlined in the Wessex Institute for Health Research and Development Reviews Team Guidelines. RCTs were scored according to the Jadad scale (see Other Publications of Related Interest no.1) and systematic reviews according to the NHS CRD quality criteria for systematic reviews (see Other Publications of Related Interest no.2). Decisions were made by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. RCTs were awarded a point score according to each of the four Jadad criteria (maximum score=5 points) and systematic reviews were graded either ‘yes’ or ‘no’ for each of the six NHS CRD criteria.

Data extraction
Data were extracted by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. Tables reported in the review include the following types of data: bibliographic details, study design details, patient details, outcome measures, results, quality of study, data analysis details and other comments.
Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
Studies were subgrouped according to drug type, severity of illness and quality of studies.

Results of the review
Twenty-two RCTs (with a total of n=3629 participants) and two systematic reviews were included. Six cost-utility studies were also discussed.

Azathioprine (n=2 RCTs, n=1 systematic review):
Jadad quality score=2-4.
CRD NHS quality score=4.
Results suggested azathioprine may reduce rates of relapse in patients with relapsing-remitting, relapsing-progressive and progressive MS. However, side-effects were common, particularly gastrointestinal disorders, and these may affect compliance.

Beta interferon (n=3 RCTs):
Jadad quality score=4-5.
There was evidence of limited benefit in relapsing-remitting and secondary progressive MS, respectively although all three trials had methodological limitations. Side-effects were common, particularly flu-like symptoms and injection site reactions.

Cladribine (n=2 RCTs):
Jadad quality score=3.
Results suggested that cladribine may be effective in delaying disease progression in chronic progressive MS but no significant treatment effect was found in disease progression or relapse rate in relapsing-remitting MS.

Cyclophosphamide (n=5 RCTs):
Jadad quality score=1-4.
One study suggested that in progressive MS cyclophosphamide combined with adenocorticotropic hormone may be of some benefit, while another suggested that boosters of cyclophosphamide may slow progression. A wide range of side-effects were reported in all studies.

Glatiramer (n=2 RCTs, n=1 systematic review):
Jadad quality score=3.
CRD NHS quality score=3.
The results suggested that relapse rate may be reduced by glatiramer treatment but the size of the benefit was not clear.

Intravenous immunoglobulin (n=3 RCTs):
Jadad quality score=3-5.
The results suggested that relapse rate may be significantly reduced by intravenous immunoglobulin therapy at 3yrs. A wide range of adverse effects was commonly reported.

Methotrexate (n=2 RCTs):
Jadad quality score=2-4.

The results suggested a treatment effect in chronic progressive MS only when using a composite outcome measure of treatment failure. Side-effects were similar to those reported for placebo.

Mitoxantrone (n=2 RCTs):
Jadad quality score=3-4.

Results suggested the mitoxantrone may be of benefit in disability progression and relapse rate, although one study was of short duration and combined mitoxantrone with methylprednisolone. A range of side-effects was reported.

Cost information
Yes. Six cost-utility studies were identified (5 for beta interferon and one for glatiramer). Annual drug costs per patients were estimated to be: £50-£1,200 for azathioprine, £10,000-£20,000 for beta interferon, £5,800-£8,800 for cladribine, <£100 for cyclophosphamide, around £10,000 for glatiramer, £1,600-£10,000 for intravenous immunoglobulin, £18-£58 for methotrexate and around £3,600 for mitoxantrone.

Authors' conclusions
The evidence for the effectiveness of immunodulatory drugs in MS is problematic because: 1. There are too few good quality trials for each drug.
2. Trials often have methodological limitations or poor reporting of data.
3. Trials are often of small size and short duration.
4. There is no consistency in treatment regimens, patient groups and outcome measures.
5. The clinical significance of reported benefits is not clear.

CRD commentary
This is a clearly presented, good quality review. The inclusion criteria are clearly stated and a thorough search of the literature was used to locate both published and unpublished work. However, limiting the review to only English-language studies may have resulted in bias and relevant data been omitted.

Throughout the review systematic methods were used to select studies, assess study validity and extract data, although it would appear that the two reviewers involved in these processes did not work independently. Each study was assessed using clearly stated quality criteria and discussed in a narrative synthesis. Details of the studies were also clearly presented in table format. Considering the heterogeneity identified by the authors the use of a narrative synthesis appears appropriate. Overall, the conclusions and implications reported by the authors appear to be supported by the data presented.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.

Research: The authors state that 'well-conducted trials using outcome measures with clinical significance for different groups of MS patients and long-term follow-up are needed'.

Database of Abstracts of Reviews of Effects (DARE)
Produced by the Centre for Reviews and Dissemination
Copyright © 2017 University of York
Funding
NHS R&D Health Technology Assessment (HTA) Programme, project number 99/05/01.

Bibliographic details

Original Paper URL
http://www.hta.ac.uk/project.asp?PjtId=1163

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adjuvants, Immunologic /economics /therapeutic use; Azathioprine /economics /therapeutic use; Cladribine /economics /therapeutic use; Cost-Benefit Analysis; Cyclophosphamide /economics /therapeutic use; Drug Costs /statistics & numerical data; Immunoglobulins, Intravenous /economics /therapeutic use; Immunosuppressive Agents /economics /therapeutic use; Interferon-beta /economics /therapeutic use; Methotrexate /economics /therapeutic use; Mitoxantrone /economics /therapeutic use; Multiple Sclerosis /drug therapy; Peptides /economics /therapeutic use; Research Design /standards; Technology Assessment, Biomedical; Treatment Outcome

AccessionNumber
12000008344

Date bibliographic record published
31/05/2001

Date abstract record published
31/05/2001

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.