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Rapid review

Disease-modifying drugs for multiple sclerosis: a rapid and systematic review

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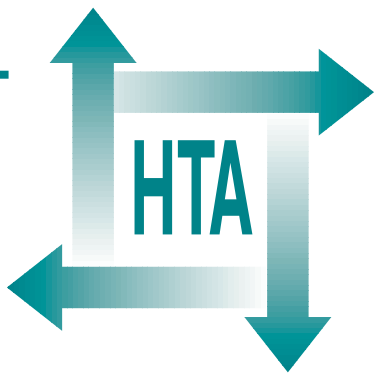
Health Technology Assessment
NHS R&D HTA Programme



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Disease-modifying drugs for multiple sclerosis: a rapid and systematic review

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The research reported in this monograph was commissioned by the HTA programme (project number 99/05/01) on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources. Any views expressed in this rapid review are therefore those of the authors and not necessarily those of the HTA programme, NICE or the Department of Health.

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Glossary and list of abbreviations

ACTH	adrenocorticotrophic hormone
AI	Ambulation Index
ANOVA	analysis of variance
CI	confidence interval
CNS	central nervous system
CPMS	chronic progressive MS (either primary or secondary progressive disease)
CRD	[NHS] Centre for Reviews and Dissemination*
CSF	cerebrospinal fluid*
DSS	Kurtzke Disability Status Scale (see EDSS)
EDSS	Kurtzke Expanded Disability Status Scale
ERMS	exacerbating–remitting MS
Exacerbation or relapse	The development of new neurological symptoms or worsening of existing ones, lasting ≥ either 24 or 48 hours, and preceded by stability or improvement (or slowly progressing neurological state in SPMS).
Fab	fragment antigen binding
FS	functional systems, in which changes form part of the assessment of the Kurtzke EDSS
GP	general practitioner
IDSS	Integrated Disability Status Scale*
IHQL	Index of Health-related Quality of Life*
IFβ	beta interferon
Ig	immunoglobulin
i.m.	intramuscular*
IQR	interquartile range*
ITT	intention-to-treat [analysis]*
i.v.	intravenous
MIU	million international units
MRI	magnetic resonance imaging
MS	multiple sclerosis
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health [USA]*
NNT	numbers-needed-to-treat
NS	not significant*
NSAID	non-steroidal anti-inflammatory drug
NRS	Scripps Neurologic Rating Scale
OR	odds ratio*
PMS	progressive MS – either primary or secondary; may be referred to as severe progressive
PPMS	primary progressive MS – progressive disease from onset of illness
PRISMS	Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in MS trial
QALY	quality-adjusted life year
q.d.s.	four times daily (*quater die sumendum*)*
Q_M	Mantel's extension of Mantel–Haenzel procedure

* Used only in tables and appendices

continued

RCT	randomised controlled trial
relapse	see exacerbation
RR	relative risk*
RRMS	relapsing–remitting MS
RPMS	relapsing–progressive MS (or progressive–relapsing MS) – in which patients have a continually deteriorating baseline but with superimposed fluctuations or relapses; often regarded as secondary progressive
s.c.	subcutaneous*
spinal MS	demyelination principally focused on the spinal cord
SD	standard deviation
SE	standard error
severity of exacerbations/ relapses	defined as an NRS of 0–7 (mild), 8–14 (moderate), > 15 (severe) for PRISMS and IFβ-1b in RRMS trials; or on Activities of Daily Living scale: mild: no effect; moderate: significant effect; severe: hospital admission in PRISMS trial
SPMS	secondary progressive MS (in which progressive disease follows at least one relapse
SRS	Scripps Rating Scale (see NRS) sustained worsening in disability in RRMS trials defined as ≥ 1 EDSS (for either 3 or 6 months)
WBC	white blood cell count*

* Used only in tables and appendices

Executive summary

Background

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) which affects the CNS myelin and axons. It is believed that MS is primarily an inflammatory condition in which autoimmune attack is associated with breakdown of the normal barrier separating blood from the brain.

There are three current approaches to the treatment of MS.

1. ***Prevention of disease progression and relapse rates.*** This is the aim of the disease modifying (or immunomodulatory) drugs. The drugs examined in this report are: azathioprine, beta interferon (IFβ), cladribine, cyclophosphamide, glatiramer, intravenous immunoglobulin, methotrexate and mitoxantrone. Azathioprine is licensed for use in all forms of MS. IFβ-1a and 1b are licensed for use in relapsing–remitting MS and secondary progressive MS, and IFβ-1b is licensed for use in secondary progressive MS. Cladribine, cyclophosphamide, glatiramer, intravenous immunoglobulin, methotrexate and mitoxantrone are not licensed in the UK for use in MS.
2. ***Treatment of acute exacerbations.*** Steroids are the treatment for acute worsening of symptoms or new neurological disturbances that do not spontaneously resolve. Steroids reduce the severity of the exacerbation but do not affect consequent disability.
3. ***Treatment of chronic symptoms*** – such as spasticity by physiotherapy and antispasticity drugs, and fatigue by psychological and physiological treatments, and by neurorehabilitation.

Objectives

The aim of the report is to provide a rapid review of the effectiveness and costs of disease-modifying drugs in MS.

Methods

Methods involved searching electronic databases and bibliographies of related papers for randomised controlled trials (RCTs) and systematic reviews, and contacting experts and pharmaceutical companies for further information. Inclusion and quality criteria were assessed, and data extraction undertaken by one reviewer and checked by a second reviewer, with any discrepancies being resolved through discussion.

Results

Azathioprine

Evidence on the effectiveness of azathioprine comes from a good quality systematic review of the literature, as well as from one good and one poor quality RCT. Results suggest that azathioprine may reduce rates of relapse in patients with relapsing–remitting, relapsing–progressive and progressive MS. However, side-effects are common, particularly gastrointestinal disorders, and may affect compliance. Annual drug costs per patient are estimated to be between £50 and £1200.

Beta interferon

There is evidence from three large RCTs that IFβ-1a (two trials) and IFβ-1b (one trial) have limited benefit in relapsing–remitting and secondary progressive MS, respectively, although all the trials have methodological limitations. Benefits, in terms of reduced relapse rate and severity, are achieved at high cost with the annual cost per patient estimated to be between £10,000 and £20,000. Side-effects are common, particularly flu-like symptoms and injection site reactions.

Cladribine

Evidence on the effectiveness of cladribine comes from two small RCTs, one in chronic progressive MS patients and the other in relapsing–remitting MS patients. Results suggest 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. The annual drug cost per patient is estimated to be £5800–8800.

Cyclophosphamide

The quality of evidence on the effectiveness of cyclophosphamide comes from five RCTs, of variable design and quality, and in which different

types and severity of MS and different treatment regimes are considered. One study in progressive MS suggests that cyclophosphamide combined with adenocorticotrophic hormone may be of some benefit, while another suggests that boosters of cyclophosphamide may slow progression. A wide range of side-effects is reported in all studies. The annual drug cost per patient is estimated to be less than £100.

Glatiramer

Evidence for the effectiveness of glatiramer comes from one systematic review of two RCTs and a paper in which additional outcomes are reported from one of the RCTs included in the systematic review. The results suggest that relapse rate may be reduced by glatiramer treatment but the size of the benefit is not clear. The annual drug cost per patient is estimated to be about £10,000.

Intravenous immunoglobulin

Evidence for the effectiveness of intravenous immunoglobulin comes from three good RCTs. The results suggest that relapse rate may be significantly reduced by intravenous immunoglobulin therapy at 3 years. A wide range of adverse effects is commonly reported. The annual drug cost per patient is estimated to be between £1600 and £10,000.

Methotrexate

Evidence for the effectiveness for methotrexate comes from two RCTs, one for chronic progressive MS and the other including all forms of MS. The results suggest 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. The annual drug cost per patient is £18–58.

Mitoxantrone

Evidence for the effectiveness of mitoxantrone comes from two RCTs in relapsing–remitting MS. Results from both trials suggest that 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 is reported. The annual drug cost per patient is about £3600.

Conclusions

Evidence for the effectiveness of immunomodulatory drugs in MS is problematic because:

- there are few good quality trials for each drug
- trials often have methodological limitations or poor reporting of data
- trials are often of small size and short duration
- there is no consistency in treatment regimes, patient groups and outcome measures
- the clinical significance of reported benefits is not clear.

Recommendations for research

Well-conducted trials using outcome measures with clinical significance for different groups of MS patients and long-term follow-up are needed.

Chapter 1
Introduction

Aim of the review

To provide a rapid review of the effectiveness and cost of different disease-modifying (immunomodulatory) drugs in multiple sclerosis (MS). The drugs included are beta interferon (IFβ), glatiramer, azathioprine, intravenous immunoglobulin (Ig), methotrexate, cladribine, mitoxantrone and cyclophosphamide. From the outset it was not intended to undertake a meta-analysis or cost-effectiveness analysis.

Description of the underlying health problem

Background

MS is a disease of the central nervous system (CNS) which affects CNS myelin and axons. The cause and pathogenesis of MS are unknown. However, it is believed that it is primarily an inflammatory condition in which autoimmune attack is associated with breakdown of the normal barrier separating blood from the brain. This leads to the destruction of myelin sheaths that normally facilitate nerve conduction. The site of inflammatory episodes may be reflected in clinical symptoms, although data from magnetic resonance imaging (MRI) studies suggest that many episodes are asymptomatic. The CNS has a limited capacity to repair areas of demyelination and repeated inflammatory attack often leads to scarring and loss of nerve cells themselves. Scarring and neuronal loss probably underlie many of the chronic symptoms of MS, including limitation of mobility, ataxia, spasticity, pain, cognitive dysfunction and mood disturbance.

MS usually presents with an episode of neurological dysfunction, often attributable to inflammation at a single site within the CNS. Such presentations include visual loss from optic neuritis, isolated numbness, leg weakness and urinary sphincter disturbance from spinal cord disease, or disturbance of coordination and eye movements due to brain-stem inflammation.

Clinically, people with MS tend to experience four types of disease pattern.

1. Relapsing–remitting (RR) MS (or exacerbating–remitting (ER) MS) in which patients have discrete motor, sensory, cerebellar or visual attacks that come on over 1–2 weeks and often resolve over 4–8 weeks, with or without treatment.[1] Some patients accrue disability with each episode or exacerbation while remaining clinically stable between relapses. Others have many years of unrestricted activity punctuated by short-lived disturbances that resolve completely. About 85% of patients initially experience this form of MS; however, within 10 years about 50% develop the secondary progressive form.[2]
2. Secondary progressive (SP) MS. Patients who previously had RRMS experience gradually increasing disability with or without discrete relapses.
3. Progressive (P) MS from the outset with unrelenting advancement of the disease and maximum disability ensuing within months or over several years,[3] not necessarily causing cognitive loss. This form is experienced by approximately 15% of patients.[2] The presence or absence of relapses determines the type, that is, relapsing–progressive (RP) MS or primary progressive.
4. A small proportion of patients have a benign course with minimal disability after 10–15 years.

The terminology used to identify people with different types of MS is not standardised; hence, other terms are used in the individual drug appraisal sections (e.g. RPMS rather than secondary progressive). The different terms used are defined and cross-referenced in the list of abbreviations and definitions.

Current approaches to treatment

There are three current approaches to the treatment of MS.

1. Prevention of disease progression and relapse rates. This is the aim of disease-modifying (or immunomodulatory) drugs; these are considered in this report.
2. Treatment of acute exacerbations. Steroids are the treatment for acute worsening of

symptoms or new neurological disturbances that do not spontaneously resolve. Steroids reduce the severity of the exacerbation but do not affect consequent disability.

3. Treatment of chronic symptoms. For example, spasticity can be treated by physiotherapy and antispasticity drugs, and fatigue by psychological and physiological treatments, and by neurorehabilitation.

Incidence/prevalence

The UK prevalence of MS varies geographically, with higher rates occurring in the north. Surveys in the south of England estimate the age-standardised prevalence as about 1:800 to 1:1000, with twice as many females as males affected.[4] Reasonable figures for estimating district-based patient numbers might be 80–160 per 100,000 population (Professor A Compston, Addenbrooke's Hospital, Cambridge; personal communication, 1999).

The relative proportion of patients suffering from the different types of MS varies with the age of the population, geographical location and length of follow-up. At the onset of disease, most patients will have a relapsing–remitting course; after two or three decades, a large proportion will have converted to progressive disease.

MS is a highly heterogenous condition, with a complex and variable natural history. An important issue for policy makers is how many people fall into each of the subcategories. It is expected that the Trent report on the epidemiology and natural history of MS[5] will supply more information on this when complete. Preliminary indications are that a typical health authority will have approximately the numbers of people shown in *Table 1* within each subcategory of MS, who might be considered for treatment.

Current service for patients with MS

Current treatment for people with MS consists of a broad range of sometimes poorly coordinated elements. These should include treatment of exacerbations and chronic symptoms, and rehabilitation. In a postal survey of 223 patients by the MS Society in 1997,[6] patients were asked to select from a list which practitioners they saw about their MS. The survey reported that some "85% of patients saw a GP, 66% a neurologist and 45% a physiotherapist/occupational therapist". A limited proportion of patients consulted complementary/alternative therapists (15%), MS or neurology specialist nurses (13%), or specialists in rehabilitation medicine (8%). It was rare for patients to be referred to continence advisers, urologists, pain specialists or clinical psychologists (less than 2% per group). It is unclear from the survey whether respondents saw the different practitioners during the previous year, 2 years, or longer. It should be noted that service usage may vary with the severity of a patient's condition.

The only drugs currently licensed to prevent disease progression are IFβ-1a and 1b and azathioprine. Their use is discussed further in chapter 3.

TABLE 1 *Average health authority: estimated number of patients with MS*

Patients per health authority (average population 500,000)	Approximate proportion of patients (%)	Estimated prevalence (0.8–1.6 per 1000)	
		Minimum	Maximum
Total number of patients		400	800
RRMS	45[5]	180	360
Potential relapsing–remitting patients considered for treatment	5–25[a]	9–45	18–90
SPMS	40[5]	160	320
Potential secondary-progressive patients considered for treatment	10–65	16–104	32–208

[a] *Proportions supplied by Dr J Zajicek (personal communication, 1999)*

Chapter 2

Methods used in the rapid review

The *a priori* methods used for the rapid review are outlined in the research protocol (see appendix 1); this was sent for expert comment to members of the advisory group for the review (see Acknowledgements, page 33). Although many helpful comments were received relating to the general content of the research protocol, there were none that identified specific problems with the methods of the review.

Some changes, additions or points of clarification have been made to the methods discussed in the original protocol.

- At the request of the National Institute for Clinical Excellence (NICE) and the Director of the HTA programme, no published or unpublished studies, costings or information on diffusion supplied by the pharmaceutical industry concerning IFβ or glatiramer were included in the rapid review. At the time when this review was in preparation, IFβ and glatiramer were due for appraisal by NICE and the purpose of the request was to clarify the review's place in relation to the planned NICE appraisal. On the same advice, however, information provided by the pharmaceutical industry for the other drugs considered has been included in this review.
- Because of the time constraints of the rapid review, only English language studies have been included in the review.
- In addition to randomised controlled trials (RCTs) being quality assessed using the Jadad scale,[7] systematic reviews are assessed for quality using the criteria developed by the NHS Centre for Reviews and Dissemination[8] (see appendix 2).
- The results from the systematic reviews included are presented in summary form rather than as the results of the separate included studies; it was considered inappropriate to undertake new meta-analyses. Although this is due in part to the time constraints placed on the rapid review, the results from the good quality systematic reviews should provide an adequate summary of the included studies.
- Studies, whether reported as scientific papers, letters or abstracts, are assessed for inclusion using the *a priori* criteria. If there was insufficient information to assess a study for inclusion, it has been excluded from the rapid review. Authors of studies have not been contacted for additional information because of the time restrictions.
- Costs include drug costs only. Costs of administration have been excluded.

Sources of information, including databases searched and key search terms, are outlined in appendix 3.

Studies identified by the search strategy were assessed for inclusion through three stages. Titles and abstracts of studies were screened for inclusion by one reviewer, with decisions checked by a second reviewer. The full text of those studies included at this stage were examined for inclusion by one reviewer and checked by a second reviewer. Data extraction and quality assessment of studies included in the review were undertaken by one reviewer and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion.

Although a cost-effectiveness analysis was not undertaken in the rapid review, other cost-effectiveness studies of the disease-modifying drugs were identified (see appendix 3 for search strategy). These studies were critically appraised using standard criteria for decision analysis and economic evaluations.[9,10] Two reviewers independently assessed and extracted data from included studies, with any differences resolved through discussion. These studies (which are summarised in appendix 15) are discussed for each drug under 'costs' in chapter 4.

Chapter 3

Interventions considered in this review

Azathioprine

Azathioprine is a cytotoxic immunosuppressant drug, which is non-specific in action; the predominant toxic effect is myelosuppression. Azathioprine requires careful monitoring during treatment. Administration is by mouth starting at a low dose, which is built up over a period of 3–4 months to a target dose of 2.5–3 mg/kg daily. Azathioprine was licensed for use in the UK in 1963 and has been used for many years to treat individual patients with MS. It was evaluated in clinical trials during the 1970s and 1980s.[11] Currently it is used for a small number of patients who either have moderate to severe MS or have frequent relapses. According to a standard reference on MS "most clinicians conclude that the clinical benefit of azathioprine falls short of satisfactory treatment for the individual patient".[12]

Side-effects are common and up to 50% of patients are unable to tolerate azathioprine because of nausea and vomiting. Other side-effects include hypersensitivity reactions (such as dizziness, fever, rigors, muscular pains, arrythmias, disturbed liver functions), hair loss, skin rashes and, rarely, pancreatitis and pneumonitis.

Beta interferon

IFβ-1a and IFβ-1b are licensed in the UK for use in people with RRMS who are ambulatory and have had at least two relapses over the previous 2-year period (see *Table 2*). The main contraindications are severe depression, poorly controlled epilepsy and decompensated liver impairment, hypersensitivity to interferons or human serum albumin and pregnancy. Dosage may be up to 44 μg (12 million international units (MIU)) and may be given by either intramuscular or subcutaneous injection. IFβ-1b is also licensed for use in SPMS at a dosage of 8 MIU by subcutaneous injection (see *Table 2*). Side-effects include irritation at the site of injection and influenza-like symptoms. Transient common side-effects include nausea and vomiting, skin rashes, blood disorders, raised liver enzymes, menstrual disorders, mood and personality changes, and, rarely, confusion and convulsions. The development of neutralising antibodies, which may be associated with disbenefits, is a further problem in IFβ usage.

Expert opinion suggests that, excluding patients on clinical trials, approximately 1500 people in the UK are currently prescribed IFβ for MS, representing about 1.5–2.0% of the patient population (Sowemimo M, Multiple Sclerosis Society: personal communication, 1999). The overwhelming majority of these patients have RRMS. Prescribing policies vary greatly between regions. Prescribing in the UK is very low compared with other countries, for example, Finland 15%, Germany 13%, France 12% (Zajicek J, Plymouth: personal communication, 1999).

It has been recommended that a neurologist should initiate treatment for IFβ-1b in RRMS.[13] Frequency of follow-up for patients will vary according to their condition. Recommendations for IFβ-1b[13] are that patients probably require clinic review several times in the first few weeks or months of treatment and subsequently every 6–12 months. However, it appears that practice varies, with some clinicians indicating that patients are seen 1 month after initiation and then at 3-monthly intervals. Additional services may be needed to assess, monitor and support patients, for example, blood counts and biochemical monitoring, including liver function testing (Sowemimo M, Multiple Sclerosis Society: personal communication, 1999).

Only a proportion of patients with either RRMS or SPMS might be considered for treatment with an IFβ. However, potentially all patients with SPMS might be eligible for treatment.[2] The lower proportion of patients with RRMS eligible for IFβ treatment is caused by several factors, namely the frequency of relapses, exclusion of patients with very mild relapses or patients who are unable to walk 100 yards (Kurtzke Expanded Disability Status Scale[20] (EDSS) of 5.5; see appendix 4).

Rebif® (IFβ-1a) has now been licensed for use at the higher dose of 12 MIU.[15] Expert opinion suggests that this dosage is unlikely to be used extensively in the UK and it is therefore not considered in detail in this review. However, this is a rapidly developing field and new results will continue to emerge.

TABLE 2 *Licensed indications, dosage schedules, contra-indications and other criteria for IFβ treatment in RRMS and SPMS*

RRMS	**IFβ-1a**		**IFβ-1b**
	Rebif®[14,15] (Serono Laboratories UK Ltd)	**Avonex®**[16,17] (Biogen Ltd)	**Betaferon®**[18,19] (Schering Health Care Ltd)
Dosage	6 MIU (22 μg)[a] s.c. three times per week	6 MIU (30 μg) i.m. weekly	8 MIU (0.25 mg) s.c. alternate days
Aim of treatment	Slowing of progression Decreasing frequency and severity of relapses	Slowing of progression Decreasing frequency and severity of relapses	Reducing frequency and severity of clinical relapses
Licensed indications	Ambulatory patients with RRMS (≥ 2 relapses over preceding 2 years)	Ambulatory patients with RRMS (≥ 2 relapses over preceding 3 years without evidence of continuous progression between relapses)	Ambulatory patients with RRMS (≥ 2 relapses over preceding 2 years)
Main contraindications	Severe depression (or suicidal thoughts); poorly controlled epilepsy and decompensated liver impairment; hypersensitivity to interferons or human serum albumin and pregnancy		
Duration of treatment	Unknown (clinical experience currently 2 years)	Unknown (clinical experience currently 2 years)	Unknown (efficacy not yet demonstrated beyond 2 years)
Criteria for discontinuation of treatment (according to manufacturer's summary of product characteristics)	Development of SPMS	Development of SPMS	Failure to respond, e.g. steady progression in EDSS for 6 months or treatment with > 3 courses of ACTH or corticosteroids over a 1-year period
SPMS	**IFβ-1b: Betaferon®**[18,19]		
Dosage	8 MIU (0.25 mg) s.c., alternate days		
Aim of treatment	Slowing disease progression and reduction in frequency of clinical relapses		
Licensed indications	SPMS (not studied in patients with mild disease or in those unable to walk)		
Main contraindications	See above for RRMS		
Duration of treatment	Unknown (efficacy not yet demonstrated beyond 2–3 years)		
Criteria for discontinuation of treatment (according to manufacturer's summary of product characteristics)	Failure to respond, e.g. steady progression in EDSS for 6 months or treatment with > 3 courses of ACTH or corticosteroids over a 1-year period		

[a] *Licensed indications have been extended to include doses of 44 μg (12 MIU) as well as 22 μg*[15]

Cladribine

Cladribine is a selective immunosuppressive anti-metabolite that is believed to retard SPMS. Total cumulative doses of 2.1 mg/kg by subcutaneous injection have been used in both RRMS and PMS. Side-effects are rare but herpes zoster has been reported. In spite of the claim that cladribine is safe, toxicity remains a concern, even in those fatal cancers for which it is currently used.

Cladribine is not licensed in the UK for MS.

Cyclophosphamide

Cyclophosphamide is a non-specific immunosuppressant given by mouth or intravenously and works mainly on bone marrow suppression. Recommended doses range from 2 mg/kg to 80–100 mg/kg. Many patients taking cyclophosphamide will suffer with severe alopecia. Other side-effects include leucopenia, transient microscopic haematuria. While taking cyclophosphamide, regular blood tests need to be performed.

Cyclophosphamide is not licensed in the UK for MS. It has been used on an open, uncontrolled basis for many years, especially in continental Europe.[12]

Glatiramer

Glatiramer (previously copolymer 1) is a synthetic copolymer with similarities to myelin basic protein and is administered by daily subcutaneous injection. Its main action is considered to be suppression of the immune response against myelin to promote immune tolerance. The recommended dose is 20 mg/day by subcutaneous injection. Side-effects are mostly mild, the most common being injection site reaction. There may be a transient systemic reaction characterised by flushing, chest tightness, palpitations and dyspnoea.

Glatiramer is not licensed in the UK for MS.

Intravenous immunoglobulin

Intravenous Ig has emerged as an important therapy for various neurological/autoimmune diseases although its mechanisms of action are not completely understood. There are probably various immunomodulatory actions, the most relevant of which are inhibition of complement deposition, neutralisation of cytokines, modulation of Fc-receptor-mediated phagocytosis, and downregulation of auto-antibody production, operating alone or in combination. Because intravenous Ig preparations are derived from a large pool of human donors, they contain IgG antibodies against a wide spectrum of normal human proteins and anti-idiotypic antibodies directed against fragment antigen binding (Fab), the antigen-binding region of these auto-antibodies.

The therapeutic dose of intravenous Ig is set empirically at 2 g/kg but, in practice, may be less. Although some practitioners divide the total dose for infusion into five daily doses of 400 mg/kg, it may be preferable to divide the total dose into two daily doses of 1 g/kg each, provided that the patient does not have underlying conditions such as congestive heart failure, renal insufficiency, or high serum viscosity.[21] In general, adverse reactions to intravenous Ig therapy are usually minor and occur in no more than 10% of patients. Mild-to-moderate headache which responds to non-steroidal anti-inflammatory drugs (NSAIDs) is common. Chills, myalgia or chest discomfort may develop in the first hour of the infusion. Fatigue, fever or nausea may occur after infusion and may last as long as 24 hours.

Intravenous Ig is not licensed in the UK for MS.

Methotrexate

Methotrexate is an immunosuppressant drug. The mechanism of action of methotrexate in MS is not clear but the drug is known to regulate and suppress immune function and fight inflammation. It inhibits the enzyme dihydrofolate reductase, essential for the synthesis of purines and pyrimidines. It is contraindicated if significant renal impairment is present, since it is excreted primarily by the kidney. It is also contraindicated in patients with severe hepatic impairment. Methotrexate is given by mouth, intravenously, intramuscularly, or intrathecally, with a dosage of 7.5–20 mg/week. Methotrexate causes myelosuppression, mucositis and, rarely, pneumonitis.

Methotrexate is a well-known and widely available chemotherapy agent that has been used successfully for many years in the treatment of certain leukaemias, lymphomas and other cancers. It has only recently been evaluated in MS.

Methotrexate is not licensed in the UK for MS.

Mitoxantrone

Mitoxantrone is given intravenously and causes myelosuppression. Dosage is 8 mg/m^2 intravenously monthly or 20 mg intravenously monthly. Mitoxantrone may render patients susceptible to infections. Anaemia and thrombocytopaenia are common and patients should be encouraged to recognise and report symptoms such as lethargy, headaches, nosebleeds and bruising. Blood transfusions are required to

correct these symptoms. The major concern with mitoxantrone is cardiomyopathy, for which the risk increases with repeated dosing. Nausea and vomiting are potential side-effects, as is loss of hair. Mitoxantrone may cause mouth ulcers to varying degrees and maintaining strict oral hygiene is of utmost importance. Medications to prevent these symptoms are given prior to treatment. Mitoxantrone is used in certain forms of cancer where it is well tolerated, apart from causing myelosuppression – the rationale for using it in MS.

Mitoxantrone is not licensed in the UK for MS.

Chapter 4
Findings

Azathioprine

Quantity and quality of research into the use of azathioprine in MS

One systematic review and two RCTs met the inclusion criteria for the review (see *Table 3* and appendix 5).[22–24] The search for trials was restricted to the period since the review (after 1991). No unpublished data were supplied by the pharmaceutical industry.

The quality of the systematic review and the RCTs varied. While the systematic review[22] adequately stated its research question, search strategy,

TABLE 3 *Summary of evidence of efficacy of azathioprine*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
Yudkin, *et al.*, 1991.[22] Systematic review of 7 RCTs (5 double- and 2 single-blind); not ITT. Intervention: azathioprine (2–3 mg/kg/day) (392) vs. placebo or no treatment (401). Patients: RRMS, RPMS and PMS; mean age range at trial entry 34–37 years; mean age at onset of MS 27–32 years; *n* = 793 patients. CRD quality score: 4/6	Difference in mean change in DSS between treated and control groups: year 1 (6 studies): –0.03 (95% CI, –0.18 to 0.12; NS); year 2 (4 studies): –0.22 (95% CI, –0.43 to 0.003; $p < 0.06$); year 3 (3 studies): –0.24 (95% CI, –0.51 to 0.03; $p < 0.09$).	OR of freedom from relapse: year 1 (7 studies): 1.51 (95% CI, 1.12 to 2.03; $p < 0.01$); year 2 (5 studies): 2.04 (95% CI, 1.42 to 2.93; $p < 0.01$); year 3 (3 studies): 1.97 (95% CI, 1.27 to 3.04; $p < 0.01$).	None	Leucopenia, anorexia, diarrhoea and vomiting, abdominal pain and gastrointestinal disturbances, abnormal liver function and skin rashes.
Milanese, *et al.*, 1993.[23] RCT (placebo-controlled, double-blind); not ITT. Intervention: azathioprine orally 2 mg/kg/day (3 years) (19) vs. placebo (21). Patients: RRMS, PMS, RPMS with ≥ 2 relapses in 2 years or ≥ 1 point progression in disability on EDSS; EDSS < 7; no immunosuppressants at 1 year; *n* = 40 patients. Jadad quality score: 4/5	Mean change in EDSS from baseline ('followed' patients): year 1 – azathioprine 0.29 vs. placebo 0.42; year 2 – azathioprine 0.26 vs. placebo 0.84; year 3 – azathioprine 0.27 vs. placebo 1.22 (NS).	RR of relapse (over 3 years): 1.6 (95% CI: 1.07 to 2.49) for placebo over azathioprine.	None	Intractable vomiting, herpes zoster, pancytopenia, macrocytosis, transient mild leucopenia.
Steck, *et al.*, 1990.[24] Open label RCT; not ITT. Intervention: azathioprine orally (2 mg/kg/day) (21) vs. cyclosporine (5 mg/kg/day) (20). Patients: RPMS > 1 year; DSS score 2–6; negative anti-*Borrelia burghdorferi* antibodies; age 20–55 years; intrathecal IgG synthesis and oligoclonal bands; no immunosuppressants at 1 year. *n* = 41 patients. Jadad quality score: 2/5	Mean DSS score: baseline: azathioprine 4.1 vs. cyclosporine 3.5; 1 year: azathioprine 4.1 vs. cyclosporine 3.3 ($p > 0.10$). Mean FS score: baseline: azathioprine 13.1 vs. cyclosporine 12.1; 1 year: azathioprine 12.53 vs. cyclosporine 10.35 ($p > 0.05$).		Mean AI score: baseline: azathioprine 3.2 vs. cyclosporine = 2.5; 1 year: azathioprine 3.7 vs. cyclosporine 2.6 ($p > 0.10$).	Azathioprine: gastrointestinal. Cyclosporine: gastrointestinal, hyper trichosis, headache, gingival hyperplasia, oral herpes.

inclusion criteria and methods for, and results of, synthesis, it lacked sufficient detail and quality assessment of its included studies and there was no intention-to-treat analysis. Of the two RCTs, the double-blind, placebo-controlled trial[23] was of relatively high quality (Jadad scale score 4/5), only lacking an adequate description of withdrawals and drop-outs, and without an intention-to-treat analysis. In contrast, the poorer quality, open RCT[24] (Jadad scale score 2/5) was neither blinded nor discussed the method of randomisation used, as well as lacking an intention-to-treat analysis.

While the systematic review[22] and one RCT[23] examined azathioprine versus placebo or no treatment for RRMS, RPMS and PMS, in the other RCT[24] azathioprine was compared with cyclosporine for RPMS. The primary outcomes assessed in the studies were the Kurtzke disability status scale (DSS) and expanded disability status scale (EDSS),[20] relapse rates, ambulation index (AI) and adverse effects of the interventions.

Assessment of effectiveness of azathioprine in MS

In all three studies[22–24] changes in either the Kurtzke DSS or EDSS were compared. The mean change and difference in mean change in DSS or EDSS between intervention and control groups showed that RRMS, RPMS and PMS patients receiving azathioprine had lower DSS or EDSS scores than those receiving either placebo or no treatment. Although not significant ($p = 0.05$), these differences increased over the period of the studies (up to 3 years) and showed a slower progression in disease severity among all included patients receiving azathioprine compared with a control group. In contrast, RPMS patients on cyclosporine had lower and decreasing mean DSS and Functional Systems (FS) scores (see appendix 4) over 1 year than those patients on azathioprine, although not significantly different.

Two studies showed significantly lower relapse rates among RRMS, PMS and RPMS patients receiving azathioprine than patients receiving placebo following 3 years' treatment. Yudkin and colleagues[22] showed an odds of freedom from relapse of 1.97 at 3 years (95% confidence interval (CI), 1.27 to 3.04, $p < 0.01$) for azathioprine patients compared with the control group, while Milanese and colleagues[23] found a relative risk of relapse among control patients of 1.6 (95% CI, 1.07 to 2.49).

Other measures used included the AI. Steck and colleagues[24] found that the mean AI for RPMS patients receiving azathioprine increased from 3.2 (baseline) to 3.7 after 1 year, while for patients on cyclosporine the AI changed little, from 2.5 to 2.6 over the same period.

Adverse effects of azathioprine include leucopenia, anorexia, diarrhoea and vomiting; abdominal pain and gastrointestinal disturbances, abnormal liver function, skin rashes, herpes zoster, pancytopennia and macrocytosis. In the trial comparing azathioprine to cyclosporine,[24] patients receiving cyclosporine had a higher proportion of adverse effects including gastrointestinal effects, hypertrichosis, headache, gingival hyperplasia and oral herpes.

Costs and cost-effectiveness of the use of azathioprine in MS

Drug costs are shown in *Table 4*. For full details see appendix 14.

No cost-effectiveness studies were identified for azathioprine.

Summary of the use of azathioprine in MS

- The effects of azathioprine compared with placebo have been considered by one systematic review (of seven RCTs) and one subsequent RCT and open label RCT (874 patients).
- All studies report non-significant delays in progression. The placebo-controlled studies report a reduction in relapse rate by one-third or more.
- Azathioprine has unpleasant side-effects, with around 11% of patients suffering intolerable vomiting.
- Non-proprietary azathioprine costs up to £300 per patient per year.

Beta interferon-1a and -1b in the treatment of RRMS

Quantity and quality of research into the use of IFβ-1a and IFβ-1b in RRMS

The three large RCTs of IFβ-1a and IFβ-1b in RRMS are summarised in *Table 5*.[25–29] Full details of the individual trials and comments on trial design are shown in appendix 6. Results in the table and subsequently are only presented for those dosages that are currently licensed. For the reasons explained in chapter 2, no unpublished data supplied by the pharmaceutical industry about the effectiveness of IFβ in MS have been included.

The trials are not directly comparable because of differences in end-points (both type and

TABLE 4 *Costs of azathioprine*

Azathioprine	Dose	Annual drug cost per patient (£)
Non-proprietary	1–3 mg/kg orally, daily (minimum 50 mg daily for 50 kg person; maximum 250 mg daily for 83 kg person)	58.55–292.73
Imuran® (Glaxo-Wellcome UK Ltd)		239.49–1197.38

TABLE 5 *Summary of the main evidence of efficacy of IFβ-1a and IFβ-1b in RRMS (data for subgroups have been presented when data for entire study were unavailable)*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
IFβ-1a PRISMS, 1998[25] (results for 6 MIU dose only). RCT, 2 years. Intervention: 6 MIU (22 µg) IFβ-1a or 12 MIU s.c.; 3 times weekly. Weekly dose: 18 MIU (66 µg) IFβ-1a vs. placebo. Placebo, *n* = 187; IFβ-1a (6 MIU), *n* = 189; IFβ-1a (12 MIU), *n* = 184. *n* = 560. Patients: RRMS. Mean EDSS at entry 2.5 (SD 1.2) Mean relapses 1.5 per year. No corticosteroids or interferon prior to study entry or immunosuppressants in preceding year. Jadad quality score: 5/5	Time to sustained progression of disability (1 EDSS) for quartile (25% of patients): placebo vs. IFβ-1a, 11.9 vs. 18.5 months ($p < 0.05$). EDSS mean changes (SD): 0.48 (1.3) placebo; 0.23 (1.3) IFβ-1a ($p \leq 0.05$). Difference from placebo: –0.25 (95% CI, –0.50 to 0).	For duration of study (1094 patient-years) mean relapses per patient: 2.56 placebo; 1.82 IFβ-1a ($p < 0.005$). Proportion of relapse-free patients over study: 16% placebo; 27% IFβ-1a ($p \leq 0.05$). Median time to first exacerbation: delayed by 3 months for IFβ-1a compared with placebo (significance level not stated). Mean number of moderate or severe relapses: 0.99 placebo and 0.71 IFβ-1a ($p < 0.005$) (NRS).		Main side-effects are influenza-like symptoms. Injection site reaction for IFβ-1a approx. 39–40% (approx. 95% CI, 30–49) more than placebo ($p \leq 0.05$).
IFβ-1a, Jacobs, *et al*., 1996.[26,27] RCT, up to 4 years follow-up. Intervention: 6 MIU (30 µg) i.m. IFβ-1a weekly vs. placebo. Placebo, *n* = 143; IFβ-1a (6 MIU), *n* = 158. Patients: RRMS. EDSS mean 2.3 (SD 0.8), median 2.0, range 1.0–3.7; mean relapses 1.2 (SD 0.6) per year, median 1.0, range 0.67–3.7. No corticosteroids, immunosuppressants or interferon prior to study entry. *n* = 301. Jadad quality score: 4/5	Time to progression of disability (1 EDSS) longer in IFβ-1a than in placebo group (Kaplan–Meier failure time, $p = 0.02$). Estimated proportion with progression of disability by 2 years: placebo 35% vs. IFβ-1a 22% (significance level not stated). Changes in EDSS from baseline not stated for entire study. Sustained changes for ≥ 2 year treatment subgroup: mean change: placebo 0.61 vs. IFβ-1b 0.02 (significance level not stated). Sustained EDSS changes from baseline greater for placebo than IFβ-1a ($p = 0.02$).	Relapse rate: placebo 0.82 vs. IFβ-1a 0.67 (per patient year) ($p = 0.04$) Proportion of exacerbation free patients: not stated for entire study. For ≥ 2 year treatment subgroup: placebo 26% (*n* = 23) vs. IFβ-1a 38% (*n* = 32). Median time to first relapse: placebo 36.1 weeks vs. IFβ-1a 47.3 weeks (NS).		Influenza-like symptoms occurred in up to 40% of placebo group and up to 61% of the treatment group (lasting a median of 7 days; $p < 0.01$).

continued

TABLE 5 contd *Summary of the main RCTs of IFβ-1a and IFβ-1b in RRMS (data for subgroups have been presented when data for entire study were unavailable)*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
IFβ-1b trial[28,29] (results for 8 MIU dose only). RCT; 2 years with 5.5 year extension. Intervention: 8 MIU (currently licensed dose) or 1.6 MIU IFβ-1b s.c. vs. placebo; alternate days. Weekly dose, 28 MIU IFβ-1b. Patients: RRMS. Mean EDSS 2.9, range 0–5.5; annual relapse rate 1.7–1.8. No previous immunosuppressants or corticosteroids. Placebo, *n* = 123; IFβ-1b (1.6 MIU), *n* = 125; IFβ-1b (8 MIU), *n* = 124. *n* = 372. Jadad quality score: 4/5	For entire study: median time (years) to progression of disability (1 EDSS): placebo 4.18 vs. 4.79 IFβ-1b (not significant, $p = 0.096$). with confirmed progression (not clear whether for entire study): placebo 46% (*n* = 56) vs. IFβ-1b 35% (*n* = 43). Changes in EDSS from baseline: NS at 2 years (not stated for entire study).	Annual relapse rate: placebo 1.12 vs. IFβ-1b 0.78 ($p = 0.0006$). Proportion of exacerbation free patients: NS after 2 years but for 2-year data 18–22% exacerbations unconfirmed. Not statistically significant if analysis restricted to confirmed exacerbations.[31] Median time to first exacerbation: not stated for entire study; at 2 years placebo 153 days vs. IFβ-1b 295 days ($p = 0.015$). Exacerbation severity (NRS) – subgroup analysis: annual exacerbation rates for moderate and severe exacerbations not stated but placebo > IFβ-1b ($p = 0.012$).		Influenza-like symptoms: up to 52% patients initially, fell to 3–8% in year 5 for IFβ-1b ($p = 0.05$). Injection site reactions (up to 80% of patients, $p = 0.05$).

definition), patient characteristics (including severity and duration of MS, and length of follow-up), and drug doses and administration. Additional results[30] from *post hoc* subgroup analyses of the trial by Jacobs and colleagues[26,27] were excluded since these were likely to yield spurious results through chance alone.

IFβ-1a trial – PRISMS, 1998[25]

The primary outcome in this trial was mean relapses per patient. This was significantly lower in both IFβ-1a treatment groups. Mean relapses per patient (for the 1094 patient-years of observation available) were 2.56 and 1.82 for placebo and 6 MIU IFβ-1a, respectively ($p < 0.005$). These equate to mean annual relapse rates of approximately 1.31 and 0.93.[a] The proportion of relapse-free patients (over 2 years) was greater in the treatment group (i.e. 16% and 27% for placebo and IFβ-1a; $p \leq 0.05$). The mean EDSS differences from placebo were not statistically significant since the 95% CIs included zero.

While those running this trial took care to avoid some of the methodological problems seen with the other trials of IFβ in RRMS, there are still some causes for concern, particularly about blinding of subjects to treatment allocation. Patients may have guessed their treatment group on the basis of the adverse effects that were listed on the consent form. Such adverse events were commoner in the treatment groups than placebo. Potential unblinding could affect the results because of the subjective nature of the outcome measures and there was no comment about training in EDSS assessment or measurement of inter- and intra-rater reliability. However, the two dose regimes may have helped to maintain blinding. The paper states that baseline characteristics were comparable between the treatment groups. However, the proportion of females varied slightly between the three groups and the median duration of MS was greater in both treatment arms. The impact of these differences on treatment efficacy is unclear.

[a] Calculated as mean relapse rate per patient divided by average duration of study participation (i.e. patient-years observed (1094) divided by total number of patients (560) = 1.95 years).

IFβ-1a trial – Jacobs and colleagues, 1996[26,27,30]

The primary outcome in this trial was time to onset of sustained worsening in disability. This was significantly greater in the IFβ-1a group than in the placebo group ($p = 0.02$). The estimated proportion with progression of disability by 2 years was 35% for placebo patients and 22% for IFβ-1a patients. The paper gives neither the raw data from which these results were calculated nor a test of the significance of the difference. In the subsequent paper,[30] the authors reanalysed the data using time to sustained disability progression of at least two EDSS points (i.e. a clinically more robust measure). The estimated proportions of patients progressing by this degree in 2 years were 18.3% and 6.1% for placebo and IFβ-1a patients, respectively ($p = 0.028$). Mean sustained EDSS changes from baseline were not reported for the entire study.

This trial had many methodological limitations. For example, it stopped early, did not account for all patients and concentrated on a subgroup of patients (i.e. not intention-to-treat analysis). Blinding could have been ineffective with patients possibly guessing their treatment group on the basis of the influenza-like symptoms that were commoner in the treatment group. In addition, trial patients did not self-inject, making generalisation of the results to the UK questionable.

IFβ-1b trial – 1995[28,29]

The primary end-points in this trial were exacerbation rate and proportion of exacerbation-free patients. During the first 2 years the annual exacerbation rates were 1.27 and 0.84 in the placebo and IFβ-1b groups, respectively, but with only 78% and 82%, respectively, of exacerbations confirmed by neurologists. This result was statistically significant ($p = 0.0001$). The numbers of exacerbation-free patients were 18 (16%) in the placebo group and 36 (31%) in the IFβ-1b group ($p = 0.007$).

This trial had a number of important methodological limitations. For example, not all patients were accounted for; there was no true intention-to-treat analysis and the results were presented inconsistently, making interpretation difficult. In addition, blinding was potentially ineffective because of the presence of side-effects.

Assessment of effectiveness of IFβ-1a and IFβ-1b in RRMS

The PRISMS study[25] apparently had fewer methodological limitations than either of the other two trials. The numbers-needed-to-treat (NNTs) to obtain clinical benefits are shown in *Table 6* with their associated 95% CIs.

Costs and cost-effectiveness of the use of IFβ-1a and IFβ-1b in RRMS

Drug costs are shown in *Table 7*; for details, see appendix 14.

Three cost utility studies of IFβ-1a and IFβ-1b in RRMS were found.[33–35] In each study the sources used for utilities and cost data are described and are credible, and sensitivity analyses were conducted. There are no studies in which the costs and benefits are fully compared with all alternative healthcare strategies. Estimates of costs and outcomes are related to the baseline risk in the treatment population only in the study by Parkin and colleagues of IFβ-1b.[35]

Annual costs per patient are reported as $17,000 in the study for the Canadian Coordinating Office for Health Technology Assessment,[35] as £9500 by Nicolson and Milne,[34] and £10,500 by Parkin

TABLE 6 *NNTs (using standard doses) to achieve benefits at 2 years in RRMS*

	Calculated from:	IFβ-1a		IFβ-1b
		Rebif® [25]	Avonex® [27]	Betaferon® [28,29]
NNT to have one patient relapse-free (95% CI)	Proportion of patients who were relapse-free	9 (5 to 36)	8[a] (4 to ∞)	7 (4 to 23)
NNT to prevent one patient from progressing – EDSS increase ≥ 1.0 (95% CI)	Proportion of patients who were progression-free	Could not be calculated from data available	8 (4 to 34)	12[b] (5 to ∞)

∞ represents no benefit

[a] *Data not available for entire study; calculated from subgroup of patients on study ≥ 2 years*

[b] *Calculated from 3-year data as 2-year data unavailable; however, still incomplete follow-up of patients*

NNTs calculated by author of this report using Centre for Evidence Based Mental Health clinical calculator[32]

TABLE 7 *Costs for IFβ*

IFβ	Dose (s.c. or i.m.)	Annual drug cost per patient (£)
Rebif®	6 MIU 3 times per week (NB: also now licensed at a higher dose of 12 MIU)	9516 (19,032)
Avonex®	6 MIU once per week	9490
Betaferon®	8 MIU 3.5 times per week	9783

and colleagues.[35] Changes in quality of life are reported as 0.018 quality-adjusted life years (QALYs) per relapse, 0.0112 QALYs per relapse and 0.0417 QALYs per relapse, respectively. Cost per QALY is calculated as $406,000 for relapses and progression avoided in the Canadian study,[33] and as £2,038,400 and £809,000 per relapse avoided by Nicolson and Milne[34] and Parkin and colleagues,[35] respectively. Best estimates for cost/QALY are £94,000 by Nicolson and Milne and £74,500 by Parkin and colleagues.

Summary of the use of IFβ-1a and IFβ-1b in RRMS

- The effects of IFβ-1a in RRMS were examined in two placebo-controlled RCTs (total 861 patients).
- The effects of IFβ-1b in RRMS were examined in one placebo-controlled RCT (372 patients).
- The effects of IFβ-1a on various measures of relapse were statistically significant, suggesting a reduction in the risk of relapse of about one-third.
- The evidence for IFβ-1b is inadequate because of methodological limitations of the trials.
- IFβ-1a and IFβ-1b commonly cause influenza-like symptoms and injections site reactions. Other adverse effects, usually transient, are also seen.
- IFβ-1a and IFβ-1b cost about £10,000 per patient per year. At the newly licensed higher dose, IFβ-1a costs about £19,000 per patient per year.

Beta interferon-1b in SPMS

Quantity and quality of research into the use of IFβ-1b in SPMS

Only one published RCT of IFβ-1b in SPMS was found;[36] this is summarised in *Table 8* and appendix 7. For the reasons explained earlier (chapter 2), no unpublished data supplied by the pharmaceutical industry about the effectiveness of IFβ in MS were included.

The published trial was double-blind and compared placebo with 8 MIU IFβ-1b in 718 patients (n = 358 and 360, respectively). Patients received subcutaneous injections on alternate days and prophylactic paracetamol or NSAIDs were allowed. Treatment and follow-up were planned for just over 3 years but the trial was stopped following a planned interim analysis of the results when all patients had been treated for at least 2 years.

Assessment of effectiveness of IFβ-1b in SPMS

The primary outcome was time to progression. The results were presented for 40% of patients (40% quantile), since in neither group did 50% progress within the study period. Time to progression was significantly delayed by 344 days in the 40% quantile of the IFβ-1b group (p = 0.0008). The time to becoming wheelchair bound was delayed by up to 9 months on IFβ-1b (odds ratio 0.63; 95% CI, 0.46 to 0.85).

The proportions of patients with confirmed progression and becoming wheelchair bound were significantly less for the IFβ-1b groups compared with placebo. The mean change in EDSS from baseline was slightly lower in the IFβ-1b group (0.47 vs. 0.60; p = 0.03). The mean annual relapse rate was also slightly lower for the IFβ-1b group (0.44 vs. 0.64; p = 0.002).

An attempt was made in the RCT to address some of the methodological problems encountered in earlier drug trials in MS. For example, all physicians rating EDSS were trained and assessed at a central reference centre before the start of trial and had annual follow-up sessions. However, despite efforts, blinding may have been ineffective because of the higher incidence of side-effects in IFβ-1b group. For example, injection site reactions occurred in up to 50% of IFβ-1b patients vs. up to 10% in placebo groups.

The NNTs to obtain clinical benefit and their associated 95% CIs are shown in *Table 9*.

Costs and cost-effectiveness of the use of IFβ-1b in SPMS

Drug costs are shown in *Table 10*; for details see appendix 14.

TABLE 8 *Summary of evidence of efficacy of IFβ-1b in SPMS*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
European Study Group on IFβ-1b in SPMS.[36,37] Multicentre in Europe (n = 32). RCT (double-blind, placebo-controlled). Intervention: alternate day s.c. injections: placebo (n = 360) or 8 MIU IFβ-1b (n = 358). Lower dose (4 MIU) for first 2 weeks. Patients: SPMS – age 18–55 years, mean 40.9–41.1 years (SD 7.2); 59–64% female. Mean disease duration (SD): 12.8 (6.6) to 13.4 (7.5) years. Baseline EDSS: 3.0–6.5, mean 5.1–5.2 (SD 1.1). Either ≥ 2 relapses or ≥ 1.0 increase in EDSS in previous 2 years. n = 718. Jadad quality score: 5/5	Change in EDSS from baseline: placebo 0.60 vs. IFβ-1b 0.47 (p = 0.03). Primary outcome – time to progression (for 40% of patients (40% quantile), since median (50%) not achieved by both groups): time to progression significantly delayed in IFβ-1b group, 893 days (95% CI, 726 to 'unable to estimate within study period') vs. placebo, 549 days (95% CI, 463 to 642; p = 0.0008). Time to becoming wheelchair bound delayed up to 9 months in IFβ-1b group: OR 0.63 (95% CI, 0.46 to 0.85). Proportion of patients with confirmed progression: placebo 49.7% vs. IFβ-1b 38.9% (p = 0.0048). Proportion of patients becoming wheelchair bound: placebo 24.6% vs. IFβ-1b 16.7% (p = 0.0277).	Mean annual relapse rate: placebo 0.64 vs. IFβ-1b 0.44 (p = 0.002). Individual annual rates not significantly different by year 3. Median time to first relapse: placebo 403 days vs. IFβ-1b 644 days (p = 0.003). Proportion of patients with moderate or severe relapses: placebo 53.1% vs. IFβ-1b 43.6% (p = 0.0083).		Treated group: influenza-like symptoms, leucopenia, injection site reactions, hypertension, rash, myalgia, hypertonia.

TABLE 9 *NNT (over 2.5 years): IFβ-1b in SPMS*

	Calculated from:	IFβ-1b Betaferon®
NNT to have one patient relapse-free (95% CI)	Proportion of patients who were relapse-free	11 (6 to 66)
NNT to prevent one person from progressing (i.e. EDSS increase ≥ 1.0) (95% CI)	Proportion of patients who were progression-free	9 (6 to 28)
NNT to prevent on person from becoming wheelchair bound (95% CI)	Overall probability of not becoming wheelchair bound	13 (7 to 50)
Point estimates from years 1, 2 & 3	Estimated probability of not becoming wheelchair bound (year 1, year 2, year 3)	17, 13, 9
Calculated by author of report using Centre for Evidence Based Mental Health clinical calculator[32]		

TABLE 10 *Costs for IFβ-1b*

IFβ-1b	Dose	Annual drug cost per patient (£)
Betaferon®	8 MIU 3.5 times per week, s.c. or i.m. injection	9783

Two cost–utility studies of IFβ-1b in SPMS were found.[34,38] The sources used for utilities and cost data are described, are credible and include sensitivity analyses. There is no full economic comparison of all healthcare strategies in either study. Estimates of costs and outcomes are related to the baseline risk in the treatment population in the study by Forbes and colleagues.[38]

Annual costs per patient are reported as £9800 and £9600, respectively. Changes in quality of life are reported as 0.239 QALYs gained by delays to progression[34] and 0.281 QALYs per 9 months of wheelchair dependence avoided.[38] Costs per QALY are estimated at £874,600[34] and £1,024,000,[38] respectively.

Summary of the use of IFβ-1b in SPMS

- One published placebo-controlled RCT (718 patients) has examined the effects of IFβ-1b in SPMS.
- There were statistically significant effects on changes in EDSS, time to wheelchair and other measure of progression. In addition, there were statistically significant effects on measures of relapse.
- IFβ-1b commonly causes influenza-like symptoms and injections site reactions. Other adverse effects, usually transient, are also seen.
- IFβ-1b costs about £10,000 per patient per year.

Cladribine

Quantity and quality of research into the use of cladribine in MS

Two RCTs met the inclusion criteria for the review[39–41] and are summarised in *Table 11* and more fully in appendix 8. One study is a 2-year placebo-controlled, double-blind crossover trial[39,40] and the other is an 18-month placebo-controlled, double-blind trial.[41] No unpublished data were supplied by the pharmaceutical industry.

The studies are of similar quality (Jadad quality score 3/5). However, in the first study[39,40] there are

TABLE 11 *Summary of evidence of efficacy of cladribine*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
Sipe, *et al.*, 1994;[39] Beutler, *et al.*, 1996.[40] RCT, double-blind crossover; not ITT. Intervention: cladribine (2.8 mg/kg in year 1; 1.4 mg/kg in year 2) vs. placebo; both i.v. infusion. Patients: CPMS for > 2 years; *n* = 48. Results for 24 matched pairs, with crossover after 1 year. Jadad quality score: 3/5	Mean paired differences in EDSS (placebo – cladribine): 1.3 (95% CI, 0.6 to 2.0) for year 1; ANOVA F(1,44) = 10.19 for year 2 ($p = 0.0026$). Mean paired differences in SRS (placebo vs. cladribine): –12.5 (95% CI, –16.7 to –8.2) for year 1; ANOVA F(1,44) = 23.46 for year 2 ($p < 0.0001$).	N/A		Cladribine: severe marrow suppression, thrombocytopenia, hepatitis B (1 death), salmonella, mild herpes zoster. Placebo: N/A.
Romaine, *et al.*, 1999.[41] RCT; double-blind, placebo-controlled; ITT. Intervention: cladribine 2.1 mg/kg (*n* = 27) vs. placebo (*n* = 25); s.c. injection. Patients: RRMS for > 1 year; 2 or more relapses in past 2 years, EDSS score of 6.5 or less at entry; *n* = 52. Jadad quality score: 3/5	EDSS baseline: cladribine 3.8, placebo 3.9; 18 months: cladribine 4.2, placebo 4.2 (18-month figures estimated from graph). SRS baseline: cladribine 75.8, placebo 76; 18 months: cladribine 78, placebo 80 (18-month figures estimated from graph).	Exacerbation rate, 7–18 months: cladribine 0.66 per year (95% CI, 0.37 to 1.05); placebo 1.34 per year (95% CI, 0.90 to 1.93).		Cladribine: mild segmental herpes zoster. Placebo: mild segmental herpes zoster.

N/A, not applicable

various methodological limitations. It is not clear how effective blinding is as two patients were replaced early in the study and it is plausible that study personnel may have been aware of their allocation. The high rates of thrombocytopenia may also have indicated active treatment. The cladribine dose in the second year was only half the dose of the first year, so treatment for the second period is not comparable. Five patients who were to receive placebo were given a single dose of cladribine, 0.7 g/kg, in error at the beginning of the phase. Separate analysis showed the response of these patients was no greater than those of other patients and they were retained in the analysis. Drop-outs for the second year are not clearly described and a clinical carry-over effect from cladribine in the first year cannot be ruled out. No intention-to-treat analysis was undertaken.

In the other study,[41] no details are given of the randomisation or the method of blinding used but intention-to-treat analysis was undertaken.

The patient groups differ in the two studies, with one being chronic progressive (CP) MS[39,40] and the other being RRMS.[41] The methods of drug administration also differ, with intravenous infusions being used in one study[39,40] and subcutaneous injections in the other.[41]

The patient outcome measures used in both studies are EDSS and Scripps Rating Scale (SRS), and in one study the joint frequency and severity of clinical response as judged by neurological examination was also assessed.

Assessment of effectiveness of cladribine in MS

For the first study,[39,40] patient outcomes were ratings on the EDSS and SRS. The treatment effect is given with point estimates and CIs at 1 year before crossover, with mean paired differences in SRS of –12.5 (95% CI, –16.7 to –8.2) and EDSS of 1.3 (95% CI, 0.6 to 2.0), suggesting that CPMS patients fared better on cladribine than placebo. However, no point estimates or CIs are given for year two. Analysis of variance (ANOVA) based on 2-year crossover results give highly significant treatment effects for EDSS ($F = 10.19$, $p = 0.0026$) and SRS ($F = 23.46$, $p < 0.0001$).

In the study by Romaine and colleagues,[41] comparison of the combined measure of frequency and severity of relapses was undertaken using Mantel's extension of the Mantel–Haenzel procedure (Q_M) and showed a significant reduction in the cladribine group compared with placebo in RRMS patients ($Q_M = 2.30$, $p = 0.021$, for months 7–12; $Q_M = 2.59$, $p = 0.010$, for months 7–18). However, it is difficult to relate this outcome to clinical benefit and there were no significant differences between treatment groups in EDSS and SRS or relapse rate.

Costs and cost-effectiveness of the use of cladribine in MS

Drug costs are shown in *Table 12;* details are given in appendix 14.

No cost-effectiveness studies were identified for cladribine.

Summary of the use of cladribine in MS

- The effects of cladribine compared with placebo have been considered in two RCTs (100 patients).
- One study showed delays in progression but the other did not. Only one study reported the effects of cladribine on relapse rate; this was non-significantly reduced.
- Cladribine is a potentially toxic immunosuppressive agent.
- The annual cost is between about £6000 and £9000 per patient.

Cyclophosphamide

Quantity and quality of research into the use of cyclophosphamide in MS

Five RCTs met the inclusion criteria for the review;[42–46] these are summarised in *Table 13* and in more detail in appendix 9. No unpublished data were supplied by the pharmaceutical industry.

The trials were of variable design and quality. Two[42,46] were of very poor quality (Jadad quality

TABLE 12 *Costs of cladribine*

Cladribine	Dose	Annual drug cost per patient (£)
Leustat® (Janssen-Cilag)	0.7 mg/kg by continuous i.v. infusion at monthly intervals for 4 months (35 mg per month for a 50 kg person; 59.5 mg per month for an 85 kg person)	5833.12–8749.68

TABLE 13 *Summary of evidence of efficacy of cyclophosphamide*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
Hauser, *et al*., 1983.[42] RCT (unblinded); ITT. Intervention groups: 1: synthetic ACTH; *n* = 20. 2: cyclophosphamide, 400–500 mg/d i.v., total dose 80–100 mg/kg; stopped when WBC < 4000/mm^3 + ACTH i.v; *n* = 20. 3: plasma volume exchanged for 5% albumin + ACTH + 'low dose' cyclophosphamide (2 mg/kg), reduced if neutropenia for 8 weeks; *n* = 18. Patients: clinically definite MS, progressive disease; *n* = 8. Jadad quality score: 1/5	Change in EDSS at 12 months: 1: + 0.7 (SE 0.3); 2: –0.5 (SE 0.2); 3: –0.1 (SE 0.3). 2 vs. 1: $p < 0.01$; 2 vs. 3: NS; 1 vs. 3: $0.05 < p < 0.1$	N/A	Changes in AI at 12 months: 1: + 1.3 (SE 0.5); 2: –0.7 (SE 0.4); 3: + 0.2 (SE 0.3). 2 vs. 1: $p < 0.01$; 2 vs. 3: $0.05 < p < 0.1$; 1 vs. 3: $0.05 < p < 0.1$.	1: mild mood changes in 50% resolved with no treatment/mild sedation; transient fluid retention in most patients. 2: complete temporary scalp alopecia in all patients; nausea, transient microscopic haematuria, leucopenia (< 1600/mm). 3: urticaria, localised herpes zoster; thinning of hair in several patients; venous access via subclavian/jugular vein required in some.
Canadian Cooperative Multiple Sclerosis Study Group, 1991.[43] Multicentre RCT; not ITT. Intervention: 1: cyclophosphamide, 1 g i.v., alternate days; stopped when WBC < 4.5 x 10^9/litre or when had received 9 g cyclophosphamide + oral prednisolone; *n* = 55. 2: plasma exchange + oral cyclophosphamide 1.5–2.0 mg/kg/day (adjusted on WBC) for 22 weeks + oral prednisolone, 20 mg, alternate days tapered over 22 weeks; *n* = 57. 3 (control): oral cyclophosphamide placebo daily + prednisolone placebo on alternate days for 22 weeks; sham plasma exchanges weekly; *n* = 56. Patients: CPMS and RRMS; *n* = 168. Jadad quality score: 2/5	Mean change in EDSS at 3 years: cyclophosphamide 0.81 (SE 0.14); plasma exchange 0.69 (SE 0.11); placebo 0.69 (SE 0.10). No statistically significant differences.	N/A	N/A	Cyclophosphamide: death from acute bronchopneumonia, haemorrhagic cystitis, septic, diabetes, herpes zoster, pulmonary embolism (non-fatal), angina, severe alopecia in those receiving > 2 g, amenorrhoea. Plasma exchange: 90% had some adverse effect including vascular collapse, hypertension, diabetes, herpes zoster, depression requiring treatment, angina, severe alopecia, amenorrhoea. Placebo: advanced liver disease (1 died), angina, severe alopecia, amenorrhoea.

continued

TABLE 13 contd *Summary of evidence of efficacy of cyclophosphamide*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
Killian, *et al.,* 1988.[44] RCT, double-blind, crossover; ITT. Intervention: cyclophosphamide, 750 mg/m^2, *n* = 6; vs. placebo, 250 ml of 5% dextrose in water, *n* = 8. Patients: RRMS; *n* = 14. Jadad quality score: 4/5	No significant difference in EDSS (no figures given).	Mean number of relapses: cyclophosphamide 0.5 (SE 0.2) vs. placebo 2.3 (SE 0.6); *p* = 0.06.	No significant difference in AI (no figures given).	Cyclophosphamide: nausea and vomiting after 8–12 hours, well-controlled by anti-emetics, subsided within 24 hours, mild hair thinning, amenorrhoea, urticaria. Placebo: mild nausea.
Likosky, *et al*., 1991.[45] RCT, single blind; not ITT. Intervention: cyclophosphamide, 400–500 mg i.v., 5 days/week till WBC < 2500/mm^3; mean total dosage 69 mg/kg (range 33–201 mg/kg); *n* = 22; vs. folic acid, 1 mg i.v., five times/week for 2 weeks; *n* = 21. Patients: CPMS for 1 or more years; *n* = 41. Jadad quality score: 2/5	Folic acid – cyclophosphamide at 1 year: EDSS = 0.03 (95% CI, –0.60 to 0.65; *p* = 0.94). Folic acid – cyclophosphamide 18 months: EDSS = 0.35 (95% CI, –0.40 to 1.10; *p* = 0.36). Folic acid – cyclophosphamide at 24 months: EDSS = 0.39 (95% CI, 0.45 to 1.23; *p* = 0.37).	N/A	Folic acid–cyclophosphamide at 1 year: AI = –0.05 (95% CI, –0.98 to 0.89). Folic acid–cyclophosphamide at 18 months: AI = 0.65 (95% CI, –0.49 to 1.79). Folic acid–cyclophosphamide at 24 months: AI = 0.85 (95% CI, –0.53 to 2.22)	Cyclophosphamide: temporary hair loss, nausea and vomiting, nausea without vomiting. Folic acid: none stated.
Weiner, *et al*., 1993.[46] RCT, single blind; ITT. Intervention: 1: cyclophosphamide, 125 mg i.v., 4 times/day over 8–18 days till WBC < 4000/mm^3, + ACTH i.v.; no boosters. 2: as 1 + booster cyclophosphamide, 700 mg/m^2 i.v., every 2 months for 2 years. 3: modified cyclophosphamide, 600 mg/m^2, i.v., on days 1, 2, 4, 6, 8 + ACTH i.m. over 14 days (40 units decreasing to 20); no booster. 4: modified cyclophosphamide as 3 + booster, 700 mg/m^2 i.v., every 2 months for 2 years. Patients: PMS; *n* = 256. Jadad quality score: 1/5	Not reported. (results expressed as stabilised/improved for booster vs. no booster; no improvement at 12 months and 18 months; slowing of progression at 24 months, 38% stable/improved with booster vs. 24% no booster, *p* = 0.04).	N/A	Not reported	All experienced complete scalp alopecia; 1/3 experienced nausea; menstrual abnormalities (50% women). Associated with induction were: fever and neutropenia, urinary tract infections, oral ulcers, candidal oesophagitis, gross haematuria, inappropriate antidiuretic hormone. Booster therapy associated with: recurrent urinary tract infections, chronic leukopenia, moderate to severe vomiting, gross haematuria.

N/A, not applicable

score 1/5), one being non-blind and the other single-blind, and neither having adequate description of withdrawals and drop-outs. Two were of poor quality (Jadad quality score 2/5): one had inadequate description of randomisation methods and was not double-blind,[45] and the other had no description of withdrawals and drop-outs.[43] One good quality study by Killian and colleagues[44] (Jadad quality score 4/5) was a small double-blind crossover study; however, only six out of the eight original placebo group crossed over to treatment.

Three trials examined CPMS of differing severity while another considered patients with RRMS and yet another included both types. Treatment regimes varied widely. Three considered the use of cyclophosphamide in conjunction with corticosteroids, using a range of doses, and did not have a comparable control for cyclophosphamide. In one trial cyclophosphamide was compared with folic acid but treatment was of different duration. Only the double-blind crossover study used a placebo control.

The main outcome measures used in the studies were Kurtzke EDSS, AI and FS scale. In two studies, the results were expressed as treatment failure if there was a decline of one point or more in EDSS, with patients categorised as improved, stabilised or worsened. In three studies non-patient outcomes were also reported.

Assessment of effectiveness of cyclophosphamide in MS

Change in EDSS was reported in three trials. Hauser and colleagues[42] found a reduction in EDSS of 0.5 (standard error (SE) 0.2) with cyclophosphamide combined with adrenocorticotrophic hormone (ACTH) at 12 months compared with an increase of 0.7 (SE 0.3) with ACTH alone ($p < 0.01$), which suggests that cyclophosphamide combined with ACTH may be of some benefit in patients with PMS. However, the Canadian Co-operative Multiple Sclerosis Study Group,[43] which included CPMS and RPMS patients, found no statistically significant differences in mean change in EDSS at 3 years, results being 0.81 (SE 0.14) in the cyclophosphamide group, 0.69 (SE 0.11) in the plasma exchange group, and 0.69 (SE 0.10) in the placebo group. Likosky and colleagues[45] reported no statistically significant differences for mean differences between folic acid and cyclophosphamide at 1 year (0.3; 95% CI, –0.60 to 0.65; $p = 0.94$) or at 2 years (0.39; 95% CI, 0.45 to 1.23; $p = 0.37$) for CPMS patients.

Killian and colleagues[44] reported on the mean number of relapses. The cyclophosphamide group showed a decrease in mean number of relapses (0.5 ± 0.2) compared with placebo (2.3 ± 0.6) in RRMS patients but results did not achieve significance ($p = 0.06$).

Weiner and colleagues[46] reported percentages of PMS patients who were stabilised/improved as measured by EDSS for a booster treatment group compared with a no booster treatment group, which showed no improvement at 12 and 18 months but significant slowing of progression at 24 and 30 months (percentages stable/improved: 24 months, booster 38%, no booster 24%, $p = 0.04$; 30 months, booster 27%, no booster 17%, $p = 0.04$). Actual EDSS values were not reported.

The main adverse effects of cyclophosphamide alone include vomiting, nausea, alopecia, amenorrhoea and urticaria.

Costs and cost-effectiveness of the use of cyclophosphamide in MS

Drug costs are shown in *Table 14*; details are given in appendix 14.

No cost-effectiveness studies were identified for cyclophosphamide.

Summary of the use of cyclophosphamide in MS

- The effects of cyclophosphamide compared with placebo have been considered in five RCTs, with differing control groups (537 patients).
- Delays in progression were reported in two trials but this was not confirmed by the other three. Only one of the trials reported relapse rate as an outcome; there was a fall but it did not reach statistical significance.
- Cyclophosphamide is an immunosuppressant that frequently causes alopecia.
- The annual drug costs are up to about £60.

TABLE 14 *Costs of cyclophosphamide*

Cyclophosphamide	Dose	Annual drug cost per patient
Cyclophosphamide is available as a generic product or as Endoxana® (ASTA Medica Ltd)	Dose information from trials	Doses used in the trials would mean a drug cost per person of between £20 and £64

Glatiramer

Quantity and quality of research into the use of glatiramer in MS

One systematic review,[47] of two RCTs,[48,49] and a paper reporting additional outcomes for one of the RCTs included in the systematic review[50] met the inclusion criteria (see *Table 15*; for additional details see appendix 10). For the reasons explained in chapter 2, no unpublished data supplied by the pharmaceutical industry on the effectiveness of glatiramer in MS were included.

Quality assessment of the systematic review showed it was of a fair standard (CRD score 3/6), lacking details of the search strategy, inclusion and quality criteria. The additional paper from the included RCT indicated that the study was of a fair quality (Jadad quality score of 3/5), lacking adequate description of the methods used for randomisation and double-blinding.

The two trials included in the systematic review and the associated paper examined glatiramer (copolymer 1), 20 mg/day, against placebo for RRMS and ERMS patients. The outcomes assessed in the studies were Kurtzke EDSS, relapse rates or exacerbations, AI, neuropsychological test scores and adverse effects of the interventions.

Assessment of effectiveness of glatiramer in MS

The two included trials examined patients' progression on the Kurtzke EDSS. Johnson and colleagues[48] found that, over 2 years, 24.8% of patients on glatiramer improved by at least one point on EDSS compared with 15.2% of patients on placebo. The proportion of progression-free patients did not differ significantly between the interventions, with 78.4% of glatiramer and 75.4% of placebo patients being progression-free. Bornstein and colleagues[49] showed that the proportion of patients with progression at 2 years was 20% for patients

TABLE 15 *Summary of evidence of efficacy of glatiramer (copolymer 1)*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
Nicholson & Milne, 1996.[47] Systematic review of two RCTs;[48,49] placebo-controlled, double-blind. Intervention: copolymer 1, 20 mg/day, 150 patients, vs. placebo, 149 patients. Patients: RRMS and ERMS; aged 18–45 years; disease duration 1–10 years; ambulatory with EDSS 0–6; ≥ 2 relapses in previous 2 years, onset of first relapse > 1 year; no steroids < 30 days;emotionally stable; *n* = 299. CRD quality score: 3/6	Proportion of patients with improved EDSS by ≥ 1 point: copolymer 1, 24.8%; placebo,15.2%.[48] NNT = 10. Proportion of progression-free patients: copolymer1, 78.4%; placebo, 75.4%; NS.[48] Proportion of patients with progression (2 years): copolymer 1, 20.0%; placebo, 47.8%.[49] NNT = 4.	Mean relapse/ exacerbation rate (2 years): copolymer 1, 1.19; placebo, 1.68; *p* = 0.007.[48] Copolymer 1, 0.6; placebo, 2.7; *p* = not stated.[49] Proportion of relapse/ exacerbation-free patients: copolymer 1, 33.6%; placebo, 27.0%; *p* = 0.098.[48] Copolymer 1, 56%; placebo, 26.0%; *p* = 0.045.[49] Median time to first relapse: copolymer 1, 287 days; placebo, 198 days; *p* = 0.097.[48] Proportion of patients with relapses by category: 0 relapses – copolymer 1, 34%, placebo, 27%; 1– 2 relapses – copolymer 1, 48%, placebo, 44%; ≥ 3 relapses – copolymer 1, 18%, placebo, 29%.[48]	Mean AI: copolymer 1, 0.27 (SD 0.94); placebo, 0.28 (SD 0.93); NS.[48]	Copolymer 1: localised injection site erythema and induration, transient systemic reaction. Placebo: localised injection site erythema and induration, transient systemic reaction.

continued

TABLE 15 contd *Summary of evidence of efficacy of glatiramer (copolymer 1)*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
Weinstein, *et al.*, 1999.[50] (Paper presents additional analysis of data in Johnson, *et al.*, 1995;[48] this is included in systematic review by Nicholson & Milne, 1996.[47]) RCT; placebo-controlled, double-blind, multicentre. Intervention: copolymer 1, 20 mg/day, 125 patients, vs. placebo (mannitol), 126 patients. Patients: RRMS; aged 18–45 years; disease duration 1–10 years; ambulatory with EDSS of 0–5; ≥ 2 relapses in previous 2 years, onset of first relapse > 1 year; no steroids < 30 days; *n* = 251. Jadad quality score: 3/5	None stated	None stated	Neuropsychological test scores: 10/36 spatial recall (i) immediate 0.15 (95% CI, –0.82 to 1.11; $p = 0.77$); (ii) delayed 0.08 (95% CI, –0.35 to 0.50; $p = 0.73$); paced auditory serial addition (i) 3 s –0.32 (95% CI, –1.74 to 1.10; $p = 0.66$) (ii) 2 s 1.17 (95% CI, –0.39 to 2.74; $p = 0.14$); symbol digit modalities –0.52 (95% CI, –2.50 to 1.45; $p = 0.60$); word list generation 0.17 (95% CI, –1.28 to 1.63; $p = 0.81$); Buschke selective reminding (i) consistent long-term retrieval –0.77 (95% CI, –4.36 to 0.81; $p = 0.18$); (ii) delayed recall –0.32 (95% CI, –0.78 to 0.13; $p = 0.16$); (iii) long-term storage –1.17 (95% CI, –3.50 to 1.15; $p = 0.32$).	None stated

receiving glatiramer and 47.8% for patients on placebo.

Mean relapse/exacerbation rates at 2 years were lower among glatiramer than placebo groups in the two RCTs, with Johnson and colleagues[48] finding a significant difference (glatiramer = 1.19; placebo = 1.68; $p < 0.05$). Similarly, the proportion of relapse/exacerbation-free patients was higher among glatiramer than placebo patients, with Bornstein and colleagues[49] showing a significant difference (glatiramer = 56%; placebo = 26%; $p < 0.05$). Median time to first relapse was longer for the glatiramer group (287 days) than for the placebo group (198 days) but not significantly ($p = 0.097$).

Other outcomes reported included the mean AI. Johnson and colleagues[49] found no significant difference between the glatiramer (0.27; SD 0.94) and placebo (0.28; SD 0.93) groups when compared on the mean AI.

Weinstein and colleagues[50] reported neuropsychological test scores for the patient groups included in the RCT by Johnson and colleagues.[48] At baseline, 12 months and 24 months, there were no significant differences between the glatiramer and placebo groups on any aspect of the neuropsychological tests.

Adverse effects of glatiramer included localised injection site erythema and induration (90%) and transient systemic reaction (15%). Among patients receiving placebo, adverse effects were localised injection site erythema and induration (59%) as well as transient systemic reaction (3%).

Costs and cost-effectiveness of the use of glatiramer in MS

Drug costs are shown in *Table 16*; details are given in appendix 14.

One cost–utility study of glatiramer[47] was found (see appendix 14). Utilities and costs were

TABLE 16 *Glatiramer costs*

Glatiramer	Dose	Annual drug cost/patient
Glatiramer	20 mg daily, s.c. injection	£10,000

obtained in an explicit and sensible way from credible sources and sensitivity analyses were performed; however, there was no comparison with other healthcare strategies and the estimates of costs and outcomes were not related to the baseline risk in the treatment population.

Annual cost of treatment was estimated at £10,100 and changes in quality of life as 0.011 QALYs per average relapse. Cost per QALY was about £500,000, with a best estimate of £90,000.

Summary of the use of glatiramer in MS

- The effects of glatiramer compared with placebo have been considered by one systematic review (of 2 RCTs) and one subsequent reanalysis of RCT data.
- The review reports improvements on some measures of progression and significant improvements in relapse. The subsequent reanalysis reports the non-significant effects of glatiramer on a variety of neuropsychological tests.
- The reported side-effects of glatiramer are restricted to localised injection site reactions and transient systemic reactions.
- Glatiramer costs about £10,000 per patient per year.

Intravenous Ig

Quantity and quality of research into the use of intravenous Ig in MS

Three RCTs met the inclusion criteria for the review and are summarised in *Table 17*;[51–54] additional details are given in appendix 11. No unpublished data were supplied by the pharmaceutical industry.

Two studies[51,54] are very good quality placebo-controlled trials (Jadad quality score 5/5). However, there has been considerable debate among neurologists about the degree of blinding in these studies, particularly whether the patients and assessors were truly blinded to the treatment regime (Dr J Zajicek, Plymouth: personal communication, 1999).

The third study[52,53] is a small, reasonable quality, crossover trial (Jadad quality score 3/5). This did not mention the method of randomisation used or give details of blinding. Results for this study are reported in the literature for those patients who completed both treatment periods. The crossover trial design used a 3-month wash-out period but no indication is given of whether this is an adequate time. There may also be problems with drop-outs in this study (rate 32%), with patients only completing the first treatment.

The inclusion criteria for subjects are similar in terms of EDSS score and relapse rate in the previous two years, but the study by Sørensen and colleagues[52,53] includes patients with RPMS as well as RRMS.

Patient outcomes were EDSS/SRS and exacerbation rates. MRI results were also reported in the crossover study. It was initiated to assess the use of frequent gadolinium-enhanced MRI for the evaluation of treatment effect and to detect a difference in the number of new lesions as the primary outcome measure; as such, it was not powered to detect a difference in patient-based outcomes.

Assessment of effectiveness of intravenous Ig in MS

The results for mean change in EDSS score from one trial[54] at 2 years suggest that there was some improvement in clinical disability in the intravenous Ig group compared with further deterioration in the placebo group (i.v. Ig –0.23 (95% CI, –0.43 to 0.03); placebo 0.12 (95% CI, –0.13 to 0.37); $p = 0.008$) for RRMS patients. The other two studies did not produce significant results.

Relapse rate was significantly reduced in the intravenous Ig group compared with placebo, reported as mean annual relapse rate (i.v. Ig 0.52 (95% CI, 0.32 to 0.72); placebo 1.26 (95% CI, 0.75 to 1.77); $p = 0.0037$) and yearly exacerbation rate (i.v. Ig 0.59; placebo 1.61; $p = 0.0006$) in the two studies including RRMS patients.[51,54] The relative risks of relapse can be estimated from the data in these two studies as 0.70 (95% CI, 0.49 to 0.92) and 0.72 (95% CI, 0.54 to 0.97), respectively, which suggests that there may be some benefit from treatment with intravenous Ig in RRMS.

Adverse effects of intravenous Ig included pathological laughing and crying, depression, headache, eczema, urticaria, hepatitis C, oedema, dizziness, arthralgia, paraesthesia, malaise and eosinophilia.

Costs and cost-effectiveness of the use of intravenous Ig in MS

Drug costs are shown in *Table 18;* for details see appendix 14.

No cost-effectiveness studies were identified for intravenous Ig.

TABLE 17 *Summary of evidence of efficacy of intravenous Ig in MS*

Author, year and study details	EDSS/DSS/FS/ SRS	Relapse rates	Other outcomes	Adverse effects
Achiron, *et al*., 1998.[51] RCT; placebo-controlled, double-blind; not ITT. Intervention: i.v. Ig loading dose, 0.4 g/kg/day for 5 days (20 patients) or saline placebo (20 patients); booster, i.v. Ig 0.4 g/kg or placebo once daily every 2 days for 2 years. Patients: RRMS for > 1 year; average yearly relapse rate 0.5– 3.0 during preceding 2 years; EDSS score 0–6; age 18–60 years; *n* = 40. Jadad quality score: 5/5	Mean EDSS: baseline, i.v. Ig 2.9 (SE 0.43); placebo 2.82 (SE 0.37); at 2 years, i.v. Ig 2.6 (SE 0.43); placebo 2.97 (SE 1.47); no significant differences.	Yearly exacerbation rate: i.v. Ig 0.59, placebo 1.61, $p = 0.0006$. RR of relapse (i.v. Ig:placebo) 0.79 (95% CI, 0.49 to 0.92).	Range of psychiatric scores: no significant difference.	i.v. Ig: pathological laughing and crying, depression. Placebo: hypomania, pathological laughing and crying. Both groups: fatigue, headache, rash, fever.
Sørensen, *et al*., 1997.[52,53] RCT; double-blind, crossover; not ITT. Intervention groups: 1: i.v. Ig, 3-month washout, placebo. 2: reverse order. *n* = 25. Ig i.v. infusion, 1.0 g/kg/day or 2 days at 4-weekly intervals for 6 months. Placebo, i.v. infusion of human albumin 2%; identical regime. Patients: RRMS or RPMS; 2 or more relapses in past year and EDSS score 2–7; no previous immunosuppressants; *n* = 25. Jadad quality score: 3/5	EDSS i.v. Ig: start 4.5; end 4.5. EDSS placebo: start 4.1; end 4.4. No significant differences. SRS i.v. Ig: start 72; end 73. SRS placebo: start 75; end 73. No significant differences.	Patients with no relapses: i.v. Ig 11; placebo 6; $p = 0.05$. Total relapses: i.v. Ig 11; placebo 15.	N/A	i.v. Ig: headache, eczema, urticaria, hepatitis C, nausea, oedema, dizziness, arthralgia, paraesthesia, malaise, depression. Placebo: headache, malaise, eczema, fever, dizziness, anaemia.
Fazekas, *et al*., 1997.[54] RCT; double-blind, placebo-controlled; ITT. Intervention: monthly dose i.v. Ig, 0.15–2.0 g/kg for 2 years (*n* = 75) vs. saline placebo (*n* = 73). Patients: RRMS; baseline EDSS 1–6; at least 2 relapses in past 2 years; age 15–64 years; age at onset 10–59 years; stopped immunsuppressants > 3 months before; *n* = 148. Jadad quality score: 5/5	Mean change in EDSS score: i.v. Ig, –0.23 (95% CI, –0.43 to 0.03); placebo, 0.12 (95% CI, –0.13 to 0.37); $p = 0.008$.	Mean annual relapse rate over study period: i.v. Ig 0.52 (95% CI, 0.32 to 0.72); placebo 1.26 (95% CI, 0.75 to 1.77); $p = 0.0037$. RR of relapse (i.v. Ig:placebo) 0.72 (95% CI, 0.54 to 0.97).		i.v. Ig: cutaneous reactions, eosinophilia (in patient on anafranil). Placebo: eosinophilia, hypogastric pain, myocardial infarction, pulmonary embolism, ileus.

N/A, not applicable

TABLE 18 *Intravenous Ig costs*

Intravenous Ig	Dose	Annual drug cost per patient (£)
Sandoglobulin® (Novartis Pharmaceuticals UK Ltd)	(i) 0.15–0.2 g/kg by monthly i.v. infusion for 2 years (min: 7.5 g monthly for 50 kg person; max: 17 g monthly for 85 kg person); or (ii) 1 g/kg i.v. for 2 days every 4 weeks for 24 weeks (min: 50 g per 2-day treatment for 50 kg person; max: 85 g per 2-day treatment for 85 kg person).	(i) 1642.68–3285.36 or (ii) 4608.60–7779.60
Vigam® S (BioProducts Laboratories)	As above.	(i) 1795.56–4189.56 or (ii) 5985.00–10,174.5

Summary of the use of intravenous Ig in MS

- The effects of intravenous Ig compared with placebo have been considered in three RCTs (213 patients).
- Two of the three trials reported no effect on progression, although the third small trial did report an effect. Relapse rate was reduced in all three trials.
- Headache is common with intravenous Ig. Other transient side-effects frequently occur within 24 hours of the infusion.
- Depending on the dose, intravenous Ig costs between £1600 and £10,200 per patient per year.

Methotrexate

Quantity and quality of research into the use of methotrexate in MS

Two RCTs met the inclusion criteria for the review[55,56] and are summarised in *Table 19* and, in more detail, in appendix 12. No unpublished data were supplied by the pharmaceutical industry.

Quality assessment of the studies indicates that one study[56] is of good quality (Jadad quality score 4/5), although lacking adequate description of randomisation methods used, and the other[55] is of poor quality (Jadad quality score 2/5), lacking adequate description of randomisation and blinding methods and with withdrawals and drop-outs not clearly described.

One study[55] included patients with all forms of MS while the other[56] included those with CPMS. Treatment regimes were similar, using 7.5 mg oral methotrexate weekly for 18 months in one study and for 2 years in the other. Patient outcome measures were either treatment failure (in one study) or the number and timing of exacerbations and worsening by one point on EDSS (in the other). Treatment failure was defined as a composite in any of the following ways for at least 2 months:

- worsening of EDSS score (by 1.0 point or more for those with an entry score of 3.0–5.0, or by 0.5 points or more for those with an entry score of 5.5–6.5)
- worsening of AI score of 2–6 by 1 point or more
- worsening of box and block/9-hole peg test (by 20% or more).

Assessment of effectiveness of methotrexate in MS

A significant treatment effect was found in one study[56] using the composite measure of treatment failure (methotrexate 16/31 (51.6%) vs. placebo 24/29 (82.8%), $p = 0.011$; estimated odds ratio of treatment failure on placebo compared with methotrexate 4.5 (95% CI, 1.36 to 14.85)) and for one element (9-hole peg test alone: methotrexate 5/31 (16.1%) vs. placebo 14/29 (48.3%), $p = 0.007$) in CPMS. No statistically significant differences were found on EDSS alone. The other study[55] showed no overall difference in outcome between treatment groups when considering all types of MS. Subgroup analyses were performed but not clearly reported.

Adverse effects of methotrexate included moderate hair thinning, abnormal liver function tests, upper respiratory tract infections, urinary tract infections, nausea, headache, fever, mucocutaneous herpes, sore muscles, backache, indigestion and diarrhoea.

Costs and cost-effectiveness of the use of methotrexate in MS

Drug costs are shown in *Table 20*; for details, see appendix 14.

No cost-effectiveness studies were identified for methotrexate.

Summary of the use of methotrexate in MS

- Two trials have reported a comparison of methotrexate with placebo (104 patients).
- There was a significant beneficial effect from methotrexate when assessed in one trial using a composite measure of treatment failure, although the other trial reported no effect on relapse rates.
- Methotrexate is a widely used immunosuppressant drug, with potentially toxic effects on the liver.
- Non-proprietary methotrexate costs up to about £60 per patient per year.

Mitoxantrone

Quantity and quality of research into the use of mitoxantrone in MS

Two double-blind RCTs (three publications)[57–59] met the inclusion criteria for the review of mitoxantrone (see *Table 21* and, for more detail, appendix 13). No unpublished data were supplied by the pharmaceutical industry.

Quality assessment of the studies indicated that both RCTs were of fair to good quality (Jadad quality scores of 3/5 and 4/5), but lacked adequate description of the methods used for double-blinding.

TABLE 19 *Summary of evidence of efficacy of methotrexate in MS*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
Currier, *et al.*, 1993.[55] RCT; double-blind; not ITT. Intervention: methotrexate, 2.5 mg oral (n = 22) vs. placebo (n = 22); every 12 hours for 3 consecutive doses, weekly for 18 months. Patients: definite MS (including ERMS, CPMS, EPMS and spinal), with worsening of function/ exacerbation in previous year; n = 44. Jadad quality score: 2/5	EDSS subgroup analysis of RRMS patients: 3/9 methotrexate patients worsened by one point vs. 5/11 placebo patients.	Number experiencing exacerbations: methotrexate 8/22 (36%) vs. placebo 9/22 (41%). Difference in mean number of exacerbations in RRMS subgroup, p = 0.05 (no data given).		Methotrexate: moderate hair thinning, abnormal liver function tests (abnormality persisted in 1 patient). Placebo: headaches, abnormal liver function tests.
Goodkin, *et al.*, 1995.[56] RCT; double-blind; ITT. Intervention: (i) methotrexate, 7.5 mg oral (n = 31), or (ii) placebo (n = 29); both weekly for 2 years. Standardised steroid protocol used to treat exacerbations. Patients: clinically definite CPMS; no exacerbation in previous 8 months or > 1 exacerbation in previous 2 years; age 21–60 years; disease duration > 1 year; entry EDSS score 3.0–6.5 inclusive; entry AI score 2.0–6.0 inclusive; no steroids within previous month, or immunosuppressants in previous year, or exposure to lymphoid irradiation; n = 60. Jadad quality score: 4/5	Treatment failure rates using composite outcome: methotrexate 16/31 (51.6%) vs. placebo 24/29 (82.8%); p = 0.011. Estimated OR of treatment failure for placebo vs. methotrexate 4.5 (95% CI,1.36 to 14.85). Treatment failure for EDSS alone: methotrexate 11/31 (35.5%) vs. placebo 15/29 (51.7%); p = 0.205.	N/A	Treatment failure for AI alone: methotrexate 12/31 (38.7%) vs. placebo 11/29 (37.9%); p = 0.951. 9-hole peg test alone: methotrexate 5/31 (16.1%) vs. placebo 14/29 (48.3%); p = 0.007. Box & block test alone: methotrexate 4/31 (12.9%) vs. placebo 10/29 (34.5%); p = 0.068.	Reported to be similarly distributed between treatment groups. Included upper respiratory tract infections, urinary tract infections, nausea, headache, fever, mucocutaneous herpes, sore muscles, backache, indigestion, diarrhoea.

N/A, not applicable

TABLE 20 *Costs of methotrexate*

Methotrexate	Dose	Annual drug cost per patient (£)
Non-proprietary	7.5 mg once-weekly, adjusted according to response; maximum weekly total dose 20 mg, oral	17.80–47.47 maximum 57.27

In the two trials, different treatment regimes were examined in RRMS and SPMS patient groups. In the study reported by Bastianello and colleagues[57] and Millefiorini and colleagues,[58] mitoxantrone versus placebo in RRMS patients was examined, while Edan and colleagues[59] considered the addition of mitoxantrone to methylprednisolone among patients with RRMS and SPMS. The primary outcomes assessed in the studies were the Kurtzke EDSS, relapse rates or exacerbations and adverse effects.

Assessment of effectiveness of mitoxantrone in MS

Patients' progression on the Kurtzke EDSS was examined in both trials. Millefiorini and colleagues[58] found that over 2 years of treatment an additional 18% (95% CI, 5 to 38; p = 0.02) of RRMS patients on placebo progressed one point

TABLE 21 *Summary of evidence of efficacy of mitoxantrone*

Author, year and study details	EDSS/DSS/FS/SRS	Relapse rates	Other outcomes	Adverse effects
Bastianello, *et al*., 1994;[57] Millefiorini, *et al*., 1997.[58] RCT; placebo-controlled, double-blind; ITT. Intervention: mitoxantrone, 8 mg/m^2 (27 patients) vs. placebo (24 patients). Patients: RRMS; aged 18–45 years; disease duration 1–10 years; EDSS 2–5; ≥ 2 exacerbations in previous 2 years; *n* = 51. Jadad quality score: 4/5	Difference in proportion of patients with progression of 1 point on EDSS (placebo: mitoxantrone): years 0–1: 18% (95% CI, 5 to 38; *p* = 0.08); years 1–2: 25% (95% CI, 7 to 43; *p* = 0.01); years 0–2: 18% (95% CI, 5 to 38; *p* = 0.02).	Difference in mean number of exacerbations (placebo: mitoxantrone): years 0–1: 1.02 (95% CI, 0.36 to 1.68; *p* = 0.001); years 1–2: 0.73 (95% CI, 0.18 to 1.28; *p* = 0.005); years 0–2: 1.73 (95% CI, 0.62 to 2.84; *p* = 0.0002). Difference in proportion of exacerbation-free patients: years 0–1: 45% (95% CI, 21 to 69; *p* = 0.003); years 1–2: 36% (95% CI, 11 to 63; *p* = 0.01); years 0–2: 42% (95% CI, 15 to 65; *p* = 0.006).		Nausea, upper respiratory tract infection, urinary tract infection, headache, diarrhoea and transient amenorrhea.
Edan, *et al*., 1997.[59] RCT; double-blind; not ITT. Intervention: mitoxantrone, 20 mg/month i.v., and methylprednisolone, 1 g/month i.v., 21 patients, vs. methylprednisolone, 1 g/month i.v., 21 patients. Patients: RRMS and SPMS; age 18–45 years; disease duration < 10 years; 2 relapses in previous year or progression of 2 points on EDSS for SPMS; EDSS, 6 or less; *n* = 42. Jadad quality score: 3/5	Mean change in EDSS (baseline to 6 months): methylprednisolone and mitoxantrone –1.1 (SD 1.1); methylprednisolone –0.1 (SD 1.1); *p* < 0.05.	Number of relapses (baseline to 6 months): methylprednisolone and mitoxantrone 7; methylprednisolone 31. Annual relapse rate per patient: methylprednisolone and mitoxantrone 0.7; methylprednisolone 3.0; *p* < 0.01. Patients free from exacerbations (baseline to 6 months): methylprednisolone and mitoxantrone 14; methylprednisolone 7; *p* < 0.05.		Methylprednisolone and mitoxantrone: amenorrhoea, alopecia, nausea/vomiting, other digestive events, cutaneous events, asthenia, upper tractus infections, urinary tract infections, other neurological events, tachycardia, menorrhagia, leucopenia, anaemia. Methylprednisolone: digestive, cutaneous events, upper tractus infections, urinary tract infections, tachycardia, hepatitis, headache, anaemia.

on EDSS compared with patients on mitoxantrone. Edan and colleagues[59] showed that RRMS and SPMS patients treated with mitoxantrone and methylprednisolone had a significantly greater improvement in mean EDSS (mean –1.1; SD 1.1) compared with patients receiving methylprednisolone alone (mean –0.1; SD 1.1) after 6 months of treatment ($p < 0.05$).

Relapses and exacerbations were found to be significantly lower among patients receiving mitoxantrone than placebo or other treatment.

Millefiorini and colleagues[58] showed that RRMS patients receiving mitoxantrone had 1.73 (95% CI, 0.62 to 2.84; $p = 0.0002$) fewer exacerbations than patients on placebo during 2 years of treatment. In addition, 42% (95% CI, 15 to 65; $p = 0.006$) more mitoxantrone and methylprednisolone patients were exacerbation-free over the 2 years compared with methylprednisolone alone. Similarly, Edan and colleagues[59] found significantly different mean annual relapse rates per patient of 0.7 for mitoxantrone and methylprednisolone and 3.0 for methylprednisolone alone ($p < 0.01$) over 6 months of treatment. The number of RRMS and SPMS patients free from exacerbations differed significantly between the mitoxantrone and methylprednisolone (14/21 patients) and methylprednisolone groups (7/21) ($p < 0.05$).

Adverse effects of mitoxantrone include nausea, upper respiratory tract infections, urinary tract infections, headache, diarrhoea and transient amenorrhea. When mitoxantrone and methylprednisolone are given adverse effects include amenorrhoea, alopecia, nausea/vomiting, other digestive events, cutaneous events, asthenia, upper tractus infection, urinary tract infections, other neurological events, tachycardia, menorrhagia, leucopenia and anaemia. Patients receiving methylprednisolone alone incurred digestive problems, cutaneous events, upper tractus infections, urinary tract infections, tachycardia, hepatitis, headache and anaemia.

Costs and cost-effectiveness of the use of mitoxantrone in MS

Drug costs are shown in *Table 22*; for details see appendix 14.

No cost-effectiveness studies were identified for mitoxantrone.

Summary of the use of mitoxantrone in MS

- In two trials (93 patients in all), the effects of mitoxantrone were considered; in one trial it was compared with both placebo and in the other the effect of its addition to methylprednisolone was considered.
- Both trials reported significant delays in progression and reductions in relapse rate.
- Mitoxantrone is a cytotoxic agent commonly causing nausea, amenorrhea and alopecia.
- It costs about £3500 per patient per year.

TABLE 22 *Mitoxantrone costs*

Mitoxantrone	Dose	Annual drug cost per patient (£)
Novantrone® (Wyeth Laboratories)	8 mg/m^2 monthly or 20 mg monthly; i.v. infusion	3610.08

Chapter 5

Comments

Principal findings

The main findings of the rapid review of disease-modifying drugs for MS are as follows.

- Azathioprine may reduce relapse rates in patients with RRMS, RPMS and PMS. Unpleasant side-effects, which some patients are unable to tolerate, are common. The annual cost of azathioprine is between £50 and £1200 per patient.
- IFβ-1a and IFβ-1b result in limited benefit in RRMS and SPMS, respectively. There was inadequate evidence of the effect of IFβ-1b on RRMS. Side-effects are common, especially the characteristic influenza-like symptoms. Any benefit from IFβ comes at a high cost – between £10,000 and £20,000 per patient per year.
- Cladribine may be effective in delaying disease progression in CPMS but appears to have limited effect in RRMS. Annual drug costs per patient are between £5800 and £8800.
- Cyclophosphamide when combined with ACTH or when used as a booster may slow the progression of MS. However, cyclophosphamide is associated with a wide range of side-effects. The annual drug cost per patient is under £100.
- Glatiramer appears to reduce relapse rates in RRMS but the size of effect is unclear. The annual cost of glatiramer per patient is about £10,000.
- Intravenous Ig appears to reduce relapse rates among patients with RRMS but with a wide range of side-effects. The annual cost per patient is estimated at between £1600 and £10,000.
- Methotrexate appears to have some limited beneficial effect on patients with CPMS, although this is only evident through a composite measure of treatment failure. The annual drug cost per patient is £18–58.
- Mitoxantrone may benefit patients with RRMS through delayed disability progression and reduced relapse rates, although side-effects are reported. The annual drug cost per patient is about £3600.

Strengths and limitations of the review

This rapid review has certain strengths including the following.

1. The rapid review brings together for the first time the evidence on the effectiveness of a wide range of the disease-modifying drugs for MS, applying consistent methods of critical appraisal and presentation.
2. The review was guided by the principles for undertaking a systematic review.[8] Prior to undertaking the rapid review, the methods for it were set out in a research protocol (see appendix 1), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review.
3. An advisory group has informed the rapid review from its initiation through to the development of the research protocol and completion of the report. Invaluable advice has been provided on defining the research question, as well as comments on the research protocol and on a draft of the report. The advisory group had a representative from a patient group, as well as from academic and clinical neurology, and public health.

The review had certain limitations, specifically as follows.

1. The rapid review includes published studies identified through searching of electronic databases, checking of references from relevant studies and contact with experts. No additional published or unpublished studies were received from the pharmaceutical industry, despite requests for such information being sent to all the companies manufacturing the drugs (with the exception of those companies manufacturing IFβ and glatiramer; submissions from companies manufacturing these drugs were excluded from the review at the request of both NICE and the HTA programme).

2. As set out in the protocol, the focus of the rapid review is chiefly on patient outcomes, such as relapses, disease progression and side-effects. Non-patient outcomes, including MRI, were only to be assessed if such patient outcomes were not presented in the included studies. As all included studies presented patient outcomes, non-patient outcomes were excluded from the report. The exclusion of MRI results could be criticised (and was, by certain members of the Advisory Group) as greatly weakening the value of the review. Critics argued that MRI results provide invaluable information on the effects of treatments on the underlying pathology. There are three points to be made in response.
   - First, if MRI results had been included in the review, it is not clear how they should have been interpreted. They would not be directly comparable with the patient outcomes that are the main focus of the review (and from which patient utilities can in principle be assessed). If MRI results had been included in the review, it would not be possible to understand their importance in terms of patient-based outcomes and, hence, to assess their importance in clinical and policy terms. There appears to be poor correlation of MRI findings with clinical improvement[17,60] and it is not surprising, therefore, that there is disagreement between experts about the usefulness of MRI as a proxy outcome measure. For instance, a recent meta-analysis of the predicted value of MRI in MS concluded: "although disturbance of the blood–brain barrier as shown by gadolinium enhancement in MRI is a predictor of the occurrence of relapses, it is not a strong predictor of the development of cumulative impairment or disability".[61]
   - Second, this was a **rapid** review. To have included MRI results would have greatly increased the workload of the team producing the report and inevitably delayed its completion for the HTA programme.
   - Third, because this restriction was planned from the outset, it is unlikely to have introduced any bias into the review.
3. Because of the time restrictions placed upon the rapid review, no formal meta-analysis was undertaken. Although the primary outcomes reported by the included studies were consistent, the measures used to assess these outcomes varied. As such, the narrative review presents the outcome measures reported in the studies with no additional analysis.
4. Similarly, the constraints on the review meant that no cost-effectiveness analysis was undertaken, although previous cost-effectiveness studies were critically appraised and data extracted. Costs of the different drugs were listed but no additional cost information, such as costs of administration or monitoring, were provided. It should be noted that for some drugs these may be considerable; for example, cyclophosphamide may have inpatient costs for drug administration of between £1000 and £2000 for 8–18 days hospitalisation.
5. The quality of the RCTs was assessed using the Jadad scale.[7] Although the Jadad scale includes key elements by which to assess the quality of RCTs, including randomisation, blinding and withdrawals/drop-outs, it could be criticised for excluding other elements that may cause bias (e.g. not including the level of withdrawals/drop-outs). It has also been pointed out that the Jadad scale "gives more weight to the quality of reporting than to actual methodological quality".[62]

Implications for research

In undertaking the rapid review of disease-modifying drugs for MS, certain implications for research have become evident. These include the following.

1. The included studies used a range of outcome measures, such as the EDSS, DSS, SRS, AI and other derivations or composites of these measures. Although there may be justification for using different outcomes to assess the effect of interventions on patients in different disease states, when there is overlap some consensus should be reached as to the most appropriate measure. This would allow clearer and consistent comparison of interventions. The NHS R&D HTA programme has commissioned a team based at the National Hospital for Neurology and Neurosurgery to undertake a project entitled 'Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome'. This should greatly help future evaluations in this difficult area.
2. The strength of evidence provided by several of the RCTs was limited by small sample sizes, short study and follow-up periods and

methodological problems (including poor randomisation, ineffective blinding and high drop-out rates). Although some limitations are difficult to avoid, particularly effective blinding of some interventions, subsequent RCTs should endeavour to limit the potential for bias.

3. Searching for economic analyses of the different disease-modifying drugs for MS demonstrated that very few good quality studies have been undertaken. Further studies are required to help compare the cost-effectiveness of these drugs.

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Appendix 1

Rapid review methods from the research protocol

Research question

- To undertake a rapid review of the effectiveness, cost and utility of different drugs in modifying the course of MS.
- The systematic review will not undertake a meta-analysis or cost-effectiveness analysis.

Inclusion criteria

Interventions

- Drugs that modify the course of MS, specifically IFβ, glutiramer (copolymer 1), azathioprine, intravenous Ig, methotrexate, cladribine, mitoxantrone, cyclophosphamide, and other new drugs such as peptides.

Participants

- Patients diagnosed with MS who meet the criteria for treatment with disease-modifying drugs.

Study design

- Systematic reviews of RCTs and RCTs comparing different disease-modifying drugs with placebo or other disease-modifying drugs.

Types of outcome measure

- Patient outcomes, including relapses, disease progression and side-effects, will be the primary outcome measures extracted.
- Non-patient outcomes, such as MRI, will be extracted if the study does not include any patient outcomes. When studies do include patient outcomes, non-patient outcomes will not be extracted.

Search strategy

- Electronic databases to be searched include: Cochrane Systematic Reviews Database; Cochrane Controlled Trials Register; NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness and NHS Economic Evaluation Database; MEDLINE (SilverPlatter); PubMed; EMBASE; and National Research Register. These will be searched for the period 1980–July 1999 and the search will be limited to English language studies.

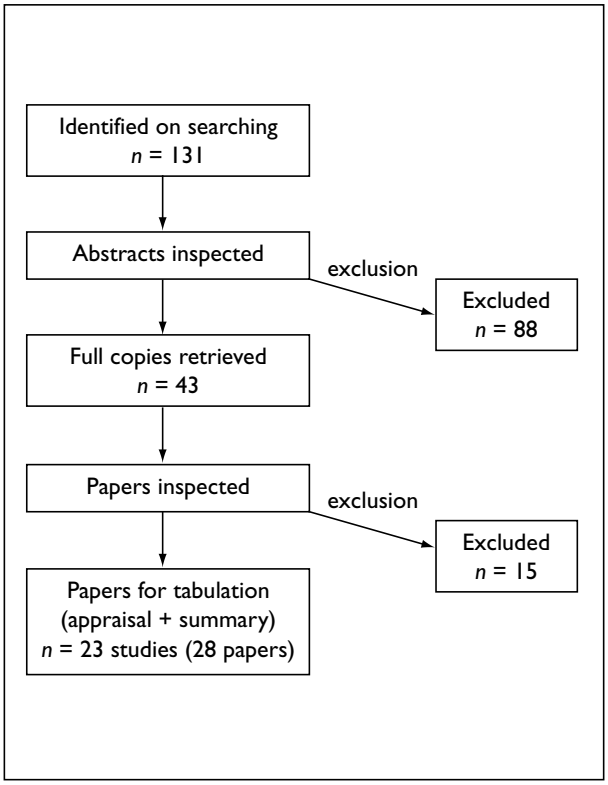

FIGURE 1 *Flowchart for studies included and excluded from the rapid review*

- Bibliographies of related papers will be assessed for relevant studies.
- Pharmaceutical companies and experts associated with MS will be contacted to identify additional published and unpublished references. No information from pharmaceutical companies associated with IFβ or copolymer 1 will be accepted for inclusion in the report.

Figure 1 is a flowchart showing the selection of studies to be included in or excluded from the review.

Quality criteria

- Included studies will be assessed using the critical appraisal criteria outlined in the

Wessex Institute for Health Research and Development Reviews Team Guidelines.
- Studies will be scored using Jadad and colleagues' quality scale.[7]

Review methods

- Narrative review through subgroup analysis based on specific drugs, severity of patients' MS and quality of studies.

Application of review methods

- Inclusion criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.
- Data extraction will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.
- Quality criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Appendix 2

Methods for assessing the quality of systematic reviews and RCTs

Criteria for assessing good quality systematic reviews[8]

Systematic reviews were examined to determine how many of the following criteria for methodological quality they met.

1. ***Does the review answer a well-defined question?***
   A good review should focus on a well-defined question, making the objectives of the review easy to understand. The most important components in a review question include the target population, healthcare intervention and outcomes of interest.

2. ***Was a substantial effort made to search for all the relevant literature?***

3. ***Are the inclusion/exclusion criteria reported and are they appropriate?***
   Criteria for the inclusion of individual studies in a review have two major dimensions: relevance and validity. A relevant study should be useful to answer review questions in terms of patients, intervention and outcomes. The validity issue is related to the methodological standard of an individual study.

4. ***Is the validity of included studies adequately assessed?***

5. ***Is sufficient detail of the individual studies presented?***
   Details of the individual studies included in a review include study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate, effectiveness results and side-effects. The importance of the study details may differ for different review topics.

6. ***Have the primary studies been combined or summarised appropriately?***

If at least four of the above criteria are met, the paper will be considered to be of good quality.

Instrument to measure the likelihood of bias in RCTs (Jadad quality score)[7]

Questions to assess the likelihood of bias

1. Is the study described as randomised (this includes the use of the words such as randomly, random and randomisation)?
2. Is the study described as double-blind?
3. Is there a description of withdrawals and drop-outs?

Scoring the items

Either give a score of 1 point for each 'yes' or 0 points for each 'no' There are no in-between marks.

Give 1 additional point if:

- for question 1, the method to generate the sequence of randomisation is described and it is appropriate (table of random numbers, computer-generated, etc.)

and/or

- if, for question 2, the method of double-blinding is described and it is appropriate (identical placebo, active placebo, dummy, etc.).

Deduct 1 point if:

- for question 1, the method to generate the sequence of randomisation is described and it is inappropriate (patients were allocated alternately or according to date of birth, hospital number, etc.)

and/or

- for question 2, the study is described as double-blind but the method of blinding is inappropriate (e.g. comparison of tablet vs. injection with no double dummy).

Guidelines for assessment

Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allows each study participant to have the same chance of receiving each intervention and the investigators could not predict which

treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

Double-blinding

A study must be regarded as double-blind if the term 'double-blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if, in the absence of such a statement, the use of active placebos, identical placebos, or dummies is mentioned.

Withdrawals and drop-outs

Participants who were included in the study but did not complete the observation period or were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the report of the study. If there is no statement on withdrawals, this item must be given 0 points.

Appendix 3

Sources of information, including databases searched and search terms

Databases searched	Issue or dates
Cochrane Library	1999 issue 2
MEDLINE (SilverPlatter)	1980–July 1999
NHS CRD (University of York): Database of Abstracts of Reviews of Effectiveness	To July 1999
NHS Economic Evaluation Database	To July 1999
PreMed	To July 1999
EMBASE	1980–July 1999
National Research Register	1999 issue 1

Using Mesh terms

Multiple-sclerosis
Publication type = Clinical trial (MEDLINE only)
Publication type = Review or meta-analysis
Interferon-beta
Azathioprine (also RN[†] = 444-86-6)
Copolymer
Copaxone
Glatiramer
Immunoglobulin
Cladribine (also RN = 4291-63-8)
Mitoxantrone (also RN = 65271-80-9)
Cyclophosphamide (also RN = 50-18-0)
Methotrexate (also RN = 59-05-2)

Using text words

multiple sclerosis
multiple?sclerosis
random*
blind*
interferon-beta
azathioprine
immunoglobulin
cladribine
mitoxantrone
cyclophosphamide
methotrexate
cost utility
qaly
utility
quality adjusted life year*
"Quality-Adjusted-Life-Years"
incremental cost effectiveness ratio* or icer

[†] *RN, CAS Registry Number*

Appendix 4

Functional systems and EDSS

Functional systems[20]

Pyramidal functions

0 Normal
1 Abnormal signs without disability
2 Minimal disability
3 Mild or moderate paraparesis or hemiparesis; severe monoparesis
4 Marked paraparesis or hemiparesis; moderate quadriparesis; or monoplegia
5 Paraplegia, hemiplegia, or marked quadriparesis
6 Quadriplegia
V Unknown

Cerebellar functions

0 Normal
1 Abnormal signs without disability
2 Mild ataxia
3 Moderate truncal or limb ataxia
4 Severe ataxia, all limbs
5 Unable to perform coordinated movements due to ataxia
V Unknown
X Is used throughout after each number when weakness (grade 3 or more on pyramidal) interferes with testing

Brain stem functions

0 Normal
1 Signs only
2 Moderate nystagmus or other mild disability
3 Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
4 Marked dysarthria or other marked disability
5 Inability to swallow or speak
V Unknown

Sensory functions (revised 1982)

0 Normal
1 Vibration or figure-writing decrease only, in one or two limbs
2 Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory (c/s figure writing) decrease alone in three or four limbs
3 Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
4 Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
5 Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head; sensation essentially lost below the head
V Unknown

Bowel and bladder functions (revised 1982)

0 Normal
1 Mild urinary hesitancy, urgency, or retention
2 Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence
3 Frequent urinary incontinence
4 In need of almost constant catheterisation
5 Loss of bladder function
6 Loss of bowel and bladder function
V Unknown

Visual (or optic) functions

0 Normal
1 Scotoma with visual acuity (corrected) better than 20/30
2 Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59
3 Worse eye with large scotoma, or moderate decrease in fields but with maximal visual acuity (corrected) of 20/60 to 20/99
4 Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
5 Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
6 Grade 5 plus maximal visual acuity of better eye of 20/60 or less
V Unknown
X Is added to grades 0 to 6 for presence of temporal pallor

Cerebral (or mental) functions

0 Normal
1 Mood alteration only (does not affect DSS score)
2 Mild decrease in mentation
3 Moderate decrease in mentation
4 Marked decrease in mentation (chronic brain syndrome – moderate)
5 Dementia or chronic brain syndrome – severe or incompetent
V Unknown

Other functions

0 None
1 Any other neurologic findings attributed to MS (specify)
V Unknown

EDSS[20]

0 Normal neurologic examination (all grade 0 in FS; Cerebral grade 1 acceptable).
1.0 No disability, minimal signs in one FS (i.e. grade 1 excluding Cerebral grade 1).
1.5 No disability, minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1).
2.0 Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5 Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0 Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.
3.5 Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
4.0 Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 500 metres.
4.5 Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 metres.
5.0 Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (e.g. to work full day without special provisions) (usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0).
5.5 Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities (usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0).
6.0 Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk about 100 metres with or without resting (usual FS equivalents are combinations with more than two FS grade 3+).
6.5 Constant bilateral assistance (canes, crutches or braces) required to walk about 20 metres without resting (usual FS equivalents are combinations with more than two FS grade 3+).
7.0 Unable to walk beyond about 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfer alone; up and about in wheelchair some 12 hours a day (usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone).
7.5 Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair (usual FS equivalents are combinations with more than one FS grade 4+).
8.0 Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms (usual FS equivalents are combinations, generally grade 4+ in several systems).
8.5 Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions (usual FS equivalents are combinations, generally grade 4+ in several systems).
9.0 Helpless bed patient; can communicate and eat (usual FS equivalents are combinations, mostly grade 4+).
9.5 Totally helpless bed patient; unable to communicate effectively or eat/swallow (usual FS equivalents are combinations, almost all grade 4+).
10.0 Death due to MS.

Appendix 5

Summary of trials of azathioprine in MS

Study	Research question	Inclusion criteria	Search strategy
Yudkin, *et al.*, 1991.[22] Overview of azathioprine treatment in MS. CRD quality score: 4/6	To assess the efficacy of azathioprine in MS.	RCTs comparing azathioprine with placebo or no treatment. Azathioprine dosage range 2.0–3.0 mg/kg daily. Patients included those with all forms of MS. Outcome measures were Kurtzke DSS and relapse rate. Outcome assessed after 1, 2 and 3 years of treatment.	Trials identified from: MEDLINE, 1966–89; reference lists of published trials; discussion with other investigators; advertisement of overview in letter to *Lancet*. Keywords not included.

Results

- 10 RCTs identified; 7 included in overview (n = 793).
- 2 studies excluded because of open design, with patients and neurologists being aware of treatment given; 1 excluded because necessary data not available.
- 5 trials were double-blind, 2 single-blind. To avoid bias, results calculated twice, with and without single-blind data.
- 5 trials continued for ≥ 2 years; 3 continued for ≥ 3 years.
- Treatment was randomly allocated and analysis of results was by ITT.
- Results similar across studies and variations discussed.
- Combined results show no difference in increased Kurtzke DSS between treated and untreated groups at 1 year; a small difference at 2 years in favour of azathioprine (–0.22; 95% CI, –0.43 to 0.003); this difference maintained but not increased at 3 years.
- Probability of freedom from relapse significantly greater in azathioprine-treated group (relative odds over 3 years 1.97; 95% CI, 1.27 to 3.04).
- More treated than control patients stopped treatment due to side-effects (diarrhoea, vomiting, anorexia, abdominal pain and other gastrointestinal disturbances).
- χ^2 tests showed no significant evidence of heterogeneity for either outcome measure.

Comments

- Review addressed a clear question in terms of target population, interventions and outcomes.
- Literature search limited to one electronic database only. Reference checking was conducted and experts contacted.
- Inclusion criteria and methods of rejecting studies described.
- Data extraction methods not described in detail.
- Quality criteria not described in detail for each trial.
- Treatment effect in terms of changes in Kurtzke DSS and relative odds of freedom from relapse reported for individual studies and combined for 1, 2 and 3 years. Adverse effects discussed.
- Reviewers concluded that benefits are small and may not outweigh adverse effects.

continued

continued

CRD quality criteria for systematic reviews	
1. Was an appropriate question asked in terms of intervention, patients and outcomes?	Yes
2. Was a search strategy provided?	Yes
3. Were appropriate inclusion discussed?	Yes
4. Were adequate quality criteria used?	No
5. Were sufficient study details provided?	No
6. Was synthesis of evidence appropriate?	Yes
Total score	4/6

Study and design	Intervention	Patients	Outcome measures
Milanese, *et al*., 1993.[23] Italy. RCT; double-blind.	Azathioprine orally, 2 mg/kg/day (rounded) vs. placebo (lactase tablets) for 3 years. Relapses treated with dexamethasone, 8 mg/day i.m. tapered over 2 weeks.	Azathioprine, *n* = 19; controls, *n* = 21. Inclusion: clinically definite MS (McDonald criteria); RRMS, PMS and RPMS included; two or more relapses in 2 preceding years for RRMS, or progression of disability by at least 1 point on EDSS scale for PMS or RPMS; EDSS less than 7; no immunosuppressants in preceding year. Setting: not stated.	Patient outcomes assessed for 3 years of study using EDSS and FS: number of relapses per year; number of patients experiencing relapses during study; progression of disability expressed as mean change in EDSS; number of patients who remained stable; stable defined. Non-patient outcomes: none.

Results

Reported for 'followed' (defined as 'regardless of length of treatment or adherence to protocol'; placebo 19/21, azathioprine 14/19) and 'treated' (according to protocol) groups. Figures below are for 'followed' group. Not analysed by ITT. Lack of actual numbers in outcome categories prohibits performing ITT analysis.

1. Mean annual change in EDSS score: no statistically significant difference.

2. Cumulative proportion of stable patients (0–3 years): cumulative survival graphed. At 3 years, percentage of those followed deteriorated by 1 or more points on EDSS: 82% placebo group vs. 38% of azathioprine ($p = 0.051$).

3. Mean number of relapses/year (for years 1, 2 and 3): azathioprine, entry 0.69 (SD 0.77); year 1 0.58 (SD 0.79); year 2 0.60 (SD 0.91); year 3 0.47 (SD 0.60); vs. placebo, entry 0.50 (SD 0.58); year 1 0.70 (SD 0.80); year 2 0.72 (SD 0.61); year 3 0.78 (SD 0.56). No statistically significant difference.

4. Free from relapses (0–3 years): azathioprine 40% vs. placebo 10% ($p = 0.07$). RR relapse 1.6 (95% CI, 1.065 to 2.49).

Adverse effects Azathioprine group: intractable vomiting 2/19 (11%); herpes zoster 1/19 (5%); pancytopaenia (remitted after drug withdrawn) 1/19 (5%); macrocytosis 5/19 (26%); transient mild leucopenia 4/19 (21%).

Placebo: haemorrhagic cystitis 1/21 (5%).

Comments

- Inclusion criteria defined. Terms such as relapse and stable used in outcomes defined. Interventions described. Randomisation using code numbers supplied by drug company. Comparable placebo used. Assessment of all by blinded neurologist every 3 months. Trial described as double-blind. Laboratory results checked by non-blinded physician. Defined criteria for stopping treatment.
- Treatment groups comparable at baseline with respect to age of onset, disease duration, numbers with different types of MS and EDSS score. Azathioprine group had slightly higher baseline relapse frequency (0.69 vs. 0.50). Both groups treated equally.
- Appropriate patient outcomes used but no evaluation of patient's view.
- Analysis not by ITT. Results based on follow-up of 19/21(90%) placebo and 14/19 (73%) azathioprine group. Drop-out rate: overall 21/40 (53%), azathioprine group 12/19 (63%); placebo 9/21 (43%). Reasons not stated for 7 azathioprine and 6 placebo patients. 13/40 required double-blind regime to be interrupted, reasons not stated. Differences in EDSS score changes analysed using appropriate non-parametric tests (Mann–Whitney U test). Common relative risk estimated using Mantel–Haenzel method. Log rank test used to compare survival curves. Results presented as proportions and survival curves of 'followed' patients. Follow-up period 3 years.
- No prior sample size estimation.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 1 (adequacy of method)
Was the study described as double-blind?	1 + 1 (placebo in identical form)
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Azathioprine 12/19 (63%) dropped out; placebo 9/21 (47%) dropped out.

Study and design	Intervention	Patients	Outcome measures
Steck, *et al.,* 1990.[24] Switzerland. RCT; open.	Cyclosporine, 5 mg/kg/day in drinking solution (blood trough levels monitored and dose adjusted to ensure within range 200–750 mg/ml) vs. azathioprine tablets, 2 mg/kg/day (levels not monitored). Exacerbations treated using steroid protocol.	Cyclosporine: *n* = 20 patients + 1 switched from azathioprine due to side-effects. Azathioprine: *n* = 21 patients. Inclusion: clinically definite MS, active disease with RPMS for > 1 year, Kurtzke score 2–6, negative *b. burgdorferi* antibodies, age 20–55 years, intrathecal IgG synthesis and oligoclonal bands, no immuno suppressants in past year. Setting: not stated.	Patient outcomes measured at 1 year: 1. FS; 2. DSS; 3. AI. Non-patient outcomes: blood tests. Serial immune evaluation.

Results (reported for the 14/21 azathioprine and 17/20 cyclosporine who completed treatment)
1. Serial mean scores for DSS, FS, and AI: no significant difference.

2. Frequencies of concomitant steroid therapy: no significant difference.

3. Total frequency of side-effects: higher in cyclosporine group.

No estimation of size of treatment effect

Adverse effects Cyclosporine: gastrointestinal 2/17 (12%); hypertrichosis 7/17 (41%); headache 5/17 (29%); gingival hyperplasia 2/17 (12%); oral herpes 1/17 (6%). Abnormal laboratory results: creatinine 7; transaminase 1; leucopenia 2; anaemia 5; hyperkalaemia 3.

Azathioprine: gastrointestinal 2/14 (14%). Abnormal laboratory results: γ-glutamyltransferase 2; transaminase 7; leucopenia 4; anaemia 6.

Comments
- Inclusion criteria defined as are outcomes and interventions; no details given of methods used for randomisation. Two active treatments compared; no placebo control group. 31/42 patients randomised (74%) completed treatment; analysis limited to those completing treatment.
- Evaluators not blinded. It is not stated that patients were blinded but since treatments differed (drink vs. tablets), blinding of patients is unlikely.
- No assessment of baseline comparability of those randomised. Patients who completed treatment appear to have been comparable at baseline. Treatment of groups appears to have been similar.
- Outcome included DSS, FS and AI.
- Data analysis details. Wilcoxon rank-sum test used to compare group means. Wilcoxon signed rank test used for paired comparison and χ^2-squared test used to analyse contingency tables. No estimate of size of treatment effect reported. Follow-up was over 1 year of active treatment. Drop-outs are described by treatment group but full reasons not included (see below).
- No mention made of any prior sample size/power calculation.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Cyclosporine drop-outs, 6/20 (30%); azathioprine drop-outs, 6/21 (29%).

Appendix 6

Summary of trials of beta interferon in RRMS

Study and design	Intervention	Patients	Outcome measures
PRISMS (1998).[25] Multicentre in Europe, Canada & Australia (n = 22). Randomised, double-blind, placebo-controlled trial; ITT. Up to 2 years treatment; up to 2 years follow-up (1094 patient-years observed).	Self-injected s.c. injection 3 times weekly: placebo or 6 or 12 MIU IFβ-1a. Dose gradually increased over 4–8 weeks. Prophylactic paracetamol allowed.	Total 560 patients: 1. 22 µg (6 MIU) IFβ-1a (n = 189); 2. 44 µg (12 MIU) IFβ-1a (n = 184); 3. placebo (n = 187). Patients with RRMS: • age, median 34.9 years (IQR 29.1–40.4) • 69% female • EDSS 0–5.0 at entry, mean 2.5 (SD 1.2) • relapses in 2 years prior to entry, mean 3.0 (SD 1.2).	Primary outcome: relapses (severity determined by Scripps NRS or the Activities of Daily Living scale). Secondary outcomes: (1) times to first and second relapses (2) proportion of relapse-free patients (3) progression in disability (4) AI (5) arm-function index (6) steroid therapy (7) hospital admissions (8) psychological status in an English-speaking subgroup (9) IDSS, a summary measure derived from area under time/EDSS curve (10) cranial MRI; analysis excluded from this report as surrogate measures (11) results for subgroup of patients with EDSS (4 not presented here as patient numbers small (only 17% in total). Main analysis between the high dose (12 MIU) and placebo groups.

Results (p-values all refer to comparison of (each) treatment arm against placebo)
Primary outcome (for 1094 patient-years of observation available):

• mean relapses/patient: 2.56, 1.82, 1.73 for placebo, 6 MIU and 12 MIU IFβ-1a, respectively ($p < 0.005$);

• mean number moderate/severe relapses: 0.99, 0.71, 0.62 for placebo, 6 MIU, 12 MIU groups, respectively ($p < 0.005$);

• no difference in duration of relapses (mean 47 days in all treatment groups).[14]

Secondary outcomes:

(1) median time to first relapse delayed by 3 and 5 months in 6 MIU and 12 MIU groups, respectively (significance level not stated);

(2) proportion of relapse-free patients (over 2 years): 16, 27, 32% for placebo, 6 MIU ($p \leq 0.05$), 12 MIU ($p < 0.005$) IFβ-1a, respectively;

(3) progression in disability;

(4) time to sustained progression for first quartile (i.e. first 25% patients) 11.9, 18.5, 21.3 months for placebo, 6 MIU, 12 MIU groups, respectively ($p < 0.05$);

(5) changes in EDSS: mean changes (SD), 0.48 (1.3), 0.23 (1.3), 0.24 (1.1) for placebo, 6 MIU, 12 MIU, respectively ($p \leq 0.05$); differences from placebo, –0.25 (95% CI, –0.50 to 0) for both 6 MIU and 12 MIU groups;

continued

continued

Results (*p*-values all refer to comparison of (each) treatment arm against placebo)

(6) two-step change in AI (for 3 months) 13, 12 (not significant) and 7 ($p \leq 0.05$) for placebo, 6 MIU, 12 MIU, respectively;

(7) arm-function index, no significant changes in any group;

(8) mean number of steroid courses, 1.39, 0.97, 0.75 for placebo, 6 MIU ($p \leq 0.05$), 12 MIU ($p < 0.005$), respectively;

(9) mean number hospital admissions, 0.48, 0.38 (NS), 0.25 ($p < 0.005$) for placebo, 6 MIU, 12 MIU, respectively;

(10) psychological status in subgroup (English speaking), no significant difference between groups;

(11) IDSS, median IDSS for patients who received IFβ-1a stayed at 0, whereas IDSS for placebo group gradually increased 0.4 IDSS steps per year ($p < 0.05$).

Comments

- Computer-generated randomisation, stratified by centre.
- Paper states that baseline characteristics comparable between treatment groups. However, proportion of females varied slightly between the three groups: 75%, 67%, 66% for placebo, 6 MIU, 12 MIU, respectively. In addition, median (IQR) duration of MS was greater in both treatment arms: 4.3 (2.4–8.4), 5.4 (3.0–11.2), 6.4 (2.9–10.3) years for the placebo, 6 MIU, 12 MIU groups, respectively.
- Effect of centre not found to be significant.
- Blinding could have been ineffective, which may have led to measurement bias. Patients may have guessed their treatment group on basis of adverse effects listed on consent form, since these effects were commoner in treatment groups than placebo (see appendix 5). Potential unblinding could affect results due to subjective nature of outcome measures. However, the two dose regimes may have helped to maintain blinding.
- Planned subgroup analysis by exacerbation severity may not be clinically meaningful. Involved arbitrary divisions of NRS score or Activities of Daily Living scale. Subsequently only combined figures for moderate and severe exacerbations presented.
- No comment about training in EDSS assessment or measurement of inter- and intra-rater reliability.
- IDSS attempts to quantify temporary and unremitting disability. However, authors acknowledge that further research is needed to assess IDSS as a surrogate marker of long-term outcomes.

NNT (12 MIU dose of IFβ-1a) over 2 years (Calculated by author of this report using Centre of Evidence Based Mental Health clinical calculator[32])	Rebif®[25] IFβ-1a – 12 MIU
NNT to prevent one patient from relapsing (95% CI) – primary outcome	6 (4 to 13)
NNT to prevent one patient from progressing (EDSS increase ≥ 1.0) (95% CI)	Could not be calculated from data available.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1

Study and design	Intervention	Patients	Outcome measures
Jacobs, *et al.*, 1996.[27] Multicentre in USA (n = 4). RCT; double-blind, placebo-controlled trial, planned ITT. Planned up to 2 years' treatment and up to 4 years' follow-up.	Weekly i.m. injection: placebo or 6 MIU IFβ-1a. Injection by study nurse (for 50% patients) or local health professional. Paracetamol, 650 mg q.i.d., for 24 hours after injection.	Total 301 patients: 6 MIU IFβ-1a (n = 158) vs. placebo (n = 143). ERMS patients: aged 16–55 years (mean 36.8 years, SD 7.4); 73% female. EDSS 1.0–3.5 at entry, mean 2.3 (SD 0.8). Demographic and baseline characteristics comparable between treatment groups.	Primary outcome: time to onset of sustained disability worsening. Secondary outcomes: (1) change in EDSS from baseline; (2) exacerbation rate; (3) upper extremity function (9-hole peg test and box & block test); (4) lower extremity function (AI and timed tandem gait); (5) MS functional disability assessment; (6) comprehensive neuro-psychological battery; (7) self-report measures (including overall emotional status and quality of life); (8) CSF analysis. Cranial MRI: analysis excluded from this report as surrogate measure.

Results (Data for subgroup have been presented when unavailable for entire study)
Primary outcome: time to onset of sustained disability worsening – significantly greater in IFβ-1a than placebo group (based on Kaplan–Meier failure-time curve of cumulative percentage progressing against time; p = 0.02); proportion of patients with probability of sustained disability progression at 104 weeks (for entire study and estimated from Kaplan–Meier analysis), placebo 34.9% vs. IFβ-1a 21.9% (p-value not stated).

Secondary outcomes:

(1) changes in EDSS from baseline – mean change in sustained EDSS from baseline not stated for entire study; for patients on study ≥ 2 years (SE), placebo 0.61 (0.18) vs. IFβ-1a 0.02 (0.14);
distributions of EDSS changes from baseline for patients on study ≥ 2 years, sustained change greater for placebo than IFβ-1a (p = 0.02).

(2) annual exacerbation rates (per patient-year) for entire study, placebo 0.82 vs. IFβ-1a 0.67 (p = 0.04);
time to first exacerbation (Kaplan–Meier estimate of median time), placebo 36.1 weeks vs. IFβ-1a 47.3 weeks (NS).

Results not presented in paper for following secondary outcomes: upper extremity function; lower extremity function; MS functional disability assessment; comprehensive neuropsychological battery; self-report measures (including overall emotional status and quality of life); CSF analysis.

Comments

- Paper describing methods[26] suggested a good trial design; however, trial had following methodological limitations.
- Blinding possibly ineffective, leading to measurement bias because of subjective nature of outcome measures; patients with MS tend to be well-informed and this trial followed the much-publicised IFβ-1b trial with similar side-effects (especially the influenza-like symptoms that were commoner in treatment group).
- No reason given for follow-up and treatment being shorter than originally planned. Subsequently, drug company stated that the NIH's Safety and Monitoring had recommended that trial should cease since there was sufficient evidence of efficacy. There were 172 patients (57%) at 2-year visit and 31 (10%) at 3-year visit.
- A single examining physician measured EDSS for a particular study patient to minimise variability. Examining physicians underwent pre-study training to standardise scoring procedures. Effect of this training on reliability was assessed pre-study[63] but not subsequently.
- Effect of treatment centre not reported.
- ITT analysis cannot be verified by readers from raw data presented. In addition, results concentrated on subgroup of patients who received ≥ 2 years' treatment (thus not an ITT analysis) that accounts for only 87 (67%) placebo and 85 (54%) IFβ-1a patients.

continued

continued

Comments *contd*

- Not all patients entering trial accounted for; unclear if this would have altered statistical significance of outcome measures, e.g. only accounted for 10/23 patients who withdrew from trial. Determination of primary outcome was not possible for eight patients.[30]
- Subgroup analyses involved small patient numbers and interpretation requires caution.
- Severity of exacerbations not described (e.g. by hospitalisations or steroid treatment).
- Trial results may not be generalisable to clinical practice populations because patients did not self-administer injections. If patients had self-injected, compliance may have been lower than in trial. However, current UK practice is for patients or their carers to administer majority of injections.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1

Study and design	Intervention	Patients	Outcome measures
IFNB Multiple Sclerosis Study Group (1993).[28] Multicentre, USA & Canada (*n* = 11). Randomised, double-blind, placebo-controlled trial. Initially 2 years' treatment.	Self-injected s.c.: placebo or 1.6 MIU or 8 MIU on alternate days.	Total 372 patients: 1. 1.6 MIU IFβ-1b (*n* = 125) 2. 8 MIU IFβ-1b (*n* = 124) 3. Placebo (*n* = 123) ERMS patients: aged 18–50 years (mean 35.5 years); 70% female. EDSS 0–5.5 at entry, mean 2.9. Ambulatory. Demographic and baseline characteristics comparable between three groups.	Primary outcomes: (1) annual exacerbation rate (2) proportion of exacerbation-free patients. Secondary outcomes: (1) time to first exacerbation (days) (2) exacerbation duration and severity (3) change in EDSS & NRS from baseline (4) quantitative lesion burden (by annual cranial MRI) and disease activity by MRI in substudy (frequently scanned); (5) analysis excluded from this report as surrogate clinical measures.

Results Unless otherwise stated, 2-year data are presented (only includes results for 338/372 total patients).
Primary outcomes:
(1) exacerbation rate (number/year): placebo, 1.27; 1.6 MIU IFβ-1b, 1.17; 8 MIU IFβ-1b, 0.84; placebo vs. 1.6 MIU, $p = 0.01$; 8 MIU vs. placebo, $p = 0.0001$; 8 MIU vs. 1.6 MIU, $p < 0.01$;
(2) exacerbation-free patients, placebo 18 (16%); 1.6 MIU 23 (21%); 8 MIU 36 (31%); 8 MIU vs. placebo, $p = 0.007$; (placebo vs. 1.6 MIU not stated); 8 vs. 1.6 MIU, $p = 0.076$ (NS); however, after 3 years, 8 MIU vs. placebo no longer statistically significant.

Secondary outcomes:
(1) median time to first exacerbation (days): placebo 153; 1.6 MIU 180; 8 MIU 295; 8 MIU vs. placebo, $p = 0.015$; (8 vs. 1.6 MIU, $p < 0.05$);
(2) exacerbation duration and severity: annual exacerbation rate:
- mild exacerbations, placebo 0.54, 1.6 MIU 0.62, 8 MIU 0.45 (significance level not stated);
- moderate and severe exacerbations, placebo 0.28, 1.6 MIU 0.32, 8 MIU 0.15; 8 MIU vs. placebo, $p = 0.002$;
- no evidence for effect on duration of exacerbations;[18]
- mean change in EDSS and NRS from baseline: no significant change in any treatment group in any of 3 years studied; at 3 years, progression-free patients, placebo 72%, 1.6 MIU 72%, 8 MIU 80% ($p = 0.161$).

Additionally, number of hospitalisations during 3 years: placebo 65, 8 MIU 37, $p = 0.046$; number of patients hospitalised: placebo 33, 8 MIU 21, $p = 0.05$; number of hospital stays, placebo 471, 8 MIU 344, $p = 0.023$.

Comments
This trial had many methodological limitations.
- Method of randomisation not described.
- Possible effects of treatment centre not reported.
- Some patients who entered trial unaccounted for; reasons for withdrawal from trial are unclear, e.g. of the 65 patient withdrawals before 2 years, at least 24 were unexplained; no explanation of discrepancies in data for the 2- and 3-year analyses (2-year exacerbation rate data for 338 patients, whereas 3-year results for all 372 patients) – unclear whether this would have altered statistical significance of outcome measures.
- Analysis not on an ITT basis despite statement in original paper.
- Blinding may have been ineffective, as in IFβ-1a trial, which could have resulted in measurement bias; the treating (but not examining) neurologist was aware of drug's side-effects and patients may have guessed their treatment based on knowledge of side-effects; however, the two dose regimes may have helped to maintain blinding.
- Presentation of results inconsistent and included different time-scales which makes interpretation difficult; exacerbation rates only included severity for 2-year data; duration of exacerbations (a secondary outcome for study) not reported; numbers of hospitalisations and disability information only for 3-year data.
- Planned subgroup analysis by exacerbation severity involved arbitrary divisions of NRS score (mild 0–7, moderate 8–14, severe > 15); however, subsequently researchers only presented combined figures for moderate and severe exacerbations; this subgroup analysis may not be clinically meaningful.
- No explanation of difference between hospitalisations and hospital stays. Either the evaluating neurologist or the unblinded treating neurologist could decide to hospitalise the patient;[64] hence, interpretation of statistically significant differences between 8 MIU IFβ-1b and placebo groups requires caution.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1

Study and design	Intervention	Patients	Outcome measures
IFNB Multiple Sclerosis Study Group and University of British Columbia MS/MRI Analysis Group (1995).[29] Continuation of previous trial up to 5.5 years of treatment (initially 2 years of treatment). Multicentre, USA and Canada (*n* = 11). Randomised, double-blind, placebo-controlled trial.	As linked study, i.e. self-injected s.c.: placebo or 1.6 MIU or 8 MIU on alternate days.	As linked study, i.e. total 372 patients; 1. 1.6 MIU IFβ-1b (*n* = 125) 2. 8 MIU IFβ-1b (*n* = 124) 3. Placebo (*n* = 123). ERMS patients: aged 18–50 years (mean 35.5 years); 70% female. EDSS patients: 0–5.5 at entry, mean 2.9. Ambulatory. Demographic and baseline characteristics comparable between three groups. Median time on study similar for all three groups (45–48 months).	Primary outcomes: (1) time to worsening ≥ 1 EDSS point; (2) mean change in confirmed EDSS from baseline. Secondary outcomes: (1) annual exacerbation rates; (2) proportion of exacerbation-free patients; (3) severity of exacerbations (by NRS score); (4) activity and lesion burden (by annual cranial MRI) (analysis excluded from this report as surrogate clinical measure). Primary and secondary outcomes were reversed between original study and extension study.

Results Data for entire study presented unless otherwise stated.

Primary outcomes:

(1) time (years) to worsening disability: placebo 4.18, 1.6 MIU 3.49, 8 MIU 4.79:
  – 8 MIU vs. placebo, $p = 0.096$, i.e. NS;
  – proportion of patients with disability progression: placebo 46%, 1.6 MIU 47%, 8 MIU 35% (NS);

(2) mean change in confirmed EDSS from baseline: not stated.

Secondary outcomes:

(1) annual exacerbation rates (pooled) (number/year):
  – placebo 1.12; 1.6 MIU 0.96; 8 MIU 0.78; placebo vs. 1.6 MIU, $p = 0.0057$; 8 MIU vs. placebo, $p = 0.0006$; 8 MIU vs. 1.6 MIU, NS;
  – exacerbation rates each year: 8 MIU vs. placebo not statistically significant after year 2;

(2) proportion of exacerbation-free patients: not stated;

(3) exacerbation duration and severity:
  – moderate and severe exacerbations (annual rates), 8 MIU vs. placebo, $p = 0.012$; 1.6 MIU vs. placebo, $p = 0.023$;
  – actual rates not stated;
  – duration of exacerbations not stated.

Comparison of patients who completed study and those who dropped out: annual exacerbation rates – placebo patients who completed trial had lower exacerbation rates than those who dropped out (0.98 vs. 1.6, $p = 0.006$).

Except for this, annual exacerbation rates and median annual change in EDSS were not significantly different for comparisons of completers and drop-outs within 'treatment' groups.

Comments

- Paper failed to account for all patients who entered trial and did not specify number of patients used in each analysis which makes interpretation impossible. Total number of patients and drop-outs are inconsistent between extension and original papers.
- Only 5 patients completed 5 years of treatment. In total, 154 (41%) people dropped out of study (49, 57 and 48 in placebo, 1.6 MIU and 8 MIU groups, respectively). 10% of both placebo and IFβ-1b patients withdrew at end of initial trial (i.e. did not enter extension). Excess steroid use accounted for 11% of placebo compared with 2% of IFβ-1b withdrawals. In contrast, more IFβ-1b than placebo patients withdrew due to worsening (perceived by either patient or investigator) or adverse events (9% vs. 5% and 7% vs. 2%, respectively). Other unspecified reasons accounted for withdrawals by 8% IFβ-1b and 6% placebo patients.
- Paper did not give all results for three of stated outcomes, suggesting they may have been insignificant.
- Without giving reason, authors reversed primary and secondary outcomes between original and extension studies.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1

Appendix 7

Summary of trial of beta interferon-1b in SPMS

Study and design	Intervention	Patients	Outcome measures
European Study Group on IFNB-1b in secondary progressive MS.[36,37] Multicentre in Europe (n = 32); randomised, double-blind, placebo-controlled trial; ITT. Planned up to 3 years of treatment (but interim analysis planned after ≥ 2 years). Mean follow-up, 892–901 days (i.e. 2.47 years).	Alternate day s.c. injections: placebo or 8 MIU IFβ-1b. Lower dose (4 MIU) for first 2 weeks. Prophylactic paracetamol or NSAIDs allowed.	Total 718 patients: IFβ-1b, n = 360; placebo, n = 358. SPMS: aged 18–55 years, mean 40.9–41.1 years (SD 7.2); 59–64% female – mean disease duration (SD) 12.8 (6.6)–13.4 (7.5) years – baseline EDSS, 3.0–6.5; mean 5.1–5.2 (SD 1.1) – either ≥ 2 relapses or ≥ 1.0 increase in EDSS in previous 2 years. Exclusion of patients previously treated with immunosuppressants or immunomodulatory drugs (within (undefined) time limits). Demographic and baseline characteristics comparable between treatment groups.	Primary outcome: Time to progression (≥ 1 EDSS (or 0.5 EDSS for baseline EDSS of 6.0–6.5) sustained for ≥ 3 months). Secondary outcomes: (1) time to becoming wheelchair bound (i.e. EDSS ≥ 7.0); (2) proportion of patients with confirmed progression; (3) proportion of patients becoming wheelchair bound; (4) EDSS at endpoint; (5) annual relapse rate; (6) time to first relapse; (7) proportion of patients with moderate or severe relapses; (8) steroid use; (9) hospitalisations; (10) Montgomery Asberg Depression Rating Scale; (11) cranial MRI; analysis excluded from this report as surrogate measure. The following outcomes were not subsequently reported: (12) AI; (13) cognitive functions; (14) clinical global impression of change quality of life.

Results Primary outcome, time to progression (for 40% of patients (40% quantile), since median (50%) not achieved by both groups): significantly delayed in IFβ-1b group (893 days (CI, 726 to 'unable to estimate within study period') vs. placebo 549 days (CI, 463 to 642; p = 0.0008).

Primary outcome remained statistically significant even when patients lost to follow-up added to either progressed or not progressed groups.

Secondary outcomes:

(1) time to becoming wheelchair bound delayed up to 9 months in IFβ-1b group: OR 0.63 (95% CI, 0.46 to 0.85);

(2) proportion of patients with confirmed progression: placebo 49.7% vs. IFβ-1b 38.9%; p = 0.0048;

(3) proportion of patients becoming wheelchair bound: placebo 24.6% vs. IFβ-1b 16.7%; p = 0.0277;

(4) change in EDSS from baseline: placebo 0.60 vs. IFβ-1b 0.47; p = 0.03;

(5) mean annual relapse rate: placebo 0.64 vs. IFβ-1b 0.44; p = 0.002); individual annual rates not significantly different by year 3;

(6) median time to first relapse: placebo 403 days vs. IFβ-1b 644 days; p = 0.003);

(7) proportion of patients with moderate/severe relapses: placebo 53.1% vs. IFβ-1b 43.6%; p = 0.0083;

(8) proportion of patients with MS-related steroid use: placebo 67.9% vs. IFβ-1b 53.6%; p < 0.0001);

(9) proportion of patients hospitalised: placebo 52.8% vs. IFβ-1b 46.4%; p = 0.0435); number of MS-associated hospital admissions per patient reduced for IFβ-1b vs. placebo, p = 0.0003.

(10) No increase or worsening of depressive symptoms for IFβ-1b treated patients.

continued

continued

Comments

- Central randomisation schedule.
- Training and assessment of all physicians rating EDSS at central reference centre before start of trial and annual follow-up sessions; included manuals, videotapes and written guidelines. Whenever possible same EDSS rater performed all scheduled neurological assessments for a given patient. Effect of training on reliability not specified.
- Good attempts to maintain blinding of treatment allocation. However, blinding may have been ineffective due to the higher incidence of side-effects in IFβ-1b group (especially injection site reactions).
- Effect of centre taken into consideration by statistical analyses.
- Discrepancies in *p*-values between table 5 and text (page 1495) for mean EDSS change from endpoint and overall mean annual relapse rates (most conservative estimate used in this report), although all remained statistically significant.
- Not specified how severity of relapses was determined.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1

Appendix 8

Summary of trials of cladribine in MS

Study and design	Intervention	Patients	Outcome measures
Sipe, *et al.*, 1994.[39] USA. Interim report at 12 months before crossover. Matched pairs with each pair randomised to treatment. Beutler, *et al.*, 1996.[40] Reports on year 2 (crossover) of trial, with results from survival analysis for first year plus results from 6 months unblinded follow-up.	Year 1:[39] cladribine, 0.1 mg/kg daily (total 2.8 mg/kg), vs. placebo. Year 2: [40] cladribine, 4 courses – (i) 0.7 mg/kg, (ii) & (iii) 0.35 mg/kg, (iv) saline placebo (total 1.4 mg/kg) – vs. placebo. All treatments given as 4-monthly courses, each of 7-day i.v. infusions via central line using portable pump. Steroids used for exacerbations. Blood count determined readiness for next infusion. Continuation of medications for troublesome symptoms of MS permitted.	Cladribine, *n* = 27; controls, *n* = 24. 24 pairs matched for age, sex, and severity of disease. Inclusion: clinically definite/laboratory supported chronic PMS (Poser) for > 2 years. Excluded: renal impairment (defined); abnormal liver function tests (defined); neutrophils < 1600/μl; platelet < 130,000/μl; inadequate contraception; steroids or immunosuppressants in past 6 months; decreased marrow reserve (defined). Setting: year 1, not stated; year 2, outpatient.	Patient outcomes: scored monthly for year 1 and every 6 months for year 2 1. NRS; 2. EDSS; 3. Patients complaints (for year 1). Non-patient outcomes: chemical analysis and blood counts monthly; MRI; volumetric analysis using T2 and proton density weighted images; CSF total protein and Ig concentration with heights of oligoclonal bands measured at baseline, 6 monthly intervals.

Results

Year 1[39] (parallel group design)

Results refer to 24 matched pairs and exclude three patients on cladribine who did not complete first year.

Mean paired differences (placebo minus cladribine):

(1) NRS at 1 year: –12.5 (95% CI, –16.7 to –8.2);

(2) EDSS at 1 year: 1.3 (95% CI, 0.6 to 2.0);

(3) Relative oligoclonal Ig concentrations 7.3 (95% CI, 0.5 to 14.1).

2-year crossover trial[40]

ANOVA based on two-period crossover design with absolute change in EDSS and NRS as end-points revealed no significant carry-over effects between patients or period effects within patients.

EDSS and NRS scores presented in graph format from 1–30 months.

(1) Highly significant treatment effects, F(1,44) for treatment effects for EDSS = 10.19 (p = 0.0026); F(1,44) for treatment effects for NRS = 23.46 (p < 0.0001).

(2) Kaplan–Meier time to failure showed cladribine group fared better than those receiving placebo in year 1. Log-rank (L) used to compare times-to-failure in year 1: failure defined as gain of 1 EDSS point, L = 6.313 (p = 0.012); failure defined as gain of 1.5 EDSS points, L = 5.254 (p = 0.024); failure defined as loss of 10 NRS points, L = 8.299 (p = 0.004); failure defined as loss of 15 NRS points, L = 6.800 (p = 0.009).

(3) Results from 6-month unblinded follow-up: stabilisation of disease produced by lower dose of cladribine may be of shorter duration than that seen with higher dose. After 2 years, in unblinded observations, fairly rapid deterioration documented in group initially on higher dose of cladribine. Suggests rebound worsening of disease may occur between 24 and 30 months after initiation of therapy at higher dose.

Adverse effects, year 1[39]

Cladribine group: severe bone marrow suppression in patient also on phenytoin (recovered over months); thrombocytopenia (< 80,000/μl) in four patients and between 100,000 and < 80,000/μl in another three; hepatitis B infection (history of probable exposure); salmonella; mild herpes zoster (two patients).

Adverse effects, year 2[40]

Cladribine at 50% dose used in year 1: platelets < 100,000/μl in only one patient; segmental herpes zoster in six patients (includes two in first year).

continued

continued

Comments

Year 1[39]

- Clearly defined inclusion and exclusion criteria. Interventions and outcomes described. Original intention was to use 6 courses of treatment but rates of thrombocytopenia unexpectedly high and 4 courses subsequently decided upon. One patient received 5 courses, one received 2, two received 3, the rest, 4 courses. Comparable control treatment used. Each matched pair randomised using random number tables. One additional unpaired patient started on cladribine. Two patients on cladribine who dropped out before 3 months replaced. Reported[40] that two additional patients were appropriately matched by blinded neurologist and assigned by statistician to cladribine.
- Examining neurologists, nurses, and patients blind to treatment group. Inter-rater agreement assessed. Unblinded investigator monitored all laboratory studies and patient complaints and illness. Authors acknowledge that thrombocytopenia-delaying drug doses may have indicated active treatment. Patients and controls treated equally. Patient outcomes were ratings on two disability scales.
- Analyses reported from 24 matched pairs. Point estimates and 95% CI of treatment effect reported. Analysis of paired difference in scores undertaken using non-parametric repeated measures ANOVA with other comparisons using both parametric and non-parametric one-sample procedures. Analysis undertaken included unpaired ITT and paired analysis including data for two patients on cladribine lost by 3 months. Comparison based on matched pairs with last available observation being carried forward for those patients who did not complete 12 months. Paired analysis incorporating data from two cladribine patients lost by month 3 (and replaced) reported to give results similar to those reported. Results reported in abstract differ slightly from those reported in text.
- Lower dose and treatment carried out as outpatient using portable pump in second period; thus treatment in second period not comparable. Power estimated for crossover design, hence results for parallel group[39] from underpowered sample. Prior sample size estimated to detect 15% NRS improvement on cladribine if no improvement on placebo with power of 0.90, and alpha 0.05. Estimated sample as 22 patients per treatment arm.

2-year crossover[40]

- Blinding and randomisation as above.
- Cladribine dose used in year 2 was only half of dose used in year 1.
- Five patients who were to receive placebo given a single dose of cladribine 0.7 mg/kg in error at beginning of second phase. Separate analysis showed response of these patients no greater than that of other patients. These patients retained in analysis.
- Analyses reported based on 24 matched pairs. For analysis, last available observations carried forward for patients who completed at least 18 months of study. Analysis repeated treating these patients as missing and assumed to be missing at random. These alternative analyses reported as yielding similar results to those presented.
- Outcomes limited to significance of treatment effects on EDSS and NRS scores and on MRI scan findings. No point estimates or CIs of treatment effect reported.
- Analysis included both parametric and non-parametric methods. Investigation undertaken to assess carry-over effects between patients or period effects within patients. Though no statistically significant effect found for absolute changes in EDSS or NRS, authors comment that 'the improvement in NRS scores seem to peak at about 18 months and be well maintained for the 24 months of follow-up in the patients initially treated with 2.8 mg/kg cladribine'. These comments would suggest that a clinical carry-over effect cannot be ruled out.
- Drop-outs during year 2 not described by treatment group; ascribed as being due to 'various causes unrelated to study'.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1 (method)
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and drop-outs?	0 (not for year 2)
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Year 1: cladribine, 27 entered, drop-outs, *n* = 3; placebo, 24 entered, drop-outs, *n* = 1. Year 2: "4 additional patients were lost in the second year for reasons unrelated to study."[40] No treatment group given; possibly 1 placebo and 3 cladribine in year 2. Total drop-outs at year 2 given as cladribine 6/27 (22%); placebo 2/24 (8%).

Study and design	Intervention	Patients	Outcome measures
Romine, *et al*., 1999.[41] USA. RCT, double-blind.	Cladribine, 0.07 mg/kg/day, 5 consecutive daily s.c. injections; 6 active and 2 placebo courses (total 2.1 mg/kg); vs. equivalent volume of saline placebo; 8 placebo courses. Fractionated into 2/3 sites, monthly for 6 months. Active drug if blood count met criteria.	Cladribine, *n* = 27; control, *n* = 25. Inclusion: clinically definite RRMS for at least 1 year; two or more relapses in past 2 years; EDSS score of 6.5 or less at entry. Exclusion: immunosuppressants in past 3 months; creatinine > 1.5 mg/dl; abnormal liver function tests (specified); neutropenia, < 1600/µl; thrombocytopenia, < 130,000/µl; previous total lymphoid irradiation/prior extended myelosuppressant chemotherapy. Setting: not stated.	Patient outcomes assessed over months 7–12: (1) joint frequency and severity of clinical relapses as judged by neurological examination. Secondary outcomes (assessed every month for year 1, then every 3 months for 6 months): (2) EDSS score; (3) NRS score.

Results Placebo effect noted in first 6 months.

(1) Joint frequency and severity of clinical relapses for months 7–12 (extended Mantel–Haenzel procedure): significant reduction in frequency and severity of exacerbations in cladribine group vs. placebo; QM = 2.30, 2*p* = 0.021. For months 7–18, Q_M = 2.59, 2*p* = 0.010. Relapse rate over 7–12 months: cladribine 0.77/year (95% CI, 0.37 to 1.41) vs. placebo 1.67/year (95% CI, 1.02 to 2.57). Exacerbation rate over 7–18 months: cladribine 0.66/year (95% CI, 0.37 to 1.05) vs. placebo 1.34/year (95% CI, 0.90 to 1.93); no statistical comparison of difference reported. Poisson regression identified following as significant predictors of relapse over months 7–12: cladribine treatment, lower baseline EDSS and fewer number of exacerbations in year prior to baseline.

(2/3) EDSS and NRS score: no significant differences between treatment groups over 18 months.

Adverse effects

Cladribine: mild segmental herpes zoster (2/27); placebo: mild segmental herpes zoster (1/25).

Drop-outs: cladribine, *n* = 2 (moved, worsening MS); placebo, *n* = 6 (conversion disorder, moved *2, unspecified *2, worsening MS).

Comments

- Interventions and outcomes described; included patients are defined as 'definite RRMS' but no reference to criteria used to define MS; patients stratified by gender, age in 10-year intervals, degree of disability measured by NRS and stratified groups randomised in blocks of four. Pharmacist dispensed treatment according to patient code; no details given of method used to allocate patient code. Comparable control treatment used.
- Analysis was ITT but data from 4 patients (2 cladribine, 2 placebo who were unblinded from 12–18 months) not included in analysis of frequency and severity of exacerbations after unblinding. Trial profile included.
- Patients, neurologist, nurses and neuroradiologist blinded. Relapses defined and determined by neurologist.
- Equal assessments undertaken of both groups with EDSS and NRS being scored every month for first year, then every 3 months for 6 months. Inter-rater variability assessed.
- Groups stratified by gender, age, and NRS score and were similar in mean EDSS. Cladribine group had greater number of exacerbations in previous year.

continued

Comments

- Primary outcomes included patient and non-patient outcomes. No assessment of patient's opinion. Comparison of joint frequency and severity of relapses undertaken using Mantel's extension of Mantel–Haenzel procedure. Poisson regression model used to evaluate significance of covariates in predicting clinical relapse. Comparison of frequency of enhancing lesions performed using McNemar's test for paired data (within treatment groups) and Fisher's exact test (between treatment groups). Non-parametric repeated measures ANOVA used to compare EDSS and NRS score between treatment groups. Difference in numbers of relapses between groups not assessed, with CIs being reported only within treatment groups, not between groups.
- Cladribine: 27 randomised, 26 followed to 12 months; 25 followed to 18 months. Controls: 25 randomised, 24 followed to 12 months, 19 followed to 18 months. No data values were input for any patient not observed to 18 months.
- Prior sample size calculations estimated that 25 patients per group would detect decline in annual rate of relapse from 1 in placebo to 0.5 in cladribine groups with two-sided Poisson test at 0.05.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Cladribine: *n* = 27 randomised, *n* = 2 drop-outs (7%); controls: *n* = 25 randomised, *n* = 6 drop-outs (24%).

Appendix 9

Summary of trials of cyclophosphamide in MS

Study and design	Intervention	Patients	Outcome measures
Hauser, *et al.*, 1983.[42] USA. RCT.	1. Synthetic ACTH, 25 units i.v. over 8 hours on days 1–3, decreasing by 5 units per 3 days till day 15, 40 units i.m. days 16–18, 20 units i.m. days 19–21. 2. Cyclophosphamide, 400–500 mg/day i.v., divided doses for 10–14 days (total dose 80–100 mg/kg); stopped when WBC < 4000/mm^3 + i.v. ACTH as above. 3. Plasma exchange, 1–1.5 times plasma volume exchanged for 5% albumin; 4/5 exchanges in 2 weeks + ACTH as above + 'low dose' cyclophosphamide (2 mg/kg), reduced if neutropenia for 8 weeks. Other interventions as used.	1. *n* = 20 2. *n* = 20 3. *n* = 18 Inclusion: age 20–52 years, clinically definite MS. Severe progressive disease with worsening (defined) in preceeding 9 months. 53 ambulatory. Exclusion: incompatible medical illness. Setting: inpatient.	Patient outcomes assessed on admission, discharge, 6 & 12 months: (1) DSS score (details given); (2) quantitative neurological examination score derived from MS Cooperative ACTH study; (3) standard FS score; (4) AI (details given) study measures used; (5) clinical assessment recorded by attending physician. AI and DSS used to categorise clinical response as improved, unchanged, worsened or treatment failure. Further categorised as stabilised (improved/unchanged) and worse (worse/treatment failure). Non-patient outcomes: lumbar punctures: incidence of pleocytosis and Ig abnormalities; T-lymphocytes.

Results (at 12 months)

1. ACTH, stabilised 4/20 (20%); worse, 16/20 (80%);
2. cyclophosphamide + ACTH, stabilised 16/20 (80%); worse, 4/20 (20%);
3. plasma exchange + ACTH + cyclophosphamide, stabilised 9/18 (50%); worse, 9/18 (50%).

Fisher's exact test used to compare differences between groups in stabilised vs. worse at 12 months:

cyclophosphamide + ACTH vs. ACTH (p = 0.0004); cyclophosphamide + ACTH vs. plasma exchange (p = 0.087); ACTH vs. plasma exchange (p = 0.087). No differences noted between patients according to treatment centre for cyclophosphamide/ACTH vs. ACTH groups.

Physician's clinical assessment at 12 months of numbers stabilised using Fisher's exact test:

cyclophosphamide + ACTH vs. ACTH (p = 0.0002); cyclophosphamide + ACTH vs. plasma exchange (p = 0.056); ACTH vs. plasma exchange (p = 0.027).

Adverse effects

- ACTH – mild mood changes in 50%, resolved with no treatment/mild sedation; transient fluid retention in most patients
- cyclophosphamide + ACTH – complete temporary scalp alopecia in all patients; nausea in 33%; transient microscopic haematuria in 4/20; leucopenia (< 1600/mm^3) in 55%
- plasma exchange – urticaria in 1/20; localised herpes zoster in 1/20; thinning of hair in several patients; venous access via subclavian/jugular vein required in some.

Comments

- Inclusion criteria for patients and outcomes and interventions clearly described. Treatment took place in three different hospitals. Methods of randomisation not stated. Three different interventions studied with no placebo control group. Nature of treatments and side-effects made blinding impossible. Evaluations performed at similar times for all patients. Results reported for all who were randomised.
- Treatment groups similar at baseline for age, age of onset, duration of chronic progressive disease, disability status, FS and neurological score. Gender ratio differed among groups.
- Outcome measures included patient outcomes rated on four scales. Opinions of patients not sought. Follow-up period 1 year.

continued

continued

***Comments* contd**

- No mention of prior sample size calculations though mentioned that study designed to include 75 patients and was halted when significant difference existed between treatment groups. Assessment of effect of treatment centre on ACTH vs. cyclophosphamide difference. Treatment effects reported as *p*-values for differences according to Fisher's exact test, with *t*-tests used to assess differences between treatment groups on four scales measured. Since scores used may not have had normal distribution, non-parametric tests may have been more appropriate than *t*-tests. No point treatment effects or CIs given. No mention of any withdrawals from treatment.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Drop-outs not mentioned.

Study and design	Intervention	Patients	Outcome measures
Canadian Cooperative Multiple Sclerosis Study Group, 1991.[43] Canada. Multicentre RCT; single masked.	1. Cyclophosphamide: 1 g alternate days; stopped when WBC < 4.5 x 10^9/litre or when had received 9 g cyclophosphamide + oral prednisolone, 40 mg/day, for 10 days, then reduced until discontinued on day 16. 2. Plasma exchange of 1 volume done weekly for 20 weeks and replaced with 5% albumin + oral cyclophosphamide, 1.5–2.0 mg/kg/day (adjusted on WBC) for 22 weeks + oral prednisolone 20 mg alternate days tapered over 22 weeks. 3. Control: oral cyclophosphamide placebo daily + prednisolone placebo on alternate days for 22 weeks; sham plasma exchanges weekly. Co-intervention with steroids if required.	1. Cyclophosphamide, *n* = 55. 2. Plasma exchange, *n* = 57. 3. Control, *n* = 56. Inclusion: clinically definite or laboratory supported MS in progressive phase (defined) over 12 months; EDSS 4.0–6.5; age > 14 years (included chronic PMS and RPMS). Exclusion: specified previous treatment/illness; risk of pregnancy; difficult venous access. Setting: inpatient.	Patient outcomes: EDSS scored every 6 months for 3 years. Categorised as treatment failure if worse on EDSS score by 1.0 or more points at two consecutive examinations. Secondary analysis: number of patients improved, stabilised or worsened; mean/median changes in EDSS; number requiring co-intervention; time to co-intervention with steroids.

Results

Primary analysis: comparison of cumulative treatment failure rates: no statistically significant differences (Breslow's test); (cyclophosphamide 19 (35%); plasma exchange 18 (32%); control 16 (29%)).

Secondary analysis: no statistically significant differences in EDSS between control group and either active treatment group after allowance for multiple comparisons over time; (cyclophosphamide 0.81 (SE 0.14), plasma exchange 0.69 (SE 0.11), placebo 0.69 (SE 0.10)). Analysis of co-interventions suggested that steroids used earlier and more often in placebo group than in either active treatment group. Results from statistical comparisons not reported.

Adverse effects

Cyclophosphamide: death from acute bronchopneumonia 1/55 (2%); haemorrhagic cystitis 2/55; septic during hospitalisation 3/55 (5%); diabetes 1/55; herpes zoster 1/55; pulmonary embolism non-fatal 1/55; angina 1/55; severe alopecia in those receiving > 2 g cyclophosphamide 100%; amenorrhoea 16/37 (42%) women.

Plasma exchange: 90% had some adverse effect; vascular collapse during treatment 1/57; hypertension 1/57; diabetes 1/57; herpes zoster 1/57; depression requiring treatment 3/57; angina 1/57; severe alopecia 51%; amenorrhoea 25/33 (77%).

Placebo: advanced liver disease (died) 1/56; angina 1/56; severe alopecia 16%; amenorrhoea 4/32 (11%).

Comments

- Inclusion and exclusion criteria clearly defined. Interventions described. Control intervention similar to only one of treatments (plasma exchange) and could not be considered a comparable control for cyclophosphamide group. Outcomes including treatment failure clearly described.
- Randomisation sequence generated for each centre. Patients stratified by centre and EDSS score (< 6 and 6 or over). All randomised patients contributed to survival curve until treatment failure, death or end of follow-up. Patients who did not complete treatment regime followed. ITT analysis. Reducing numbers evaluated at each time point due to variable lengths of follow-up because of sequential intake spread over 36-month enrolment period.
- Trial single-blinded. Patients not blinded to allocation group. Efforts made to blind assessor and assessor's ability and patient's ability to identify treatment groups at end ascertained. Patients in cyclophosphamide group certain they were on active treatment. Final outcome of nine patients not assessed by blinded evaluating neurologist. Monitoring neurologist, who was not blinded, assessed patients every 6 months and treated exacerbations.
- Groups similar at baseline with respect to age of onset, duration of MS, gender, and EDSS score.
- All participants assessed at similar intervals.

continued

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***Comments* contd**

- Outcomes assessed included EDSS score, time-to-treatment failure, and number of co-interventions/time-to-co-interventions (proxy for exacerbations). No assessment of patient's opinion. Analysis included survival analysis of treatment failure. Two-tailed *p*-values given for differences (control vs. each active treatment) in proportions of patients improved, stable or worse on EDSS at each assessment. Authors acknowledge that since EDSS is an ordinal scale, parametric tests may not be appropriate. No point estimates or CIs of treatment effect reported.
- Adverse reactions given but no mention of numbers failing to complete each treatment regime. Information is given in form of '85% of patients took more than 80% of their medications' and '90% of patients in the plasma exchange and placebo groups completed at least 90% of planned treatments'. Follow-up 3 years.
- Prior sample size estimated to detect 30% difference in failure rate between control and one of active treatments to give power of 90%.
- Authors report that strict entry requirements restricted number of eligible patients and forced extended enrolment period; this may indicate limited generalisability of results.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1 (method)
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Cyclophosphamide, *n* = 55 entered; plasma exchange, *n* = 57 entered; controls, *n* = 56 entered. Numbers failing to complete treatment not given (see comments).

Study and design	Intervention	Patients	Outcome measures
Killian, *et al*., 1988.[44] USA. RCT; double-blind for 1 year then open crossover (with 6/8 placebo and follow-up of 6/6 original active therapy).	Cyclophosphamide, 750 mg/m^2, vs. placebo, 250 ml of 5% dextrose in water. Both given i.v. over 1 hour, repeated monthly for 12 months + i.m. prochlorperazine/ promethazine hydrochloride every 6 hours. Bolus of dexamethazone given to prevent nausea in 4/6 receiving cyclophosphamide after crossover.	Cyclophosphamide, *n* = 6; placebo, *n* = 8. Inclusion: RRMS; oligoclonal bands/elevated Ig in CSF; 3 or more exacerbations in previous 2 years; minimum EDSS score of 1. Setting: not stated. Patient characteristics: groups appear similar in age and gender. Duration of disease longer in treatment group (8 years) compared with placebo (5 years). In year before study placebo group had more episodes than cyclophosphamide group, while later had worse EDSS.	Patient outcome measures used at 1 year of parallel group: (1) mean number of relapses; (2) mean duration of episodes; (3) Kurtzke DSS; (4) AI. After crossover: number and duration of episodes. Non-patient outcomes: blood tests.

Results (parallel 1 year)

(1) Mean number relapses: cyclophosphamide 0.5 (SE 0.2) vs. placebo 2.3 (SE 0.6); $p = 0.06$;

(2) Mean duration of episodes: cyclophosphamide 0.5 (SE 0.2) vs. placebo 3.6 (SE 1.0); $p = 0.06$;

(3) Kurtzke DSS: no significant difference;

(4) AI: no significant difference.

No estimation of effect size.

After crossover of six placebo patients to cyclophosphamide:

– number of episodes: year 1 (receiving placebo) 18 vs. year 2 (receiving cyclophosphamide) 3; $p = 0.03$;

– duration of episodes: year 1 (receiving placebo) 29 vs. year 2 (receiving cyclophosphamide) 4, $p = 0.0$;

– number of episodes for all who received cyclophosphamide: pretreatment year 31 vs. treatment year 6; $p = 0.003$;

– number and duration of episodes for those receiving cyclophosphamide year 1, nil year 2: numbers same for both outcomes and both periods.

Adverse effects

Cyclophosphamide: monthly nausea and vomiting beginning after 8–12 hours, well-controlled by antiemetics, subsided within 24 hours 4/6 (67%); mild hair thinning 2/6; amenorrhoea 1/5 women; urticaria 1.

Placebo: mild nausea 2/8 (25%).

Comments

- Inclusion criteria defined. No exclusion criteria stated. Interventions and outcomes described. Computer randomisation used to allocate treatment. During first year (parallel groups), patients and evaluating neurologist blinded. After crossover at 1 year, trial was open. Blinded neurologist evaluated patients at relapses.
- Results reported at 1 year for all 14 patients who were randomised. Effectiveness of randomisation may have been impaired by nausea and vomiting experienced by 67% of active treatment group. Crossover study only included 6/8 from original placebo group and all 6 original cyclophosphamide group.
- Insufficient data presented to assess baseline comparability of treatment groups, although treatment group had longer duration of disease. Both groups appear to have been similarly treated during first year. Treatment not similar in second year.
- Outcomes include number of relapses, and changes in DSS and AI. Other relevant outcomes, such as number of patients without relapses, not included.
- Size of treatment effect estimated.

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Data analysis details

- 1-year parallel group design: analysis used Wilcoxon nonpaired rank sum test; Wilcoxon signed rank test used to compare pretreatment and treatment of disease activity. Drop-outs described with reasons and by treatment group.
- Year 2 crossover: not true crossover trial, only the six patients originally allocated to placebo group who were continuing to experience 2 or more attacks per year treated with cyclophosphamide; analysis did not include assessment of treatment-period or carry-over effects.
- Sample size/power calculation estimated that 50 patients required to detect two-fold difference between treatment groups with alpha 0.05, power 0.80. Only 14 patients entered. Authors report difficulty in recruiting eligible patients which may indicate results not generalisable.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Year 1 (parallel group design): cyclophosphamide, 6 entered, no drop-outs; placebo, 8 entered, 1 drop-out (12.5%).

Study and design	Intervention	Patients	Outcome measures
Likosky, *et al*., 1991.[45] USA. RCT; single-blind.	Cyclophosphamide, 400–500 mg i.v. 5 days per week till WBC < 2500/mm^3, mean total dosage 69 mg/kg (range 33–201 mg/kg), vs. folic acid, 1 mg i.v. 5 times weekly for 2 weeks.	Cyclophosphamide, *n* = 22; folic acid, *n* = 21. Inclusion: clinical and laboratory finding consistent with MS, chronic progressive disease for 1 or more years (defined), gait impaired but able to walk, age 18–60 years. Exclusion: debilitating chronic disease or recent immunosuppressant therapy. Setting: outpatient.	Primary: change in disability at 1 year (folic acid minus cyclophosphamide) using EDSS. Other outcomes: changes in disability at 18 and 24 months. Disability evaluated using EDSS, AI, FS scale at baseline, 12, 18, 24 months. Incapacity status and environmental status at baseline and 24 months. Non-patient outcomes: blood count, urine analysis, serum sodium monitored throughout i.v. period.

Results (folic acid – cyclophosphamide)

At 1 year: EDSS, 0.03 (95% CI, –0.60 to 0.65; p = 0.94); AI, –0.05 (95% CI, –0.98 to 0.89).

At 18 months: EDSS, 0.35 (95% CI, –0.40 to 1.10; p = 0.36); AI, 0.65 (95% CI, –0.49 to 1.79).

At 24 months: EDSS, 0.39 (95% CI, 0.45 to 1.23; p = 0.37); AI, 0.85 (95% CI, –0.53 to 2.22).

Adjusted (for gender, age, duration of disease and baseline EDSS) difference in mean change in EDSS at 12, 18, 24 months, 0.01.

Correlation of EDSS change at 1 year in cyclophosphamide group with total dose received, total mg/kg bodyweight, lowest WBC, and lowest lymphocyte count, r = 0.16 (p = 0.34).

Stability at 1 year with respect to each of seven specified functional systems: no significant difference (pyramidal, cerebellar, brain stem, sensory, bowel/bladder, vision, cerebral).

Adverse effects

Cyclophosphamide: temporary hair loss (100%); nausea and vomiting (9/22, 41%) + nausea without vomiting (7/22, 32%).

Folic acid: none stated.

Comments

- Inclusion and exclusion criteria clearly stated. Intervention, outcomes and terms such as stable and worse described. Study described as randomised but no details given of methods used.
- Results reported for 42/43 randomised patients. One (folic acid group) was subsequently found to have been misdiagnosed and excluded from analysis. Analysis by ITT at 1 year of remaining 42 patients. Two of folic acid group 'crossed-over' to cyclophosphamide treatment; these analysed in their original group.
- Trial described as single-blind. Placebo control may not have been comparable both with respect to duration of therapy and different adverse reactions observed in each treatment group. Evaluating physicians blinded to treatment group. Ratings of 9 evaluating physicians reviewed to ensure following of protocol by blinded author.
- Treatment groups similar at baseline on demographic characteristics and neurological impairment. Treatment of groups may have differed during infusion period.
- Outcomes included: EDSS, AI, and FS.
- Data analysis details: non-parametric tests used to compare EDSS change scores. Multiple regression models used to adjust differences in EDSS scores for baseline EDSS, age, gender, duration of disease. Log-rank test used to compare time to failure. χ^2 used to evaluate differences in proportions of stable/worse patients. Point estimates and 95% CI of treatment effect on EDSS and AI calculated. Primary outcomes assessed at 12 months with follow-up results reported at 18 and 24 months. Drop-outs described with reasons and by treatment group.
- No prior sample size/power calculation is mentioned.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Cyclophosphamide, 0/22 (0%) drop-outs at 12 months; folic acid, 1/21 (5%) (misdiagnosis) drop-outs at 12 months. 1/21 'crossed-over' to cyclophosphamide by 12 months; 1/21 received cyclophosphamide just before 24 months (for lung cancer).

Study and design	Intervention	Patients	Outcome measures

Weiner, *et al*., 1993.[46] USA. Multicentre RCT; single blind.	1. Cyclophosphamide, 125 mg i.v. 4 times daily, over 8–18 days till WBC < 4000/mm^3 + i.v. ACTH. No boosters.
	2. As (1) + booster, cyclophosphamide, 700 mg/m^2 i.v., every 2 months for 2 years.
	3. Modified cyclophosphamide, 600 mg/m^2 i.v., on days 1, 2, 4, 6, 8 + i.m. ACTH over 14 days (40 units decreasing to 20).
	4. Modified cyclophosphamide as (3) + booster, cyclophosphamide, 700 mg/m^2 i.v. every 2 months for 2 years.
		261 randomised.
		Number randomised to each treatment not stated.
		Groups categorised as follows (total *n* = 256):
		no boosters (1 & 3), *n* = 129;
		boosters (2 & 4), *n* = 127;
		modified (3 & 4), *n* = 139;
		published (1 & 2), *n* = 117.
		Inclusion: clinically definite MS, at least 1 point worsening on Kurtzke EDSS or AI scale in past 12 months.
		Age, 18–55 years, DSS 3 through 6B, requiring bilateral support for ambulation or EDSS of 7 occurring in past 2 months.
		Excluded: other diagnosis.
		Setting: inpatient.
			Patient outcome measures evaluated every 6 months for 3 years.
			Treatment failure (defined as decline of 1 point on DSS/withdrew for any reason) vs. stabilisation/improvement.
			Neurologic status assessed at admission and every 6 months to 3 years using DSS and AI.

Results

1. Comparison of published vs. modified induction: no significant differences at 6, 12 or 24 months. Survival analysis: no significant difference.
2. Comparison of maintenance boosters vs. no boosters: no improvement at 12, 18 months. Significant slowing of progression at 24 months (38% stable/improved vs. 24%; $p = 0.04$). Significant differences detected with AI at 24 months ($p = 0.04$). Survival analysis: no significant differences over 3 years.
3. Comparison of different centres: slowing of progression at 24 and 30 months examined. Similar positive effects seen at centres treating over 8 patients. No positive effect seen at centres with < 7 patients.
4. Identification of responsive subgroups: analysed by age (< 41 years vs. > 41 years); MS type (chronic PMS from onset vs. others).

No estimate of size of treatment effect.

Adverse effects

All experienced complete scalp alopecia; 1/3 experienced nausea; menstrual abnormalities (50% women).

Associated with induction: fever and neutropenia, 29; urinary tract infections, 14; oral ulcers, 1; candidal oesophagitis, 1; gross haematuria, 3; inappropriate antidiuretic hormone, 2.

Associated with booster therapy: recurrent urinary tract infections, 4; chronic low WBC, 7; moderate to severe vomiting, 16; gross haematuria, 1.

Comments

- Participants and outcomes described. 26 patients who were randomised, found to be ineligible and not treated. Reasons for ineligility not stated. Details of dose of ACTH presented elsewhere. Individual randomisation schemes prepared for each of 21 centres with treatments being assigned centrally.
- Four different interventions used with no placebo control group. 261 eligible patients randomised. Data from 256 patients used in analysis (baseline data unavailable for 5 patients). Evaluations performed in single-blind manner by examining neurologists who were usually also treating physician. Treatment regimes differed. Formal inter-rater variability not assessed.
- Baseline characteristics compared for categories of treatment regime: no boosters, boosters, modified and published. No comparison presented for groups according to treatment regimes.
- Analysis by ITT; details given of how data from patients who dropped out handled.
- Outcome measures included treatment failure (including requiring steroid therapy/withdrawals).
- Data analysis details: Mantel–Haenzel trend test to compare defined groups; proportional hazards model to assess survival; logistic regression to identify subgroups of patients more prone to stabilisation/improvement; follow-up period 3 years; size of treatment effect not calculated; not clear whether subgroups analysed were determined in advance or *post hoc*.

continued

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***Comments* contd**

- Drop-outs described but not fully; total number of drop-outs by treatment regime not clear.
- Prior sample size/power calculation estimated that 75 patients per treatment arm required to detect 15% improvement/stabilisation on non-booster arms at 3 years compared with 40–45% stabilisation/improvement on booster arms with 95% power and 5% type 1 error.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Boosters: 34/127 (27%) drop-outs; no boosters: 29/ 129 (22 %) drop-outs. Total number of drop-outs not clear.

Appendix 10

Summary of trials of glatiramer (copolymer 1) in MS

Study	Research question	Inclusion criteria	Search strategy
Nicholson & Milne, 1996.[47] Systematic review of copolymer 1 in MS.	To evaluate the effect of copolymer 1 compared with no treatment in the progression of RRMS.	None stated.	None stated.

Results

1. EDSS:
   Proportion of patients with improved EDSS by ≥ 1 point: copolymer 1 24.8%, placebo, 15.2%.[48]
   Proportion of progression-free patients: copolymer 1 78.4%, placebo 75.4%; NS.[48]
   Proportion of patients with progression (2 years): copolymer 1 20.0%, placebo 47.8%.[49]
2. Relapse/exacerbation rate:
   mean relapse/exacerbation rate (2 years): copolymer 1 1.19, placebo 1.68; $p = 0.007$;47 copolymer 1 0.6, placebo 2.7; p not stated;[48]
   proportion of relapse/exacerbation-free patients: copolymer 1 33.6%, placebo 27.0%; $p = 0.098$;[49] copolymer 1 56%, placebo 26.0%; $p = 0.045$;[49]
   median time to first relapse: copolymer 1 287 days, placebo 198 days; $p = 0.097$;[48]
   proportion of patients with relapses by category: 0 relapses, copolymer 1 34%, placebo 27%; 1–2 relapses, copolymer 1 48%, placebo 44%; ≥ 3 relapses, copolymer 1 18%, placebo 29%.[48]
3. Other outcomes:
   mean AI: copolymer 1 0.27 (SD 0.94), placebo 0.28 (SD 0.93); NS.[48]
4. Adverse effects:
   copolymer 1 – localised injection site erythema and induration (90%); transient systemic reaction (15%);
   placebo – localised injection site erythema and induration (59%); transient systemic reaction (3%).

Comments

- Review addressed clear question in terms of target population, interventions and outcomes.
- No search strategy, inclusion criteria or quality criteria provided.
- Methods of undertaking review not discussed.

CRD quality criteria for systematic reviews

1. Was an appropriate question asked in terms of intervention, patients and outcomes?	Yes
2. Was a search strategy provided?	No
3. Were appropriate inclusion discussed?	No
4. Were adequate quality criteria used?	No
5. Were sufficient study details provided?	Yes
6. Was synthesis of evidence appropriate?	Yes
Total score	3/6

Study and design	Intervention	Patients	Outcome measures
Weinstein, *et al.*, 1999.[50] USA. RCT; double-blind; multicentre.	Copolymer 1 (alternative name glatiramer acetate), 20 mg/day, vs. placebo (mannitol); both s.c. self-administered daily for 2 years. Drugs for spasticity, bladder control, fatigue and other MS symptoms were continued. Exacerbations treated using a protocol for steroid therapy.	Copolymer 1, *n* = 125; placebo, *n* = 126. Inclusion: clinically definite/laboratory definite MS, age 18–45 years, ambulatory with EDSS score 0 through 5, history of at least 2 clearly defined and documented relapses in past 2 years, onset of first relapse > 1 year before, neurologically stable, no steroids in past 30 days. Exclusion: previous copolymer 1, immunosuppressants or lymphoid radiation, pregnancy, diabetes, specified drug therapy. Setting: outpatient.	Neuropsychological evaluations at baseline, 12 and 24 months using Brief Repeatable Battery of Neuropsychological Tests (consists of Buschke selective reminding, 10/36 spatial recall, symbol digit modalities, paced auditory serial addition, word list generation).

Results (neuropsychological)
Mean scores lower than established normal baseline but within 2 SD. Exception was word list generation which was below normal in both groups. Improved at 12 and 24 months in both groups. No significant difference between groups. No significant interactions between level of treatment and either time/baseline level of impairment.

Comments

- Inclusion, exclusion criteria, interventions and outcomes clearly described. Randomisation performed using centralised randomisation scheme. Comparable placebo control therapy used.
- 85% of copolymer 1 group and 87% of placebo group completed treatment schedule. Analysis by ITT.
- Patients, examining neurologist, treating neurologist, neuropsychologists and nurse coordinator all blinded to treatment group. Relapses determined by blinded neurologist. Treatment groups comparable at baseline and groups treated equally.
- Outcomes included neuropsychiatric tests.
- Data analysis details: changes in neuropsychiatric test scores assessed using repeated measures analysis of covariance models.
- Treatment and follow-up over 2 years. Reasons given for only 9/19 withdrawals from copolymer 1 group and for 3/17 from placebo group. Proportion of patients who withdrew statistically similar over duration of study using Cochrane–Mantel–Haenzel test.
- No mention of any prior sample size/power calculation.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and drop-outs?	0 (reasons only for some)
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Copolymer 1 drop-outs, 19/125 (15%); placebo drop-outs, 17/126 (13.5%).

Appendix 11

Summary of trials of intravenous immunoglobulin in MS

Study and design	Intervention	Patients	Outcome measures
Achiron, *et al.*, 1998.[51] Israel. (Barak *et al.*, 1999[65] reports psychiatric outcomes.) RCT; double-blind.	Ig, loading dose 0.4 g/kg per day i.v., vs. 9% saline placebo i.v. for 5 consecutive days, followed by booster doses of Ig i.v. (0.4 g/kg)/placebo once daily every 2 months for 2 years. Severe and moderate exacerbations treated with steroids.	i.v. Ig, n = 20; placebo, n = 20. Inclusion: clinically definite RRMS (Poser) for > 1 year; average yearly exacerbation rate during preceding 2 years, 0.5–3; EDSS score 0–6; age 18–60 years. Exclusion: IgA deficiency; long-term steroids/ cytotoxic in previous year; major psychiatric disorder; major cognitive impairment. Setting: not stated.	Patient outcomes at 1, 2, and 0–2 years. Primary: yearly exacerbation rate; proportion of exacerbation-free patients; time till first exacerbation. Secondary: exacerbation severity; neurological disability (EDSS and cumulative disability over time). Psychiatric patient outcomes:[65] anxiety, depression, cognition and general psychopathy evaluated at baseline, 1 and 2 years using the following: 1. Goldberg A 2 Hamilton Anxiety Scale 3. Goldberg D 4. Beck depression inventory 5. Mini-Mental State Examination 6. Brief Psychiatric Rating Scale.

Results (analysis (unless stated) included only patients who completed 2-year study)

1. Yearly exacerbation rate: year 1, i.v. Ig 0.75, vs. placebo 1.80, p = 0.0002; year 2: i.v. Ig 0.42, vs. placebo 1.42, p = 0.0009; 0–2 years, i.v. Ig 0.59, vs. placebo 1.61, p = 0.0006. ITT analysis: year 2, i.v. Ig 0.4, vs. placebo 1.54, $p < 0.001$.
2. Number of exacerbation-free patients 0–2 years: i.v. Ig 6, vs. placebo 0, p = 0.001.
3. Time to first exacerbation – median time: i.v. Ig 233 days, vs. placebo 82 days, p = 0.003; Kaplan–Meier survival analysis of probability of remaining exacerbation-free: log-rank statistic p = 0.003.
4. Mean EDSS: no significant difference.
5. Distribution in neurological severity: i.v. Ig – improved 23.5%, stable 62.8%, worse 13.7%, vs. placebo – improved 10.8%, stable 72.1%, worse 17.1%; p = 0.03.
6. Mean annual severity of exacerbations: no significant difference over year 1 or year 2.

Psychiatric[65] (mean scores for both groups on Goldberg A, Goldberg D, Brief Psychiatric Rating Scale and Mini-Mental State Examination reported at baseline, 1 and 2 years. Differences in mean scores at 2 years are:

(1) anxiety (Goldberg A): i.v. Ig –0.79 vs. placebo –1.1; p = 0.67;

(2) depression (Goldberg D): i.v. Ig –0.42 vs. placebo –1.0; p = 0.48;

(3) cognitive function (Mini-Mental State Examination): i.v. Ig 95 vs. placebo 0.37; p = 0.42;

(4) general psychopathy (Brief Psychiatric Rating Scale): i.v. Ig –1.95 vs. placebo –3.42; p = 0.33.

Cognitive performance correlated negatively with relapse (r = 0.37; p = 0.053).

Adverse effects

Overall incidence of notable side-effects reported as low; 'i.v. Ig infusions tolerated well'.

i.v. Ig group: pathological laughing and crying 1/20; depression requiring treatment 1/20.

Placebo group: hypomania 2/20; pathological laughing and crying 2/20.

Side-effects in both groups: fatigue, headaches, rash and low-grade fever; all resolved spontaneously.

continued

continued

Comments

- Inclusion and exclusion criteria clearly defined. Outcomes such as relapse and severity of exacerbation defined. Treatment regimes described and placebo treatment is comparable to active treatment. Treatment allocation by block-stratified randomisation designed to balance groups for yearly exacerbation rate, age and disease duration. Patients, neurological assessor, neuroradiologist and psychiatric assessor blinded to treatment group.
- Analysis of data included only patients that completed 2-year study period. ITT analysis performed but results of only one ITT analysis reported. Diagnosis of relapse made by neurologist blinded to treatment group.
- Both groups similar at baseline with respect to age, duration of disease, EDSS, gender ratio and psychiatric rating scales. Patients and controls appear to have been treated equally.
- T-tests used to compare yearly exacerbation rates, exacerbation severity; paired *t*-tests used to assess changes in yearly exacerbation rate, changes in EDSS; Fisher's exact test used to compare number of exacerbation-free patients; χ^2 test used to compare distribution of cumulative disability over time. Pearson correlation coefficient used for continuous variables and χ^2 comparison for categorical variables to evaluate correlations between neuropsychological findings and other outcomes. Mean scores of four psychiatric rating scales are presented. Not clear whether analysis of psychiatric outcomes compared differences (baseline to end) between group means or compared mean of differences in individuals (baseline to 2 years) between groups, though it seems likely that latter appropriate method may have been used. Non-parametric tests may have been considered appropriate for comparison of rating scales.
- Two drop-outs (1 from each group) reported with reasons but not with reasons by group.
- Prior sample size estimation based on mean yearly exacerbation rate = 2 (SD 1.5), $p = 0.05$ (1-tail), power = 80%, to detect 50% reduction in yearly exacerbation rate. This estimated minimum group size of 14.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1 (method)
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	i.v. Ig drop-outs, 1/20 (5%); placebo drop-outs, 1/20 (5%).

Study and design	Intervention	Patients	Outcome measures
Sørensen, *et al.*, 1997.[52] Denmark. RCT; double-blind crossover.	Group 1: placebo for 6 months; 3-month wash-out; i.v. Ig for 6 months. Group 2: reverse order. i.v. infusion of IgG, 1.0 g/kg/day for 2 consecutive days, at intervals of 4 weeks for 6 months; placebo – i.v. infusion of human albumin 2% in identical regime. Severe exacerbations (defined) treated with i.v. methylprednisolone, 1 g/day for 3 days.	n = 25. Inclusion: age 20–50 years, clinically definite MS (Poser) for > 10 years with acute exacerbations (RRMS or RPMS); two or more acute exacerbations in past year; EDSS score 2.0–7.0; at least 5 cerebral lesions on T2-weighted images on MRI; no acute exacerbation 1 month prior to entry; no steroids in past 3 months; no previous immunosuppressants. Exclusion: pregnant or at risk of pregnancy; serious systemic illness. Setting: not specified.	Patient outcomes: number of clinical attacks; neurological function on Scripps NRS and EDSS assessed every 4 weeks. Non-patient outcomes: primary outcome was new lesions on MRI.

Results (presented for 17/25 patients who completed both treatment periods)

1. Number of patients with no exacerbations: i.v. Ig 11 vs. placebo 6; $p = 0.05$, χ^2 for paired observations.
2. Total number of acute exacerbations: i.v. Ig 11 vs. placebo 15; $p > 0.10$, Wilcoxon test for paired differences.
3. Severe acute exacerbations requiring i.v. steroids: i.v. Ig 4 vs. placebo 6; $p > 0.10$, Wilcoxon test for paired differences.
4. Insignificant changes in NRS and EDSS during i.v. Ig and placebo periods.

Adverse effects (number affected) reported to be high.

i.v. Ig: headache 11; severe eczema 10; urticaria 5; hepatitis C 1; nausea 2; fever 1; oedema 1; dizziness 1; arthralgia 1; paraesthesia 1; malaise 1; depression 1.

Placebo: headache 4; malaise 3; eczema 1; fever 1; dizziness 1; anaemia 1.

No point estimates or CIs reported.

Comments

- Inclusion and exclusion criteria clearly defined. Interventions and outcomes described. Method of randomisation to order of treatments not stated. Placebo treatment comparable. Only those completing trial analysed. Trial described as double-blind but no details given of methods to ensure blinding of either clinical or investigative assessors. All participants underwent similar assessments.
- Patient and non-patient outcomes assessed with primary outcome being a non-patient one. Not clear whether person determining exacerbations was blinded or not.
- Crossover trial design used with wash-out period of 3 months. This may have been adequate period to reduce any lingering effect of first treatment period but an assessment of period effect and treatment–period interaction prior to analysis of treatment effect would have been helpful. In crossover designs, problems may arise with patients who drop out of first treatment and do not receive second treatment. Drop-out rate in this trial was 8/25 (32%). No treatment effect sizes estimated. Primary efficacy parameter (see below) not yet assessed.
- Sample size estimated to detect 50% difference in number of new lesions on MRI (alpha, 0.05, beta, 20%). Study not powered to detect difference in number of acute exacerbations.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Crossover with n = 25 entered. Percentage approximate since no timing of withdrawals stated. During i.v. Ig period: 4 withdrew (16%). During placebo period: 4 withdrew (16%), one as a result of severe eczema developed during i.v. Ig.

Study and design	Intervention	Patients	Outcome measures
Fazekas, *et al.*, 1997.[54] Austria. Multicentre RCT; double-blind. [Fazekas, *et al.*, 1997[68] (multiple sclerosis), analysed time course of treatment benefits from above study but adds no useful information.]	i.v. Ig, 0.15–0.20 *g*/kg bodyweight vs. saline placebo; every month for 2 years. Exacerbations treated with 1 g methylprednisolone for 5–10 days then tapering.	i.v. Ig, *n* = 75; controls, *n* = 73. Inclusion: clinically definite RRMS (Poser); baseline EDSS score 1.0–6; at least 2 documented relapses in past 2 years; age 15–64 years; age of onset 10–59 years; stopped immunosuppressants > 3 months before. Exclusion: steroids in past 2 weeks; unreliable contraception; primary/secondary progressive course of MS; benign course of disease (defined). Setting: not stated.	Primary: change in EDSS score from baseline to 2 years. Evaluated as: (1) between group differences in absolute change in EDSS score; (2) proportion of patients with improved, stable or worse clinical disability (defined as increase/decrease of at least 1.0 grade on EDSS score). Secondary: (3) number of relapses; (4) annual relapse rate; (5) proportion of relapse-free patients; (6) time to first relapse within study period. Relapse defined. (7) Further analysis: monthly relapse rates.

Results (ITT analysis)

(1) Mean change in EDSS score: i.v. Ig –0.23 (95% CI, –0.43 to –0.03) vs. placebo 0.12 (–0.13 to 0.37); $p = 0.008$.

(2) Improved: i.v. Ig 31% vs. placebo 14%; worse: i.v. Ig 16% vs. placebo 23%; $p = 0.41$.

(3) Number of relapses: i.v. Ig 62 vs. placebo 116.

(4) Annual relapse rate over study period: i.v. Ig 0.52 (95% CI, 0.32 to 0.72) vs. placebo 1.26 (95% CI, 0.75 to 1.77); $p = 0.0037$.

(5) Relapse-free patients: i.v. Ig 53% vs. placebo 36%; $p = 0.03$.

(6) Time to first relapse within study period: no significant difference between groups.

(7) Monthly relapse rates for each follow-up period of 6 months: graphed, no figures.

Adverse effects

i.v. Ig group – total *n* = 3 (4%); cutaneous reactions 2; eosinophilia in patient who was also taking anafranil.

Placebo – total *n* = 4 (5%); eosinophilia; hypogastric pain; myocardial infarction; pulmonary embolism; ileus.

No point estimate or CIs reported for treatment effect.

Estimated from data presented: RR of relapse (i.v. Ig vs. placebo) 0.72 (95% CI, 0.54 to 0.97).

Comments

- Inclusion and exclusion criteria clearly defined. Outcomes and interventions described.
- Randomisation performed using computer-generated schedule with stratification by centre, age, gender, and deterioration rate. Comparable control treatment used.
- All randomised patients accounted for and analysis was by ITT.
- Patients blinded as was assessing neurologist. Relapses confirmed by blinded evaluator. Treating physician, who administered treatment, not blinded.
- Treatment groups similar at baseline and there was equal treatment of patients and controls.
- Relevant outcome measures used but no evaluation of patient's view. Drop-outs with reasons listed by treatment group. 2 years of treatment and follow-up.
- Differences between groups was by non-parametric methods. Survival curves and log rank test used to assess differences in time to first relapse.
- Point estimates and CI of treatment effects not reported.
- Prior sample size estimated to give a power of 90% with significance level of 0.05% in detecting mean difference in change of EDSS score of 0.81 (SD 1.37) and allowing for 20% drop-outs. 75 patients per treatment group required. Groups of 75 and 73 patients entered.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 1 (method)
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	i.v. Ig: randomised, *n* = 75; withdrew, *n* = 11 (15%); controls: randomised, *n* = 73; withdrew, *n* = 17 (23%).

Appendix 12

Summary of trials of methotrexate in MS

Study and design	Intervention	Patients	Outcome measures
Currier, *et al.*, 1993.[55] USA. RCT; double-blind.	Methotrexate, 2.5 mg oral, vs. placebo; both every 12 hours for 3 consecutive doses, weekly for 18 months. Additional treatment with steroids for exacerbations permitted.	Methotrexate, *n* = 22; controls, *n* = 22. Inclusion: definite MS (included ERMS, CPMS and exacerbating PMS, spinal MS), with worsening of function/ exacerbation in previous year. Exclusion: renal or hepatic dysfunction, gross obesity, diabetes. Median age: 39.5 years. Setting: not specified.	Patient outcomes assessed at 18 months: number and timings of exacerbations and worsening by 1 point on Kurtzke scale. Exacerbation defined. Non-patient outcomes: blood counts and liver function tests every 2 months.

Results (overall no difference in outcome between treatment groups)

1. Number of exacerbations: methotrexate 8/22 (36%) vs. control 9/22 (41%).
2. Proportion of patients having exacerbations: no significant difference.
3. Mean number of exacerbations: $p = 0.05$ for subgroup of RRMS patients.

Results reported for various subgroups of patients including ERMS and CPMS.

No estimate of size of treatment effect.

Adverse effects (numbers experiencing) (methotrexate reported as being tolerated reasonably well)
Methotrexate: moderate hair thinning 1, abnormal liver function tests 8, with abnormality persisted in one patient.

Placebo: headaches 2, abnormal liver function tests 1.

Comments

- Broad inclusion criteria with no details of baseline characteristics of participants. Interventions, outcomes and terms such as exacerbation clearly described.
- Patients randomised to treatment groups but no details given of methods used.
- Comparable placebo control treatment used.
- 44/45 randomised patients included in analysis; 9/45 dropped out before completion of treatment. Patients and evaluator blinded, treating physician was not. Exacerbations diagnosed by 'experienced neurologist' but not clear if this evaluator was blinded.
- No comparison of baseline characteristics between treatment groups. Treatment groups appear to have been treated equally.
- Outcomes included number of exacerbations and Kurtzke DSS.
- Data analysis details: Fisher's exact test used to examine differences in proportion of patients having exacerbations; two-sample *t*-test used to compare mean difference in number of exacerbations, mean difference in number of exacerbations plus Kurtzke worsening.
- Active treatment and follow-up over period of 18 months. Reasons given for drop-outs but not described by treatment group. Results not clearly presented.
- No prior sample size/power calculation appears to have been undertaken.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and drop-outs?	0 (not described by group)
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Included in analysis, *n* = 44 (1 dropped out after taking single pill; group not stated): methotrexate included, *n* = 22; placebo included, *n* = 22. Overall 10 dropped out (22%); not described by treatment group.

Study and design	Intervention	Patients	Outcome measures
Goodkin, *et al.*, 1995.[56] USA. RCT; double-blind.	Methotrexate, 7.5 mg oral, vs. placebo; both weekly for 2 years. Standardised steroid protocol used to treat exacerbations. Symptomatic therapies permitted, e.g. antidepressants, antispasmodics, antibiotics, bladder medications, physical and occupational therapy, psychological counselling, support groups.	Methotrexate, *n* = 31; placebo, *n* = 29. Inclusion: clinically definite CPMS (Poser); none experiencing exacerbation in previous 8 months or > 1 exacerbation in previous 2 years. Age 21–60 years; disease duration > 1 year; entry EDSS score 3.0–6.5 inclusive; entry AI score 2.0–6.0 inclusive. No steroids within previous month or immunosuppressants in previous year or exposure to lymphoid irradiation. Excluded: pregnant/unreliable contraception, systemic illness/other medical illness, cognitive impairment. No significant differences on gender, age, disease duration, disease course on baseline assessment of outcome measures between groups. Setting: not specified.	Patient outcomes evaluated at entry and annually for 2 years. 1. Treatment failure defined as composite in any of following ways for at least 2 months: worsening of EDSS score (by 1.0 points or more for those with entry score of 3.0–5.0, or by 0.5 points or more for those with entry score of 5.5–6.5), worsening of AI score of 2–6 by 1 point or more, worsening of box and block/9-hole peg test by 20% or more. 2. Participants' global opinion as to whether status better, the same or worse. Non-patient outcomes: new or enlarging lesions on gadolinium-enhanced MRI scan annually for 2 years.

Results

1. Primary outcomes: sustained (> 2 months) treatment failure rates using composite outcome: methotrexate 16/31(51.6%) vs. placebo 24/29 (82.8%); $p = 0.011$. Estimated OR from data (by authors): OR of treatment failure on placebo compared with methotrexate, 4.5 (95% CI, 1.36 to 14.85).
2. Secondary outcomes: treatment failure for each component of composite –
   EDSS, methotrexate 11/31 (35.5%) vs. placebo 15/29 (51.7%); $p = 0.205$;
   AI, methotrexate 12/31 (38.7%) vs. placebo 11/29 (37.9%); $p = 0.951$;
   9-hole peg test, methotrexate 5/ 31 (16.1%) vs. placebo 14/29 (48.3%); $p = 0.007$;
   box and block, methotrexate 4/31 (12.9%) vs. placebo 10/29 (34.5%); $p = 0.068$.
3. Participants global opinion: no significant differences in status between groups as assessed by patients, study nurse, and examining physician; 68% in both groups considered that they were worse.
4. Sustained (> 2 months): treatment failure rates for subgroups analysed according to:
   EDSS score at entry (< 6 vs. ≥ 6); EDSS < 6, methotrexate 5/9 (55.6%) vs. placebo 8/10 (80.0%); $p = 0.35$; EDSS ≥ 6, methotrexate 11/22 (50.0%) vs. placebo 16/19 (84.2%); $p = 0.046$.

Primary vs. secondary progressive clinical course: primary, methotrexate 3/7 (42.9%) vs. placebo 7/11 (63.6%); $p = 0.630$; secondary, methotrexate 13/24 (54.2%) vs. placebo 17/18 (94.4%); $p = 0.005$.

Adverse effects: reported as similarly distributed between treatment groups; included upper respiratory tract infections, urinary tract infections, nausea, headache, fever, mucocutaneous herpes, sore muscles, backache, indigestion, diarrhoea.

Adverse reactions: 27 methotrexate patients reported 113; 26 placebo patients reported 103.

Comments

- Inclusion and exclusion criteria clearly defined. Characteristics of participants, interventions and outcomes described.
- Eligible patients stratified by EDSS score (< 6 vs. ≥ 6) and randomised in blocks of 10, with 'treatment assignment being made by unblinded study coordinator'. Full details not given. Placebo control comparable to active therapy. All randomised patients accounted for in clearly presented table.
- 24/31 patients completed methotrexate course and 27/29 completed placebo intervention. Analysis by ITT at 2 years.
- Patients and examining neurologist blinded. Treating physician and study coordinator were not.
- Two treatment groups similar at baseline and treated equally.
- Data analysis details: efficacy of methotrexate assessed using binomial comparison of proportions; Kaplan–Meier methods used to estimate failures and exacerbation rates with log-rank test being used to compare distributions between treatment groups; Cox-proportional hazards regression models used to examine predictors of treatment failure; analysis undertaken using only 2-year treatment data but no reasons given for excluding third observation year from analysis; drop-outs described with reasons by treatment group.

continued

continued

Comments

- Sample size/power calculation: calculations estimated sample size of 60 patients to detect 50% reduction in treatment failure rate over 2 years, with alpha = 0.05 and power = 0.90.
- Patients permitted treatment with standardised steroid protocol when experiencing (i) subjective worsening for 5 days or more accompanied by objective deterioration of SNE or (ii) subjective worsening for 2 weeks or more without objective change on neurological examination if treatment deemed clinically appropriate. Re-treatment permitted.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Methotrexate, drop-outs 7/24 (29%); placebo, drop-outs 2/ 29 (7%).

Appendix 13

Summary of trials of mitoxantrone in MS

Study and design	Intervention	Patients	Outcome measures
Millefiorini, *et al.*, 1997.[58] Italy. Multicentre RCT. Bastianello, *et al.*, 1994.[57] Reports on sub-group from above who had serial enhanced MRI scans for 1 year.	Mitoxantrone, 30 minute infusion (8 mg/m^2) every month for 1 year, vs. placebo. Other drugs allowed: cholinergics, spasmolytics, short courses of steroids for exacerbations.	Millefiorini, *et al.*: mitoxantrone, *n* = 27; controls, *n* = 24. Bastianello, *et al.* (subgroup selected from 4 centres): mitoxantrone, *n* = 13; controls, *n* = 12. Inclusion criteria: age 18–45 years, clinically/laboratory-supported RRMS (Poser criteria), disease duration 1–10 years, disability on EDSS scale 2–5, at least 2 exacerbations in previous 2 years. Exclusions: HIV-positive, previous cardiovascular disease, specified serious illness, psychiatric illness, pregnancy/risk of pregnancy, steroids in past 3 months, previous immunosuppressants.	Primary (patient): proportion with confirmed progression as measured by an increase of at least 1 point on EDSS scale from baseline to year 1 and to year 2 and total from baseline to 2 years. Secondary: annual mean number of exacerbations and proportion of exacerbation-free patients in years 1 and 2; mean number of exacerbations from 0 to 2 years; number of exacerbation-free patients from 0 to 2 years; change in mean EDSS from 0 to 2 years. Non-patient secondary outcome: mean number of new or enlarged lesions on MRI.

Results

1. Proportion of patients with progression, percentage difference (placebo – mitoxantrone): year 1, 18% (95% CI, 5 to 38); year 2, 25% (95% CI, 7 to 43); 0–2 years, 30% (95% CI, 8 to 52).
2. Mean number of exacerbations, difference (placebo – mitoxantrone): year 1, 1.02 (95% CI, 0.36 to 1.68); year 2, 0.73 (95% CI, 0.18 to 1.28); 0–2 years total: 1.73 (95% CI, 0.62 to 2.84).
3. Proportion of exacerbation-free patients, percentage difference (mitoxantrone – placebo): year 1, 45% (95% CI, 21 to 69); year 2, 36% (95% CI, 11 to 63); 0–2 years total, 42% (95% CI, 15 to 65).
4. Change in mean EDSS from baseline to 24 months: no significant difference.

Bastianello, *et al.* – outcomes at 1 year
No significant relationships between changes in EDSS score and total number of new lesions at 1 year.

Adverse effects: mitoxantrone reported to be generally well tolerated; side-effects reported for mitoxantrone group, nausea (generally mild and controlled by antiemetics) 9/51 (18%), upper respiratory tract infection 2/51 (4%), urinary tract infection 3/51 (6%), headache 3/51 (6%), diarrhoea 1/51 (2%); transient amenorrhoea in 5/17 women; no changes in ECG or left ventricular systolic function measurements.

Comments

- Clearly defined inclusion and exclusion criteria. Interventions detailed. Outcomes clearly stated and defined. Randomisation stratified by age, gender and EDSS using block design with size 8, with allocation using randomised code number supplied by relevant centre. Not clear if randomised by centre (8 centres involved). Groups comparable at baseline for age, disease duration, number of exacerbations in previous 2 years; imbalance in gender ratios; mitoxantrone group had more with higher baseline EDSS scores.
- Patients and assessors blinded, treating physician not blinded. Unblinded treating physician responsible for evaluating adverse events and exacerbations. Authors acknowledge that this may have resulted in systematic bias. Both groups received infusion with i.v. bag and tubing in black. Not clear if hospital carers blinded. Levels of intra-observer and intercentre assessment agreements rated.
- Clinical outcomes reported for all those randomised. Analysis of clinical outcomes by ITT.

continued

continued

***Comments* contd**

- Relevant clinical outcomes used. Clinical and MRI differences between two groups evaluated using non-parametric methods. χ^2 test used for categorical data. Point estimates and CIs of treatment effect stated. Follow-up period 24 months. Patients treated in eight different centres but effect of centre does not appear to have been assessed.
- Prior power calculation estimated sample size of 65 per treatment arm to detect an increase of EDSS in 25% of mitoxantrone group compared with 50% of placebo group, with alpha = 0.05, beta = 0.20. These numbers not achieved (achieved group sizes of 27 and 24). Authors acknowledge study underpowered due to recruitment difficulty. Inability to recruit adequate number of patients may suggest that generalisability limited.

Quality assessment (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1 (appropriate method)
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Mitoxantrone, *n* = 27 entered; placebo, *n* = 24 entered; no mention of withdrawals for clinical outcomes. Withdrawals from repeat MRI: mitoxantrone, *n* = 4/27 (15%); placebo, *n* = 5/24 (21%).

Study and design	Intervention	Patients	Outcome measures
Edan, *et al.*, 1997.[59] France. RCT.	Mitoxantrone, 20 mg i.v./month + methylprednisolone, 1 i.v./month, vs. methylprednisolone, 1 g i.v./month alone. Other interventions as used. Additional courses of steroids, 1 g/day i.v. for 3 days, were permitted for relapses.	Mitoxantrone, *n* = 21; controls, *n* = 21. Inclusion: clinically definite MS (Poser), age 18–45 years, duration of disease less than 10 years, either 2 relapses with sequelae within previous 12 months/progression of 2 points on EDSS scale in those with SPMS, EDSS of 6 or less; RRMS (defined) and SPMS included. Exclusion: systemic or cardiac disease, mental deficit, ineffective contraception, steroids in past month. Setting: not specified.	Patient outcomes evaluated at 6 months. Secondary: clinical outcome assessed by EDSS and number of exacerbations. Non-patient outcomes – primary: proportion of patients developing/not developing new enhanced lesions on serial gadolinium-enhanced scans.

Results (analysis at 6 months based only on those completing treatment)

1. Mean change in EDSS at 6 months: methylprednisolone + mitoxantrone, –1.1 (SD 1.1) vs. methylprednisolone, –0.1 (SD 1.1); $p < 0.05$.
2. Number of relapse 0–6 months: methylprednisolone + mitoxantrone, 7 vs. methylprednisolone, 31; annual rate of relapse per patient: methylprednisolone + mitoxantrone, 0.7 vs. methylprednisolone, 3.0; $p < 0.01$; number of patients exacerbation-free 0–6 months, methylprednisolone + mitoxantrone, 14 vs. methylprednisolone, 7; $p < 0.05$.

No estimates of size of treatment effect.

Adverse effects

Mitoxantrone + methylprednisolone: 18/21 had at least 1 adverse event – amenorrhoea 8, alopecia 7, nausea and vomiting 6, other digestive events 6, cutaneous events 5, asthenia 5, upper tractus infections 5, urinary tract infections 4, other neurological events 3, tachycardia 1, menorrhagia 1, others 4, leucopenia < 3000/mm^3 2, anaemia 4.

Methylprednisolone: 6/21 had at least 1 adverse event – other digestive events 1, cutaneous events 2, upper tractus infections 2, urinary tract infections 1, tachycardia 1, hepatitis 1, headache 1, others 1, anaemia 1.

Comments

- Inclusion and exclusion criteria defined as are interventions and outcomes. Randomisation using a central randomisation service. Not clear if patients blinded to treatment group. Assessors of EDSS and relapses not blinded. Assessors of MRI scans blinded. Study did not include placebo control group.
- Treatment groups comparable at baseline and assessed at equal intervals.
- Analysis performed using only results from patients who completed study.
- Primary outcomes non-patient ones. Patient outcomes included EDSS scores and exacerbations.
- Non-parametric methods used to test for clinical outcomes between groups. Differences in proportions assessed using χ^2 tests.
- Analysis not by ITT. Follow-up period of short duration, being only 6 months. Results did not include any estimation of treatment effect. Drop-outs described by reason and by treatment group. All those in mitoxantrone + methylprednisolone group completed study; 5/21 dropped out of steroid-only group (pronounced deterioration).
- Not stated if prior sample size/power calculation performed.

Quality assessment (Jadad score)

Question	Score
Was the study described as randomised?	1 + 1 (method)
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Methylprednisolone + mitoxantrone: randomised *n* = 21, drop-outs *n* = 0 (0%); methylprednisolone: randomised *n* = 21, drop-outs *n* = 5 (24%).

Appendix 14

Costings for MS drugs

Costs taken from BNF, March 1999, where available.[66] Indicated dose taken from BNF or from an expert paper.[67] Dose and administration information (J Zajicek, Plymouth; personal communication, 1999).

Drug	BNF price	Dose	Administration	Annual drug cost/ patient (£)	Drug cost per 100 people treated/year (£)
Azathioprine					
Non-proprietary	50 mg x 100 tablets £16.04	1–3 mg/kg orally daily (min: 50 mg daily for 50 kg person; max: 250 mg daily for 83 kg person)	oral	58.55–292.73	5855–29,287
Imuran®	50 mg x 100 tablets £65.61			239.49–1197.38	23,949–119,738
IFβ					
Rebif®	22 µg syringe (6 MIU) £61.00	6 MIU 3 times weekly (N.B. also now licensed at a higher dose of 12 MIU)	s.c. or i.m. injection	9516 (19,032)	951,600 (1,903,200)
Avonex®	30 µg vial (6 MIU) £182.50	6 MIU once weekly		9490	949,000
Betaferon®	300 µg vial (9.6 MIU) £53.75	8 MIU 3.5 times weekly		9783	978,300
Cladribine					
Leustat®	10 ml vial £364.57 (1 mg/ml)	0.7 mg/kg by continuous i.v. infusion at monthly intervals for 4 months (35 mg per month for 50 kg person; 59.5 mg per month for 85 kg person)	i.v. infusion	5833.12–8749.68	583,312–874,968
Cyclophosphamide					
Cyclophosphamide (Pharmacia Upjohn)	50 mg x 100 tablets £10.60 200 mg vial £1.65 500 mg vial £2.88 1 g vial £5.04	Dose information from trials (examples): 80–100 mg/kg i.v. (high dose)* or 2 mg/kg i.v. (low dose) with ACTH + plasma exchange or 750 mg/m^2 or 1 g i.v. (alternate days to max 9 g) or 1.5–2.0 mg/kg/day orally** for 22 weeks + plasma exchange or 33–200 mg/kg i.v. or 125 mg i.v. q.d.s. for 8–18 days or 125 mg i.v. q.d.s. for 8–18 days + 700 mg/m^2 booster every 2 months	i.v. or oral	20.16*–63.60**	2016–6360
Endoxana®	50 mg x 100 tablets £10.50 200 mg vial £1.61 500 mg vial £2.81 1 g vial £4.90			19.60*–63.00**	1960–6300
Copolymer 1	Not in BNF (price estimated in DEC report[47] as being similar to IFβ)				
Glatiramer		20 mg daily	s.c. injection	c.10,000	c.1,000,000

* *Based on 50 kg person*
** *Based on 85 kg person*

continued

Drug	BNF price	Dose	Administration	Annual drug cost/ patient (£)	Drug cost per 100 people treated/year (£)
i.v. Ig	Not in BNF (prices obtained from Southampton Drug Information Unit 14/9/99)				
Sandoglobulin®	1 g £19.01; 3 g £45.63; 6 g £91.26; 12 g £182.52	0.15–0.2 g/kg by monthly i.v. infusion for 2 years (min: 7.5 g monthly for 50 kg person; max: 17 g monthly for 85 kg person) **or** 1 g/kg i.v. for 2 days every 4 weeks for 24 weeks (min: 50 g per 2-day treatment for 50 kg person; max: 85 g per 2-day treatment for 85 kg person)	i.v. infusion	1642.68–3285.36 **or** 4608.60–7779.60	164,268–328,536 **or** 460,860–777,960
Vigam® S	2.5 g £49.88; 5 g £99.75; 10 g £199.50			1795.56–4189.56 **or** 5985.00–10,174.50	179,556–418,956 **or** 598,500–1,017,450
Methotrexate					
Non-proprietary	2.5 mg x 100 tablets £11.41 10 mg x 100 tablets £55.07	7.5 mg once weekly, adjusted according to response; max. weekly total dose 20 mg	oral	17.80–47.47 max: 57.27	1780–4747 max: 5727
Mitoxantrone					
Novantrone®	10 ml vial £150.42 (2 mg/ml) 12.5 ml vial £188.05 (2 mg/ml) 15 ml vial £225.60 (2 mg/ml)	8 mg/m^2 i.v. monthly; or 20 mg i.v. monthly	i.v. infusion	3610.08	361,008

Appendix 15

Critical appraisal of cost-effectiveness studies of disease-modifying drugs in MS

Critical appraisal: decision analysis questions and economic evaluation questions[9,10]	Study					
	Otten, 1998[33]	**Nicholson & Milne, 1999[34]**	**Parkin, *et al.*, 1998[35]**	**Nicholson & Milne, 1996[47]**	**Nicholson & Milne, 1999[34]**	**Forbes, *et al.*, 1999[38]**
	IFβ-1a	**IFβ-1a in RRMS**	**IFβ-1b in RRMS**	**Copolymer 1 in RRMS**	**IFβ-1b in SPMS**	**IFβ-1b in SPMS**
Did analysis provide a full economic comparison of healthcare strategies? (i.e. were all important strategies and outcomes included?)	No	No	No	No	No	No
Was an explicit and sensible process used to identify, select, and combine the evidence into probabilities?	Yes	Yes	Yes	Yes	Yes	Yes
Were the utilities obtained in an explicit and sensible way from credible sources? (Were the costs and outcomes properly measured and valued?)	Yes	Yes	Yes	Yes	Yes	Yes
Was appropriate allowance made for uncertainties in the analysis? (i.e. was the potential impact of any uncertainty in the evidence determined?)	Yes	Yes	Yes	Yes	Yes	Yes
Are the estimates of costs and outcomes related to the baseline risk in the treatment population?	No	No	Yes	No	No	Yes

Appendix 16

Summary of cost-effectiveness studies of disease-modifying drugs in MS

Data extraction questions	Study		
	Otten, 1998[33] **IFβ-1a**	**Nicholson & Milne, 1999[34]** **IFβ-1a in RRMS**	**Parkin, *et al*., 1998[35]** **IFβ-1b in RRMS**
1. Cost–utility analysis question addressed in the study.	For patients in the PRISMS trial, what is the likely cost/QALY in terms of reduction in relapses and slowed progression of their receiving IFβ-1a (Rebif®) rather than placebo?	For patients with RRMS, what is the cost/QALY of IFβ-1a in avoiding hospital relapses?	For patients with RRMS, what is the cost/QALY of IFβ-1b in avoiding hospital relapses (and in avoiding progression using possible but unconfirmed effects on progression at 5 and 10 years)?
2. Study design (for assessment of probabilities and costs).	Conference report and confidential copy of results from PRISMS trial. Costs from previous report from Canadian Coordinating Office for HTA on IFβ-1b.	Cost–utility analyses using RCTs of IFβ-1a (Ebers, *et al*., 1998[25] (PRISMS) and Jacobs, *et al*., 1996[27]) and cost data (BNF).[66]	Cost–utility analysis using clinical trial results plus primary data collection on costs and quality of life from a sample of patients with RRMS (Decision Analytic Model).
3. Methods used to assess quality of life.	Not stated.	Expert opinion using IHQL.	Diary and structured questionnaire to assess quality of life, administered to MS patients in catchment area of Newcastle-upon-Tyne neurology service. Interviews with sample of patients (n = 50) using time trade-off to assess utilities.
4. Discount rate for benefits and costs.	Not stated.	Costs 6%; benefits not stated.	Costs 6%; benefits – rate not stated.
5. Changes in quality of life used.	0.018 QALYs per relapse; 0.19 QALYs from avoiding progression from EDSS 3 to 5.	0.0112 QALYs lost per relapse.	0.0417 QALYs per relapse.
6. Costs and savings used per patient.	Costs: $17,000 per year (for drugs); savings: $2950 (hospital admission for relapse and progression avoided).	Costs: £9500 per year; savings: £800 per year.	Costs: £10,500; savings: £600.
7. Cost per QALY.	$406,000–490,000	£2,038,400 (95% CI, 94,000 to 34,130,300) for relapses avoided.	£809,900 per relapse avoided.
8. Lower end in sensitivity analysis.	$406,000	Best case £94,000.	£74,500 most optimistic estimate (10-year model).

Data extraction questions	Study		
	Nicolson & Milne, 1996[47] IFβ-1a	**Nicolson & Milne, 1999[34] IFβ-1a in SPMS**	**Forbes, *et al.*, In press.[38] IFβ-1b in SPMS**
1. Cost–utility analysis question addressed in the study.	For patients with RRMS what is the likely cost/QALY in terms of reduction of relapses in their receiving Copolymer 1 rather than placebo?	For patients with SPMS, what is the cost/QALY of IFβ-1b in delaying progression?	For patients with SPMS in Tayside, what is the likely cost/QALY in terms of reduction in relapses and postponed wheelchair dependency of their receiving IFβ-1b rather than placebo?
2. Study design (for assessment of probabilities and costs).	Structured review of RCTs (Johnson, *et al.*, 1995[48] and Bornstein, *et al.* 1987[49]). Cost data from drug companies and ECRs.	Cost–utility analyses using RCTs of IFβ-1b (Kappos, *et al.*, 1998[36]) and cost data (BNF[66]).	Baseline risk from Tayside population of people with MS. RR reduction from RCT. Cost data from survey data, published sources and local healthcare services.
3. Methods used to assess quality of life.	Explicit mapping of relapses on to IHQL by authors.	Expert opinion using IHQL.	Postal survey of all people with MS in Tayside using Postal Ambulation Scale and EQ-5D.
4. Discount rate for benefits and costs.	Costs 5%; benefits – rate not stated.	Costs 6%; benefits not stated.	Costs 6%; benefits 6%.
5. Changes in quality of life used.	0.011 QALYs per average relapse; 0.082 for severe relapse.	0.239 QALYs gained by delays in progression.	0.021 QALYs per community-treated or untreated relapse; 0.031 QALYs per hospital-treated relapse; 0.281 QALYs per 9 months of wheelchair dependence avoided.
6. Costs and savings used per patient.	Costs: £10,100 per year; savings: £120 per year.	Costs: £9800 per year; savings from relapses avoided not identified.	Costs: £9600 per year; savings: £45 per year.
7. Cost per QALY.	£0.5–3.6 million	£874,600 (95% CI, 611,700 to 895,000).	£1,024,000 (95% CI, 276,200 to 1,485,000).
8. Lower end in sensitivity analysis.	£90,000	Best case £661,700.	Sensitivity analysis using thresholds: decreasing costs to £4800/patient/year = £506,400; decreasing hospital/community input by 31% = £832,400; increasing QALY by 25% = £820,000.

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Feedback

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We look forward to hearing from you.

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