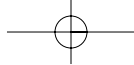


Proceedings of the MS Forum Symposium
13th ECTRIMS Congress
Istanbul, November 1997

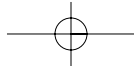
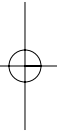
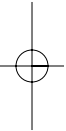


New Treatments for Multiple Sclerosis – A Review of Clinical Trial Results

Chairmen: Brian Weinshenker; David Bates



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New Treatments for Multiple Sclerosis – A Review of Clinical Trial Results

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THE MS FORUM

The MS Forum is an initiative funded by Schering AG which has been established to improve the awareness and understanding of multiple sclerosis on an international basis. Founded in 1993, the MS Forum draws its direction from an Executive Committee of internationally renowned opinion leaders. It is committed to encouraging debate and exchange of knowledge in all aspects of patient care, from which will emerge clear and practical guidelines for the care of people with multiple sclerosis.

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Introduction

Historically, multiple sclerosis (MS) was a disease without effective long-term treatment; those available only managed symptoms and shortened acute attacks. However, 1993 saw a breakthrough in the management of people with relapsing/remitting MS. On the basis of the results of a large, multicentre, controlled clinical trial – the culmination of a decade of research and development – the first agent to reduce the activity of relapsing/remitting MS was approved for clinical use by the US Food and Drug Administration. This agent, interferon beta-1b, provided the first clear alternative to simple palliative therapy for MS symptoms, and is now available throughout the world.

Two further drugs – interferon beta-1a and glatiramer acetate – have since been approved in some countries for similar indications in people with relapsing/remitting MS, and clinical development of other therapies continues. It is clear that these new agents provide the neurologist a means to offer some control over MS. However, at the same time, the choice of three different agents presents the treating neurologist with the challenge of selecting the most appropriate treatment for each individual.

There are numerous factors that can influence both the decision to treat and the choice of treatment. Perhaps the most important is the reported efficacy of these agents in controlled clinical trials. However, the clinical trial design and characteristics of the study population can influence the apparent efficacy of the drugs. Only by carefully considering the influence of these factors can the reported clinical outcomes be interpreted fully; without this, our understanding of the trial outcomes – and the implications for the treatment of people with MS – will be incomplete.

The MS Forum Symposium, held in 1997 as part of the 13th ECTRIMS Congress in Istanbul, provided the opportunity to discuss the clinical trials on which regulatory authorities based their licensing decisions on three products for the treatment of relapsing/remitting MS. The topics discussed, and issues raised, during the symposium are summarised in these proceedings, *New Treatments for Multiple Sclerosis – A Review of Clinical Trial Results*. By examining in detail the published outcomes of these three clinical trials, it is anticipated that this publication will provide a reference for clinicians considering treatment options, and will result in appropriate and carefully considered advice being given to their patients.

It is recognised that these proceedings do not include information on all of the products currently undergoing clinical investigation. Perhaps the most important of these include intravenous immunoglobulin – for which preliminary clinical results suggest a possible benefit on relapse rate – and a third beta interferon preparation for which, at the time of writing, trial results remain to be published. These results will require detailed consideration, and it is hoped that many of the issues which may affect the interpretation of the findings of these trials are highlighted.

Clinical trial outcomes have a major impact on how a clinician will manage MS. By providing insight into the design and interpretation of the outcomes of the clinical trials that have the most direct influence on clinical decisions today, it is hoped that this information will provide some perspective on the evidence available, and the information which remains to be established, about the three agents currently available for the long-term treatment of MS.

Design Features of Multiple Sclerosis Trials

Clinical trials address specific questions about a particular intervention in a defined disease area and a specific patient population. Their design, therefore, defines precisely the questions being asked and their results are the answers to the specific questions. When interpreting clinical trials in any disease area, it is essential to recognise that the results will be influenced substantially by the trial design.

Multiple sclerosis (MS) itself presents specific challenges both to the trial design and to interpretation of the results. This chapter will examine the three clinical trial designs, highlighting any aspects that may influence interpretation of the trial outcomes.

What are the Questions we want to Answer?

Prototypic MS generally follows a well-defined course from a relapsing/remitting to a progressive phase, although the prognosis for any individual, particularly at presentation, is uncertain. In the early stages of MS, each relapse is associated with transient appearance or worsening of neurological symptoms and impairment, followed by partial or complete remission, with no intervening worsening of impairment. However, as the disease progresses, relapses appear less frequently but remission is rarely complete, and impairment may increase between relapses. Ultimately, some individuals develop significant disability.

Two aspects of MS that may be altered by treatment include disease activity (relapse rate) and burden (impairment). Clinical drug trials must therefore address whether treatment can reduce disease activity and/or affect accumulation of disease burden.

Another consideration is whether treatment has beneficial effects in specific disease phases or types. As it is unclear whether the disease processes in relapsing/remitting and progressive MS are the same, trials are designed to study these specific stages of the disease. Results from trials in relapsing/remitting MS cannot, therefore, be used to predict behaviour in progressive disease, or *vice versa*.

Other factors, such as dosing and route of administration, can influence the questions being asked in a trial. Only by considering how each aspect of the various questions can influence the answers obtained, can we interpret the trial outcomes effectively.

Design of the Three Clinical Trials

The three trials – on interferon beta-1a,¹ interferon beta-1b^{2,3} and glatiramer acetate⁴ – were all prospective, multicentre, double-blind, randomised trials. All compared drug with placebo, but the interferon beta-1b trial included two drug treatment arms. Each was designed to assess 2 years of treatment, although the interferon beta-1b trial was extended for a further year under blind conditions (table 1). Controlled data in a subgroup of patients on the interferon beta-1b trial were available for up to 5 years.⁵ The dose, route and frequency of administration of the drugs differed, as did the protocols for patient follow-up, definitions of relapse and permissible additional medications.

Primary and Secondary Outcome Measures

MS clinical trial outcomes fall into three groups:

- relapse-related outcomes, e.g. frequency, time to first relapse, severity and duration, and related measures such as hospitalisation
- progression-related outcomes, e.g. change from baseline and time to confirmed progression. Progression is assessed using the Kurtzke expanded disability status scale (EDSS)⁶
- magnetic resonance imaging (MRI)-related outcomes – to assess objectively disease activity and disease burden.



	Interferon beta-1a ¹	Interferon beta-1b ²	Glatiramer acetate ⁴
Trial duration	2 years	2 years plus 1 year extension*	2 years plus 3–10 month extension
Dose and administration	6 MIU versus placebo Weekly im injection	8 MIU versus 1.6 MIU versus placebo Every other day sc injection	20 mg versus placebo Daily sc injection
Follow-up	6-monthly neurological assessment Examination if relapse suspected	12-weekly neurological assessment Examination if relapse suspected	12-weekly neurological assessment Monthly visits to treating neurologist, examination within 7 days if relapse suspected
Definition of relapse	New / worsening symptoms sustained ≥ 48 hours after ≥ 30 days stability; Δ EDSS (0.5 or Δ FS ≥ 1 (P, CII, BS, V)	New / worsening symptoms sustained ≥ 24 hours after 30 days stability	New / worsening symptoms sustained ≥ 48 hours after ≥ 30 days stability; Δ EDSS ≥ 0.5 or Δ FS =1 (any two) or Δ FS ≥ 2 (any except B/BI)
Additional medication	Paracetamol before and 24 hours after injection Conventional MS medication, steroids as appropriate	Chronic use of NSAIDs prohibited Conventional MS medication, steroids as appropriate**	Analgesics and NSAIDs prohibited Conventional MS medication, steroids as appropriate

* Controlled data available for up to 5 years in a subgroup of patients⁵; ** more than three courses terminated participation

Table 1: Design of the three clinical trials

Relapse-related criteria are particularly sensitive to treatment effects, but long-term, sustained effects on permanent disability (typically defined as progression confirmed after 3 months or more from onset) are perceived to be more important. MRI outcomes remain secondary to clinical measures,⁷ yet increasingly provide sensitive indication of both acute and long-term efficacy. MRI measures are important because of their inherent objectivity.

The outcomes of the three trials were similar, but focused on different end-points (table 2).^{1–4} Whereas the primary end-points of the interferon beta-1b and glatiramer acetate trials were relapse-related outcomes,^{2,4} it was time to confirmed progression in the interferon beta-1a trial.¹ As trials are designed to detect an effect on the primary outcome measures, the three trials addressed different aspects of the disease.

	Interferon beta-1a ¹	Interferon beta-1b ^{2,3}	Glatiramer acetate ⁴
Primary outcomes	Time to onset of confirmed progression	Relapse rate Proportion of patients relapse-free	Relapse rate
Secondary outcomes	Relapse rate Time to first relapse	Time to first relapse Relapse duration and severity Hospitalisations Change in EDSS from baseline Proportion of patients with confirmed progression	Proportion of patients relapse-free Time to first relapse Proportion of patients with confirmed progression Change in EDSS from baseline
MRI outcomes	Annual assessment of lesion number and volume	Annual assessment of disease burden 6-weekly assessment of lesion activity (subgroup of patients)	

Table 2: Outcome measures in the three clinical trials

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria define the trial population in much the same way as outcome measures define the questions asked. The inclusion and exclusion criteria for the three trials are shown in table 3.^{1,2,4} Again, there are differences, this time in inclusion criteria – the interferon beta-1a trial enrolled patients with less marked neurological impairment and with fewer recent relapses than either the interferon beta-1b or glatiramer acetate trials. Exclusion criteria more precisely define the trial population by reducing the influence of prior drug treatment or disease on clinical outcome, and minimising drop-outs which would otherwise adversely effect the power of a study to demonstrate treatment effects.

	Inclusion criteria	Exclusion criteria
Interferon beta-1a ¹	<ul style="list-style-type: none"> ● CDMS \geq1 year ● baseline EDSS 1.0–3.5 ● \geq2 relapses over previous 3 years ● relapsing MS ● no relapses in 2 months prior to entry ● age 18–55 	<ul style="list-style-type: none"> ● prior immunosuppressant or immuno-modulatory treatment ● pregnancy or nursing ● unwillingness to practice contraception
Interferon beta-1b ²	<ul style="list-style-type: none"> ● CDMS \geq1 year ● Baseline EDSS \leq5.5 ● \geq2 relapses over previous 2 years ● relapsing MS ● no relapses in month prior to entry ● age 18–50 	<ul style="list-style-type: none"> ● prior azathioprine or cyclophosphamide treatment
Glatiramer acetate ⁴	<ul style="list-style-type: none"> ● CDMS or LSDMS \geq1 year ● Baseline EDSS \leq5.0 ● \geq2 relapses over previous 2 years ● relapsing MS ● no relapses in month prior to entry ● age 18–45 	<ul style="list-style-type: none"> ● prior treatment with glatiramer acetate ● prior immunosuppressive or cytotoxic chemotherapy, or lymphoid irradiation ● pregnancy or nursing ● IDDM, HIV, HTLV-1 or Lyme disease ● unwillingness to practice contraception

Table 3: Inclusion and exclusion criteria for the three trials

The enrolled populations are important, since even minor differences between trials can alter the interpretation of the outcome. Table 4 outlines the characteristics of the populations enrolled into the three studies.^{1,2,4}

	Interferon beta-1a ¹		Interferon beta-1b ²			Glatiramer acetate ⁴	
	Treated	Placebo	8 MIU	1.6 MIU	Placebo	Treated	Placebo
N	158	143	124	125	123	125	126
Sex (m/f%)	25/75%	28/72%	31/69%	32/68%	28/72%	30/70%	24/76%
Race (white%)	93%	92%	93%	93%	94%	94.4%	93.6%
Age (year \pm SE)	36.7 \pm 0.57	36.9 \pm 0.64	35.2 \pm 0.6	35.3 \pm 0.7	36 \pm 0.6	34.6 \pm 0.22	34.3 \pm 0.23
MS duration (year \pm SE)	6.6 \pm 0.46	6.4 \pm 0.49	4.7 \pm 0.4	4.7 \pm 0.4	3.9 \pm 0.3	7.3 \pm 0.2	6.6 \pm 0.2
Pre-study relapse rate	1.2 \pm 0.05	1.2 \pm 0.05	1.7 (3.4 \pm 0.2*)	1.65 (3.3 \pm 0.1*)	1.8 (3.6 \pm 0.1*)	1.45 (2.9 \pm 0.1*)	1.45 (2.9 \pm 0.09*)
Baseline EDSS	2.4 \pm 0.06	2.3 \pm 0.07	3.0 \pm 0.1	2.9 \pm 0.1	2.8 \pm 0.1	2.8 \pm 0.09	2.4 \pm 0.1

* Relapses over previous 2 years

Table 4: Characteristics of the enrolled trial populations

Implications of Trial Designs on Interpretation of Results

Each trial had a unique trial design, inclusion and exclusion criteria and enrolled population, thereby limiting direct comparison of drug efficacy. The only way to directly compare the relative efficacy of these agents would be in head-to-head trials. However, a comparison of the trials allows us to assess the robustness of each trial to answer the questions asked (the trial design) and helps us reliably to interpret the answers obtained (the trial outcomes).

All three trials were double-blind, randomised and multicentre, but each had particular features that may influence interpretation of the results. Blinding of MS clinical trials is a challenge since drug- and disease-related events may provide clues to the treatment regimen. These trials involved two physicians – one to administer therapy and manage side-effects, and a second to perform all neurological assessment – to maintain blinding. The interferon beta-1b trial also included two doses of therapy. Thus, even if trial participants believed they were receiving treatment, they were blinded to its dose. This approach also allows a dose-response to be assessed – demonstration of a dose-response effect increases confidence in the primary clinical outcomes and suggests that greater efficacy may be achieved with a higher dose.

All the trials were placebo-controlled. The outcome of the placebo group provides a valuable indicator of how representative the enrolled population is of the general MS population. Their behaviour in a trial should reflect the natural history of a similar, un-enrolled and untreated population, but even minor variation can influence the power and sensitivity with which treatment effects can be demonstrated.⁸ A placebo group showing favourable outcome, relative to a general MS population, during a trial will reduce any apparent treatment benefit. Conversely, a placebo group showing poor outcome may overstate true clinical benefit. Thus, their behaviour is of paramount importance to the interpretation of a trial outcome.

Duration of treatment and follow-up can also affect trial outcomes. MS is a long-term disease, and therapies are required to demonstrate long-term efficacy; yet, clinical trials are typically only 2–3 years in duration. For this reason, clinical trials should be designed to reflect the extent of the disease process, but it must be realised that the outcomes of short-term trials may not translate into long-term benefit.⁹

Each trial was designed to run for 24 months, but the duration of blinded treatment varied considerably. In the glatiramer acetate trial, approximately 85% of the study population continued for 2 years. Median treatment time was not reported.⁴ The interferon beta-1b trial was extended to 3 years, but staggered enrolment resulted in median time on treatment of 45–48 months.⁵ In contrast, in the interferon beta-1a trial, only 57% of enrolled subjects received 2 years of blinded treatment. The median time on treatment was not reported.¹

The importance of long-term follow-up was dramatically highlighted by a recent trial of sulfasalazine in 199 mildly disabled participants (EDSS 1–4.0) with active relapsing/remitting or progressive MS. An 18-month interim analysis demonstrated a significant and substantial benefit on time to confirmed progression in people receiving sulfasalazine. However, upon completion of the study at 3 years, treatment showed no overall benefit over placebo.¹⁰

Further Points to Consider

Many of the points highlighted above are applicable to any relapsing/remitting MS trial. However, some specific points warrant particular attention:

- the interferon beta-1a trial enrolled patients with EDSS scores of 1–3.5,¹ compared with 0–5.5 and 0–5.0 for the interferon beta-1b² and glatiramer acetate⁴ trials, respectively. Since median *staying* time at EDSS 4–5 is lower than that at earlier EDSS stages, a population of EDSS 1–3.5 would be expected to progress more slowly than a more disabled population
- despite lower baseline EDSS, interferon beta-1a trial participants had longer disease duration (6.4–6.6 years).¹ This may explain the lower baseline relapse rate, but also suggests these patients had less active disease
- patients in the two arms of the glatiramer acetate trial differed slightly in baseline EDSS score; mean EDSS in the treated group was 0.4 points greater than in the placebo group⁴
- the two beta interferons are similar agents, but the doses used were quite different. The low- and high-dose arms of the interferon beta-1b trial received weekly equivalents of 5.6 MIU and 28 MIU, respectively,² contrasting with a weekly dose of 6 MIU interferon beta-1a¹
- clinical assessment in the interferon beta-1b and glatiramer acetate trials was every 3 months,^{2,4} twice the frequency of the interferon beta-1a trial.¹ More frequent assessment may increase sensitivity to changes in relapse-related outcomes, but may reduce the stringency of progression-related outcomes such as time to onset of confirmed progression¹¹
- the route of drug administration – intramuscular in the interferon beta-1a trial and subcutaneous in the other trials – may influence the frequency of injection-site reactions, but is unlikely to affect the pharmacokinetics of the delivered agent. However, once-weekly administration, rather than every other day, may be insufficient to maintain biological effects over a full week¹²
- concomitant medication, such as paracetamol, was prohibited in the interferon beta-1b and glatiramer acetate trials,^{4,5} but was a protocol requirement to minimise side-effects in the interferon beta-1a trial.¹

The possible influence of each of these factors on trial outcome must be considered.

Summary

The clinical trials of interferon beta-1a, interferon beta-1b and glatiramer acetate all asked the question: 'Are these agents effective in relapsing/remitting MS?' But they ask the question in different ways. The interferon beta-1a trial asked whether the agent slows progression in a relatively mildly impaired population, whereas the other two trials asked whether the drugs reduce disease activity in a moderately impaired population with more active disease. For this reason, only the trials, and not the relative efficacy of these agents, can be compared.

Many aspects of the trial designs affect the apparent outcome. Given that clinical management decisions are made on these trial outcomes, we must be vigilant in criticising where questions remain to be answered.

Clinical Outcome Measures – Relapses and Related Events

For people with relapsing/remitting multiple sclerosis (MS), disease activity and related clinical consequences such as hospitalisation are of the most direct relevance to daily activity. The clinical outcomes studied in MS clinical trials – relapse rate, duration and severity, and hospitalisation – are, essentially, markers of disease activity. Treatments that reduce relapse rate and/or severity offer tangible benefits to these people.

Whether relapse rate influences future disease progression is unknown. Relapse rate and future disability appear to correlate, albeit weakly, suggesting that reducing relapse rate may slow accumulation of disability over the long term. This chapter will review the trial outcomes on these clinical parameters, and consider the possible future benefit on disease progression.

Treatment Effects on Clinical Outcome Measures

All three clinical trials reported relapse-related clinical outcomes. Table 5 shows treatment effects on relapse-related outcomes in the trials after 2 years.^{1,2,4} In each case, the treated groups fared better than their placebo counterparts. High-dose interferon beta-1b significantly reduced relapse rate by 34% after 2 years,² sustained at

	Interferon beta-1a ¹		Interferon beta-1b ²		Glatiramer acetate ⁴		
	Treated	Placebo	8 MIU	1.6 MIU	Placebo	Treated	Placebo
Relapse rate (after 2 years)	-18%, $P=0.04$ (0.67/year, $n=158$)	0.82/year ($n=143$)	-34%, $P=0.0001$ (0.84/year, $n=124$)	-8%, $P=0.01$ (1.17/year, $n=125$)	1.27/year ($n=123$)	-29%, $P=0.007$ (1.19 relapses, $n=125$)	1.68 relapses ($n=126$)
Median time to first relapse	+31%, NS (331 days)	253 days	+93%, $P=0.015$ (295 days)	+18% (180 days)	153 days	+45%, $P=NS$ (287 days)	198 days
People relapse-free	38%, $P=0.03$ (+46% change)	26%	31%, $P=0.007$ (+94% change)	20% (+25% change)	16%	34%, $P=NS$ (+26% change)	27%

Table 5: Relapse-related outcomes in the three trials

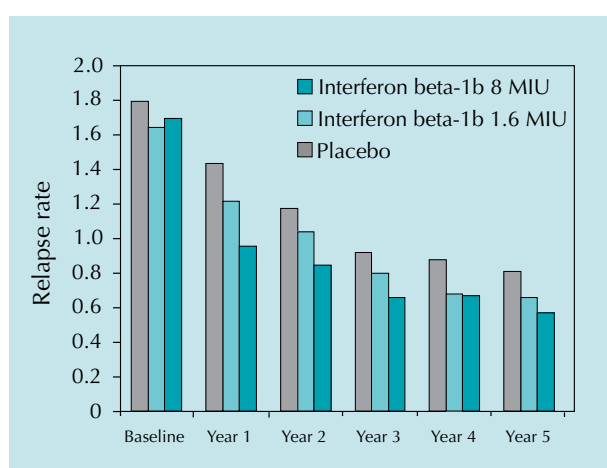


Figure 1: Relapse-rate reduction by interferon beta-1b sustained over 5 years

Several further analyses were reported for selected trials. In the glatiramer acetate and interferon beta-1a trials, the distribution of relapse frequency was reported (table 6).^{1,4} An apparent treatment benefit was seen in both trials. The link between baseline EDSS score and relapse rate was assessed for glatiramer acetate.⁴ This suggested that the most substantial

28% in patients with up to 5 years follow-up (figure 1).⁵ A dose-response effect was seen. Relapse rate in the entire treatment cohort was reduced in the glatiramer acetate trial by 29%,⁴ and in the interferon beta-1a trial by 18%.¹ These reductions were significant for all three agents.

Increased time to first relapse suggests a reduction in disease activity. Only in the interferon beta-1b trial was time to first relapse significantly prolonged.² It is important to note that absolute time to first relapse depends on baseline relapse rate – the lower the relapse rate, the greater the interval between relapses.

	Interferon beta-1a ^{a1}		Glatiramer acetate ^{b4}	
	Treated	Placebo	Treated	Placebo
0	38%	26%	34%	27%
1	31%	30%	48%	44%
2	18%	11%	18%	29%
≥3	14%	32%	18%	29%

* 2 year subset only; a – $P=0.03$; b – $P=0.023$

Table 6: Number of relapses per person in the interferon beta-1a and glatiramer acetate trials

benefit appeared to be obtained by people with low EDSS scores (table 7). Relapse rate was greater in the trial population with higher EDSS scores, suggesting that this group may have had more active disease.

Treatment effects on relapse severity and hospitalisation were reported only for the interferon beta-1b trial.² These data show that high-dose interferon beta-1b is most effective in reducing the rates of moderate and severe relapses (table 8). All hospitalisation outcomes were improved following high-dose treatment in this trial.

Glatiramer acetate* ⁴		
EDSS	Treated	Placebo
0–2	-33% (0.48/year)	0.72/year
2–4	-22% (0.72/year)	0.92/year
>4	-22% (0.88/year)	1.12/year

* Annualised relapse rate

Table 7: Correlation of relapse rate and EDSS in the glatiramer acetate trial

Interferon beta-1b* ²			
Relapse rate by severity	8 MIU	1.6 MIU	Placebo
Mild	-17% (0.45/year)	+15% (0.62/year)	0.54/year
Moderate / Severe	-49%, $P=0.002$ (0.23/year)	-29% (0.32/year)	0.45/year
Unknown	-46% (0.15/year)	-21% (0.22/year)	0.28/year
Hospitalisations	-43%, $P=0.046$ (37)	-18% (53)	65
People hospitalised	-36%, $P=0.05$ (21)	-24% (25)	33
Hospital days	-27%, $P=0.07$ (344)	-13% (411)	471

* 2 year data

Table 8: Relapse severity and hospitalisation in the interferon beta-1b trial

Interpreting these Findings

Relapse rate and related outcomes are sensitive markers of treatment effect. The trials show that all three agents have a statistically significant benefit on relapse rate, which apparently is most robust in terms of magnitude and duration in the interferon beta-1b trial. However, it should be highlighted that:

- relapse-related outcomes were not a primary end-point of the interferon beta-1a trial¹
- interferon beta-1b significantly reduced relapse rate by 12 months, indicating a rapid onset of benefit.² Benefit on relapse rate at 12 months was not reported for the interferon beta-1a or glatiramer acetate trials
- long-term benefit was demonstrated in the interferon beta-1b trial – relapse rate reduction was sustained up to 5 years⁵
- the trials also showed change in relapse rate with time even in the placebo group. This is primarily a consequence of the natural history of MS, but the greater reduction over the first 2 years of study may reveal regression-to-the-mean effects.

The validity of primary relapse-related outcomes is enhanced by positive secondary outcomes. In each trial, relapse rate benefit was reinforced by increased time to first relapse and number of patients free of relapse, although benefit on both parameters was significant only for the high-dose arm of the interferon beta-1b trial.² Benefits on hospitalisation in this trial are also valuable, but country- and centre-specific variations in criteria for hospital referral suggest that benefit may vary between health-care environments.

Relapse-related outcomes depend on the definitions used to identify and classify relapses. Their stringency varies between the trials – the glatiramer acetate trial used the most stringent definition of relapse, whereas the interferon beta-1b trial used the least stringent definition. More stringent definitions reduce ambiguity, particularly regarding mild relapses, but this may enhance apparent benefit on relapse rate if reduction in relapse

severity, rather than rate, is the principal treatment effect. This may also influence trial comparisons. Trials with more stringent relapse definitions may report only moderate and severe relapses. If this is so, then reported relapse rate benefit in these trials may more appropriately be compared with relapses identified as moderate or severe in the interferon beta-1b trial.

A number of other factors can influence the observed relapse frequency:

- age of the patient and duration of disease. Natural history studies¹³ and long-term clinical trials⁵ show declining relapse rates over time
- frequency of observation. In natural history studies, populations monitored infrequently may fail to report relapses, particularly those of minor impact. However, this may not be a major feature of clinical trials
- baseline relapse rate. Accurate assessment of this parameter requires thorough monitoring of relapses prior to recruitment into trials
- influence of participants lost to follow-up. Preferential drop out from the placebo group due to disease-related factors or perceived lack of efficacy can reduce the power of a trial to show treatment effects; conversely, preferential drop out from the treatment arm due to treatment-related factors such as side-effects can lead to an over-estimation of treatment effect. Continued monitoring of patients who discontinue the trial drug and intent-to-treat analysis can help to minimise these effects.

Implications of these Results

Reducing relapse rate has clear immediate benefits, but long-term benefit is difficult to assess from short-term trials. The correlation between short-term relapse rate and long-term clinical progression is unclear, although natural history studies provide valuable clues that may allow us to predict future disease progression.

In a longitudinal, prospective natural history study, the probability of reaching EDSS 6 according to both the number of relapses in the first 2 years of study, and the first inter-attack interval, was assessed (figure 2).¹⁴ People with fewer relapses at baseline, and those with a longer inter-attack interval, typically took longer to reach EDSS 6. However, the question remains whether these are cause-and-effect relationships, and thus whether reducing these outcomes using available treatments will have a beneficial effect on progression.

Summary

All three agents significantly reduced relapse rate. This effect was particularly marked in the glatiramer acetate and interferon beta-1b trials, and was sustained for 5 years in the latter. Supplementary outcomes support the validity of these effects, and indicate that these agents have a clinically important effect on day-to-day living.

What do these results indicate for long-term outcome? No cause-and-effect relationship has yet been shown between relapse rate and progression. However, natural history data do support this link. In this context, the sustained benefit of interferon beta-1b on relapse rate may offer promising long-term benefits.

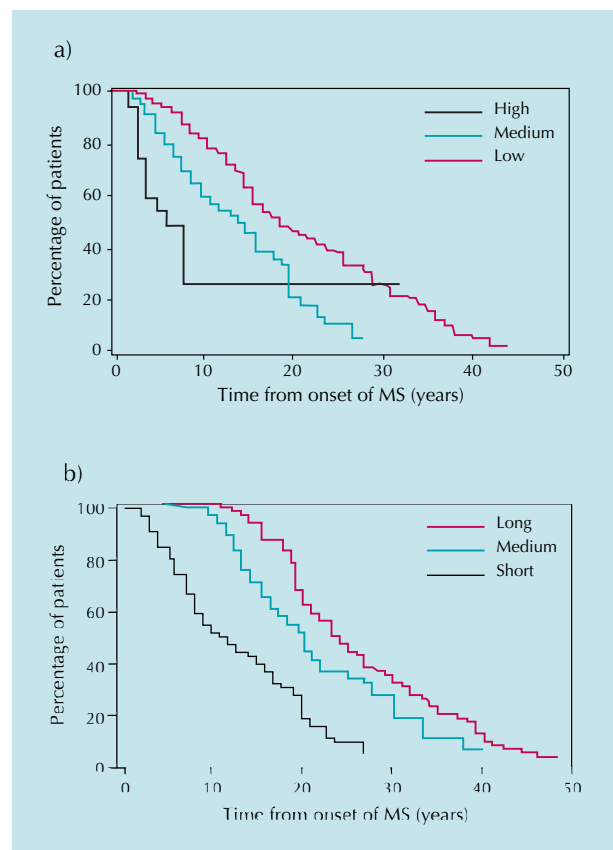


Figure 2: a) Progression to EDSS 6 by baseline relapse rate; b) Progression to EDSS 6 by first inter-attack interval

MRI Outcome Measures – Treatment Effects and Clinical Relevance

Magnetic resonance imaging (MRI) has profoundly altered our understanding of multiple sclerosis (MS). It has greatly improved the ability to diagnose MS, and has proven to be a valuable instrument for objectively measuring treatment effects in clinical trials. Increasingly, it is recognised that MRI directly visualises certain pathologies within the brain and spinal cord that are related to disease activity and burden, and provides a more sensitive approach to assess treatment effects in MS that complements clinical outcome measures.

This chapter will review the MRI outcomes of three clinical trials, highlighting the techniques and protocols used. The interpretations of these outcomes and our current understanding of the relationship between MRI and clinical measures of MS activity and burden, will be discussed.

What can MRI Tell us about MS?

MRI is typically thought of as a single technique; in reality, MRI encompasses a host of techniques.¹⁵ Just as clinical trials can only answer the questions for which they were designed, so a particular MRI technique can only reveal information about a specific aspect of disease pathology.

In parallel with clinical outcomes, MRI can be used to monitor both acute-phase (disease activity) and chronic-phase (disease burden) treatment effects. Although many MRI techniques are available,¹⁵ only two have been used extensively in MS trials:

- T2-weighted unenhanced imaging – which highlights non-specific abnormalities, including inflammation, chronic demyelination and gliosis, and provides a measure of disease burden independent of pathology
- T1-weighted, gadolinium (Gd)-enhanced imaging – which identifies regions of blood–brain barrier disruption (a sign typical of inflammation).

Interferon beta-1a ¹	<ul style="list-style-type: none"> • Gd-enhanced lesion number on annual T1-weighted images • Gd-enhanced lesion volume on annual T1-weighted images • lesion volume on annual T2-weighted images
Interferon beta-1b ³	<ul style="list-style-type: none"> • active scans by 6-weekly T2/PD-weighted imaging • new lesions on 6-weekly T2/PD-weighted images • enlarging lesions on 6-weekly T2/PD-weighted images • recurring lesions on 6-weekly T2/PD-weighted images • lesion area on annual T2/PD-weighted images
Glatiramer acetate ⁴	<ul style="list-style-type: none"> • serial Gd-enhanced lesions on T1-weighted images (subset of participants; data not reported)
PD – proton density	

Table 9: Imaging techniques and measures employed in the three trials

Disease activity can be monitored by assessing changes either in the number of new, recurrent and enlarging lesions on T2-weighted images, or the number of enhancing lesions on Gd-enhanced T1-weighted images. Disease burden is monitored by assessing the area or volume of lesions on T2-weighted images. The outcomes used in the beta

interferon clinical trials are presented in table 9.^{1,3,4} Newer approaches, such as monitoring *black holes*, magnetisation transfer ratios and MR spectroscopy, may ultimately prove to be more useful but have yet to be validated in clinical trials.

The Use of MRI in Clinical Trials

Although MRI contributes significantly to our understanding of MS, doubts remain about the correlation between MRI- and clinically-assessed pathology. While it is clear that MRI is more sensitive than clinical assessment of relapse rate, correlations between MRI burden and Kurtze's expanded disability status scale (EDSS) score are weak

Study	Correlation	r
van Walderveen ¹⁶	Change in T2 lesion load and change in EDSS	0.19
IFNB MS Study Group ⁵	T2 lesion load and EDSS at entry	0.24
	T2 lesion load and EDSS at exit	0.27
	Change in T2 lesion load and change in EDSS	0.23
Gass ¹⁷	T2 lesion load and EDSS	0.33
Koopmans ¹⁸	Change in T2 lesion load and change in EDSS	0.19
Filippi ¹⁹	New T2 lesions and change in EDSS	0.13

Table 10: Correlation between T2-weighted MRI and EDSS

Guidelines for the use of MRI in monitoring clinical trial outcomes

Position statements:

- 'High sensitivity makes MRI an excellent tool for rapid screening of therapies suppressing new pathological activity in relapsing/remitting and secondary progressive MS.'
- 'Because the long-term relationship between MRI and disability is still uncertain, MRI should not be the definitive determinant of therapeutic efficacy. A clinically significant end-point must be shown.'

Guidelines:

- MRI is a secondary outcome
- Main MRI outcome:
 - change in T1- and T2-weighted lesion load
- **Optional:**
 - annual Gd-enhanced T1-weighted measures
 - monthly T2-weighted measures
 - monthly Gd-enhanced T1-weighted measures
 - putative markers: demyelination and neural damage

to obtain these data differed substantially. In the interferon beta-1a trial, Gd-enhanced, T1-weighted scans assessed the number of enhancing lesions in all participants at baseline, 1 year and 2 years. Due to staggered enrolment, 2-year scans were available for 165 of the 301 subjects.¹ The interferon beta-1b trial analysed a cohort of 52 patients receiving treatment at one study centre using unenhanced T2-weighted scans obtained every 6 weeks for 2 years. Outcome measures included the rate of new, recurring and enlarging lesions and the proportion of scans showing disease activity.³

Disease Burden

MRI assessment also showed a marked treatment effect on measures of disease burden (table 12).^{1,3,5} Again, the protocols differed. In the interferon beta-1a trial, disease burden was assessed using two measures: T1-weighted, Gd-enhancing lesion volume on scans obtained to assess disease activity,

(table 10).^{5,16–19} Because of these uncertainties, practical guidelines were recently published, clarifying the role of MRI in MS treatment trials (see box).⁷

MRI Outcomes of the Three Clinical Trials

MRI outcomes were assessed only in the interferon beta-1a¹ and interferon beta-1b^{3,5} trials. A further post-hoc analysis of MRI outcomes was recently reported for the interferon beta-1a trial,²⁰ although no detailed consideration of these findings has been included in this publication. So far, no MRI data have been published to support the clinical findings for glatiramer acetate.

Disease Activity

The beneficial treatment effect on disease activity in the two beta interferon trials is outlined in table 11.^{1,3} The protocols used

	Interferon beta-1b* ³		
	8 MIU	1.6 MIU	Placebo
Percent active scans	-80%, <i>P</i> =0.006 (5.9%)	-60%, <i>P</i> =0.035 (11.8%)	29.4%
Active lesions/year	-83%, <i>P</i> =0.009 (0.5)	-66%, <i>P</i> =0.041 (1.0)	3.0
New lesions/year	-75%, <i>P</i> =0.002 (0.5)	-75%, <i>P</i> =0.032 (0.5)	2.0
Free of lesions	7 people, <i>P</i> =0.039	NR	1 person

* T2/PD-weighted MRI every 6 weeks for 2 years; median data; NR – not reported

Time point	Interferon beta-1a** ¹	
	Treated	Placebo
Baseline	3.17 lesions	2.32 lesions
1 year ^a	-67% (1.04 lesions)	-31% (1.59 lesions)
2 years ^b	-75% (0.80 lesions)	-29% (1.65 lesions)

** Annual Gd-enhanced T1-weighted MRI assessment; mean data;
^a – *P*=0.02; ^b – *P*=0.05

Table 11: MRI activity in the beta interferon trials



T2-weighted burden	Interferon beta-1a* ¹		Interferon beta-1b** ⁵		
	Treated	Placebo	8 MIU	1.6 MIU	Placebo
1 year	-13.1%, P=0.02	-3.3%	-4.9% P=0.0012	5.7%	6.7%
2 years	-13.2%, P=NS	-6.5%	-5.6%, P=0.0015	12.4%	11.9%
3 years	NA	NA	-3.8%, P=0.0002	6.1%	21.0%
4 years	NA	NA	-0.8%, P=0.0055	11.7%	18.7%
5 years	NA	NA	3.6%, P=0.0363	10.6%	30.2%

* Annual T2-weighted MRI assessment, volume change relative to baseline, within-person change; ** Annual T2-weighted MRI assessment, area change relative to baseline, within-group change

and unenhanced T2-weighted lesion volume. Both assessments were carried out at baseline, 1 year and 2 years. Again, patient numbers were substantially lower at 2 years than either 1 year or baseline.¹

In the interferon beta-1b trial, all participants underwent annual unenhanced T2-weighted MRI scans to assess the lesion area. Data obtained up to 5 years demonstrated no overall change in disease burden in the high-dose treatment group, but a consistent increase in the placebo group (figure 3).⁵ An additional analysis reported that the change in disease burden, stratified according to per cent change from baseline, significantly favoured people on interferon beta-1b treatment.³

Change in MRI burden	Interferon beta-1b* ³		
	8 MIU	1.6 MIU	Placebo
>10% increase	-44% (29% people)	-28% (37% people)	52% of people
Stable (10%)	-5% (17% people)	0% (18% people)	18% of people
>10% decrease	+80% (54% people)	+50% (45% people)	30% of people

* Annual T2-weighted MRI assessment, stratified area change relative to baseline, within-person change; 8 MIU versus placebo, P=0.001

Table 12: MRI disease burden in the beta interferon trials

Implications of these Results

Both beta interferons significantly reduced disease activity as measured by MRI. The interferon beta-1b trial outcomes appear to be more robust statistically than the interferon beta-1a trial outcomes, and a dose-response effect was observed.^{3,5} However, although the magnitude of treatment effect appears similar, there are several features to be considered when interpreting the outcomes:

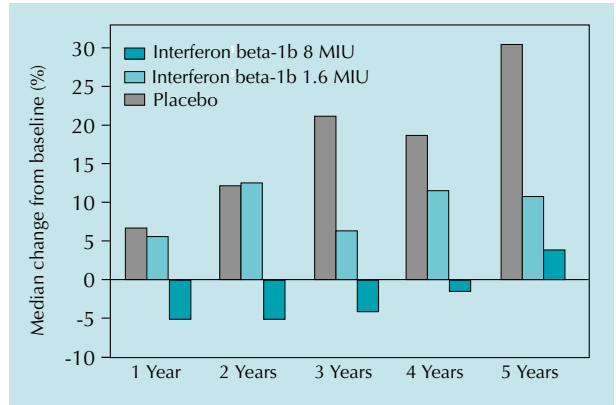


Figure 3: Change in disease burden in the interferon beta-1b trial

Figure 3 © 1995 by the American Academy of Neurology. Reprinted with permission of Lippincott-Raven Publishers, Philadelphia, PA

- the MRI techniques employed to assess disease activity are unique to each trial, and therefore, there is no single outcome with which to compare the two studies
- the analysis of disease activity measurement differed. In the interferon beta-1b trial, the cohort assessed for disease activity was assessed longitudinally every 6 weeks for 2 years.³ By contrast, subjects in the interferon beta-1a trial were assessed cross-sectionally at baseline, 1 year and, if possible, at 2 years.¹ Each approach is valid, but the two analyses are difficult to compare
- in the interferon beta-1a trial, the number of enhancing lesions in the treated group was reduced from baseline by 69% and 75% after 1 and 2 years, respectively. In the placebo arm, the number of enhancing lesions fell by 31% after 1 year, remaining 29% below baseline at 2 years.¹ This decline in the placebo group may represent a regression-to-the-mean effect
- although Gd-enhanced T1-weighted imaging was not used in the interferon beta-1b trial as it was unavailable at the start of the trial, subsequent studies have shown a marked treatment effect of beta interferons using this technique.²¹⁻²³

Disease burden outcomes offer the only comparable assessment between the beta interferon trials, yet even here technical differences may influence interpretation. In the interferon beta-1b study placebo group, T2-weighted lesion *area*, assessed annually, increased from baseline at approximately 6% per year.⁵ The investigators commented that similar progression had been seen in other trials. Against this background, the interferon beta-1b treatment effects were sustained up to 5 years of follow-up, and demonstrated a dose-response effect. The magnitude of benefit remained stable over time, and was highly significant.⁵

The interferon beta-1a trial outcome, at first sight, appears comparable. T2-weighted lesion *volume* declined substantially from baseline by 1 year, but remained static to 2 years.¹ However, the placebo group also showed a decline in lesion burden, which was sustained to 2 years. As a consequence, this outcome was significant at 1 year but non-significant at 2 years.¹ This point illustrates the need to consider the behaviour of the placebo group in clinical trials.

The interferon beta-1a trial also assessed changes in the volume of Gd-enhancing lesions – the MRI measure of disease activity.¹ This outcome was similar to that for T2-weighted lesion volume – the treated group demonstrated a substantial decline from baseline at 1 year, sustained without change at 2 years, and the placebo group showed a similar, but less substantial reduction. This outcome was statistically significant at both time points.¹

Further Points to Consider

MRI outcomes are relatively straightforward to interpret, but there are some important additional considerations that may influence the perceived value of the trial results. First, the two trials include only a single comparable outcome measure, and the application of this technique differed. Thus, it is difficult to compare the results directly. Second, although MRI outcomes are sensitive and objective and increase confidence in the clinical outcomes of the trial, there remain caveats:

- MRI in clinical trials typically neglects the spinal cord. Although this is due to valid technical reasons, the spinal cord remains the seat of the majority of lesions that confer motor disability²⁴
- correlations between clinical and MRI measures remain weak. For example, it is not unusual to identify people with little clinical evidence of disease, yet extensive MRI lesions, or those with severe disability, yet few MRI lesions in the brain
- the robust and substantial reduction in lesion frequency seen in the interferon beta-1b trial is not reflected by a similar reduction in the number of relapses. This may suggest that the mechanisms involved in acute MRI lesions and relapses may differ.

Summary

MRI offers assessment of disease activity and burden independent of clinical observations. Although it remains a secondary outcome measure, MRI results add sensitivity, objectivity and a direct relationship to disease pathology. MRI outcomes in the interferon beta-1b trial showed a highly significant and substantial effect on both disease activity over 2 years, and on disease burden over 5 years. Indeed, these outcomes set the standard for MS trials. The interferon beta-1a trial reported a significant effect on T2-weighted disease activity, and an effect on disease burden that was significant at 1 year only. Unexpected placebo group behaviour complicated the interpretation of this outcome. No MRI data were reported from the glatiramer acetate trial.

Treatment Effects on Disability

Arresting or reversing disability due to multiple sclerosis (MS) is widely regarded as the ultimate goal of MS therapy. Today, this is far from reality as it is likely to involve more intensive treatment approaches than are available. A more realistic – and highly desirable – goal, is to slow disability progression. Since accumulation of neurological damage, typically expressed as clinical deficit, appears to be slowed using existing treatments, it is possible that long-term therapy will eventually have a detectable benefit on clinical measures of disability.

Changes in disability are, however, difficult both to measure and to interpret. Existing neurological scales each have their limitations, in particular their ordinal character, focus on mobility, overlap of both neurological impairment and disability, and variable reproducibility. Change in disability may also depend on the history of an individual's MS, disease duration, baseline Kurtze's expanded disability status scale (EDSS) score, and superimposed relapses. An added consideration is whether the trials were designed to show effects on disability and how changes in the trial populations compare both with those in other trials and the natural history of MS.

Factors that Influence Assessment of Disability Progression

EDSS was used in the three trials to assess disease progression.⁶ This scale is the most widely used clinical tool for measuring neurological impairment, yet has a number of limitations. Fundamentally, the EDSS is an ordinal scale; thus, stepwise changes vary in the typical time to progression between the steps (figure 4),²⁵ or in the change in impairment represented by each step.⁸ Individuals at EDSS steps 4–5 appear to progress rapidly to the next step, whereas staying time at EDSS 1–2 or EDSS 6–7 is more prolonged. For this reason, it is important that the baseline EDSS range of subjects in a trial is considered in the interpretation of clinical outcome.

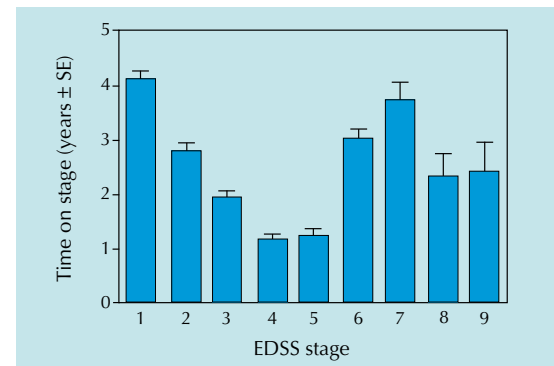


Figure 4: Mean time at each EDSS step

Changes in EDSS score at the lower levels clinically are relatively slight compared with changes at higher EDSS scores.⁶ For example, the step from EDSS 1–2 represents minor decrease in touch, pain or position sense that may not affect a person's functioning. However, the step from EDSS 5–6 signifies a decline in walking ability from 200 metres unaided to 100 metres using a cane, crutch or brace assistance. Change within the range EDSS 0–3.5 is determined by a myriad of possible changes in the neurological examination but is still consistent with normal daily functioning, while change when baseline EDSS is 4.0 or greater represents changes in ambulation likely to impact on day-to-day function.

The EDSS is also known for subjectivity. Inter-rater agreement on EDSS scores in numerous studies, particularly at the lower range of the EDSS, is less than perfect. Nevertheless, advanced training and agreement between investigators at multiple centres can maintain adequate reproducibility of EDSS assessment in clinical trials.⁸

Several aspects of disease can also influence change in impairment. Chapter two highlighted a relationship between baseline relapse rate and subsequent rate of progression, which, although weak, suggests that people with more active disease will progress faster. Relapses can also affect the assessment of EDSS – relapse severity and duration can alter the apparent EDSS score, and the challenge for designers of clinical trials is to develop criteria to minimise the impact of relapses on estimating permanent impairment.

Each trial required progression by 1 EDSS point as an end-point. Confirmation of progression was also required – after 3 months in the interferon beta-1b and glatiramer acetate trials,^{2,4} and after 6 months in the interferon beta-1a trial.¹ The longer the period of confirmation, the greater the stringency of the end-point, although this can present difficulties in the analysis of short-term trials, where the period of confirmation becomes a substantial proportion of total follow-up. A further problem with the EDSS in relapsing/remitting MS is that a confirmed change can be reported even if the deficit in the first and second examinations differs. The following hypothetical case illustrates this: at the first examination, visual acuity in the right eye is reduced; at confirmation, right eye deficit has resolved, but the left eye shows decreased acuity.

Disability Outcomes in the Three Clinical Trials

Change in disability in the trials was assessed using very similar definitions of progression (table 13).^{1,2,4} However, the duration of follow-up was variable – whereas the interferon beta-1a and glatiramer acetate trials reported on progression after 2 years,^{1,4} the interferon beta-1b trial reported progression rates at the end of 3 and 5 years of treatment.^{2,5}

Interferon beta-1a ¹	Deterioration from baseline by ≥ 1.0 EDSS point persisting for at least 6 months
Interferon beta-1b ²	Two consecutive EDSS scores, separated by 90 days, that were identical, with both showing a 1.0 point increase over the baseline score
Glatiramer acetate ⁴	An increase of at least one full step on the EDSS that persisted for at least 3 months

Table 13: Definitions of confirmed progression in the three trials

The proportion of patients with confirmed progression, and the Kaplan-Meier estimate of progression over the duration of the trial, both suggest treatment benefit (table 14).^{1,4,5} This reached statistical significance in the interferon beta-1a trial.¹ Median time to progression in the interferon beta-1b trial was

4.18 years, 3.49 years and 4.79 years for the placebo, low-dose and high-dose arms, respectively.⁵ The reason for the apparent poor prognosis with low-dose interferon beta-1b is unclear.

	Interferon beta-1a ^{a1}		Interferon beta-1b ^{b5}			Glatiramer acetate ^{c4}	
	Treated	Placebo	8 MIU	1.6 MIU	Placebo	Treated	Placebo
Confirmed progression	21.9%, $P=0.02$	34.9%	35%, $P=0.096$	47%	46%	21.6%, $P=NS$	24.6%

^a – Kaplan-Meier estimate, all people, all time on trial (2 years assessment); ^b – all people, all time on trial (5 years assessment); ^c – all patients, all time on trial (2 years assessment)

Table 14: Confirmed progression in the three trials

Each trial reported secondary analyses of progression. Stratified change in EDSS was reported for all three trials (table 15),^{1,2,4} and indicated that these agents reduced the risk of progression. Mean group EDSS change from baseline was also reported for the interferon beta-1a and glatiramer acetate; again, the outcomes support the

	Interferon beta-1a ^{a1}		Interferon beta-1b ^{b2}			Glatiramer acetate ^{c4}	
	Treated	Placebo	8 MIU	1.6 MIU	Placebo	Treated	Placebo
EDSS change							
Improved (≥ 1 point)	18.2%	8.9%	NA	NA	NA	24.8%	15.2%
Stable	63.6%	60.7%	80%	72%	72%	56.0%	54.4%
Worse (≥ 1 point)	18.2%	30.3%	20%	28%	28%	20.8%	28.8%

^a – subgroup of patients progressing by 104 weeks, confirmed at 130 weeks; ^b – 3-year data; ^c – 2-year data; NA – not applicable (improved = stable in this trial)

	Interferon beta-1a ^{a1}		Glatiramer acetate ^{b4}	
	Treated	Placebo	Treated	Placebo
EDSS change (mean)	0.25	0.74	-0.05, $P=0.023$	0.21

^a – unconfirmed change by 2 years in sub-group of patients on trial for 2 years;
^b – unconfirmed change by 2 years

Table 15: Stratified and mean change in EDSS in the three trials

benefit of treatment on progression (table 15).^{1,4}

The interferon beta-1a trial was subsequently re-analysed for several progression-related outcomes, including progression confirmed using two more stringent definitions, progression to *landmark* EDSS scores (table 16), the magnitude of EDSS change and group mean change in EDSS (table 17).²⁶ These *post-hoc* analyses add further support to the claim of an effect on progression, but it is interesting to note that mean change in EDSS from baseline to 2 years in the subgroup of patients on-study ≥ 2 years was different between the two papers. The reasons for this are unclear.

Interpreting these Findings

All three trials appear to show an effect on disability, although this is only statistically significant for the interferon beta-1a trial.^{1,26} This may, in part, be attributed to the trial designs – only the interferon beta-1a trial was designed and powered with sufficient patient numbers to show this effect. Nevertheless, many other issues may influence these findings.

Progression on the EDSS scale has been validated in people with progressive MS, but is of uncertain relevance in relapsing/remitting MS. Whereas a confirmed 1 point progression is valid in a purely progressive population, it can be difficult to distinguish irreversible progression from attack-related worsening in a relapsing/remitting population. This may affect interpretation of all trials, but is particularly important in the interferon beta-1a trial since:

- the clinical significance of a statistically significant finding must be demonstrated
- the population recruited into the interferon beta-1a trial had a lower EDSS range. Changes in impairment in this population, therefore, might be expected to be less substantial than in a population with more advanced disease
- the behaviour of the placebo group in the interferon beta-1a trial may have been unusual, and may have enhanced the power of this trial to demonstrate a treatment effect.

One problem with the EDSS in relapsing/remitting MS is that of reversion – confirmed progression with subsequent improvement – that is expected to occur in approximately 11% of those with MS.²⁷ The extended 6-month period for confirmed progression in the interferon beta-1a trial is more stringent than in either other study, but when the confirmation interval was extended to 12 months, the progression rate was considerably reduced (table 16).²⁶ Although the populations included in these analyses are not precisely comparable, this suggests that reversion occurred at a level greater than anticipated, raising questions of confidence concerning this end-point.

The trial duration has also attracted attention. In the Jacobs paper, progression rates were reported mainly for the subgroup of patients, $n=56$ (39%) and $n=55$ (35%) in the placebo and treated groups respectively, on study sufficiently long to show progression by 2 years, confirmed after 6 months.¹ Approximately 10% of the population remained on trial sufficiently long to show progression at 2 years confirmed after 12 months. Although the Kaplan-Meier analysis takes into account time on study, the proportion of patients able to show progression declined rapidly during the trial, which reduces confidence in the precision of the survival estimate

Interferon beta-1a ²⁶		
	Treated	Placebo
Probability of progression by 2 years		
– EDSS ≥ 1 , sustained 6 months	21.9%, $P=0.024$	34.9%
– EDSS ≥ 1 , sustained 12 months	11.5%, $P=0.002$	29.8%
– EDSS ≥ 2 , sustained 6 months	6.1%, $P=0.028$	18.3%
Confirmed progression to EDSS landmarks		
– EDSS 4.0	5%, $P=0.014$	14%
– EDSS 6.0	1%, $P=0.028$	7%

Table 16: Secondary measures of progression in the interferon beta-1a trial

Interferon beta-1a ²⁶		
Time point	Treated	Placebo
Baseline	2.4	2.3
6 months	2.4	2.5
12 months	2.5	2.8
18 months	2.6 *	3.0
24 months	2.5 *	3.1
30 months	2.7 *	3.4

^a – subgroup of patients on treatment for 2 years;
* – $P<0.05$

Table 17: Mean EDSS in the interferon beta-1a trial

at 2 years.

Another point of concern is the magnitude of EDSS change during the trial. An analysis of individual change in EDSS suggests a further benefit of treatment, but it also shows that individuals in both groups progressed very rapidly during follow-up (figure 5).²⁶ Mean EDSS change in the interferon beta-1a placebo group¹ was substantially greater than in the glatiramer acetate trial.⁴

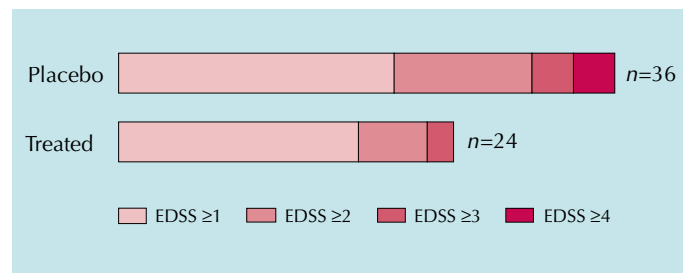


Figure 5: Magnitude of EDSS change in the interferon beta-1a trial

Evidence for an unusual placebo group outcome derives from the Kaplan-Meier curves for the interferon beta-1a and interferon beta-1b trials.^{1,5} Plotting the two analyses shows that the interferon beta-1a treated group showed progression comparable with the interferon beta-1b placebo group (figure 6). However, the interferon beta-1a placebo group showed progression which:

- indicated that a large proportion of observed progression occurred at, or very close to, the semi-annual assessments
- was particularly rapid, and may represent an unusually poor outcome which suggests that the clinical effect

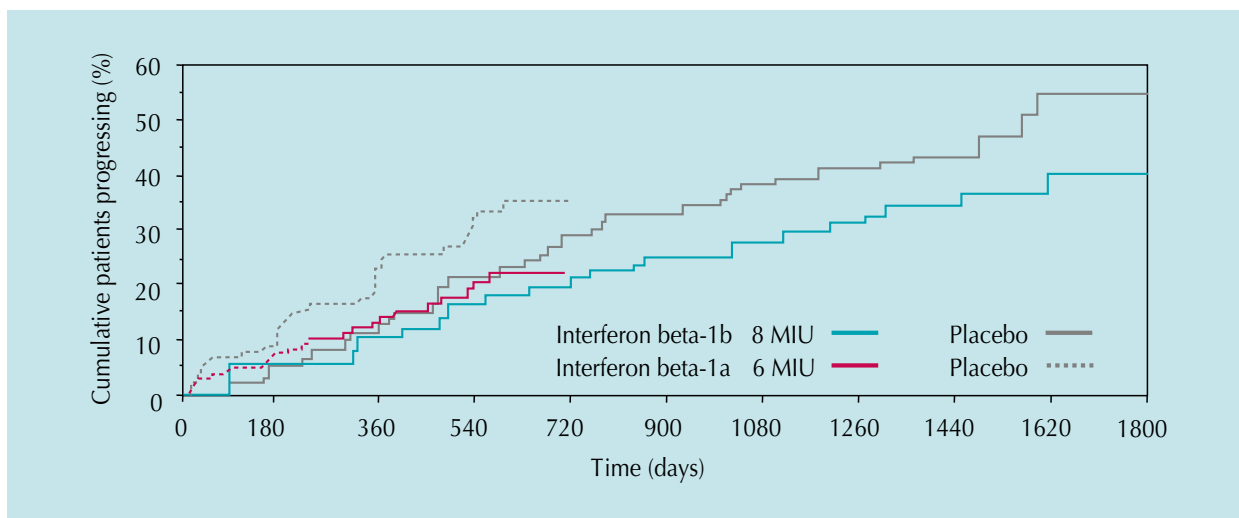


Figure 6: Kaplan-Meier risk analysis curves for the beta interferon trials

may be less than it appears.

Summary

All these agents tended to reduce the rate of progression, and this was statistically significant for interferon beta-1a. Additional *post-hoc* re-analyses of the data also support this claim. However this outcome has received considerable attention and questions have arisen. Whether a true difference exists between the three agents, or whether the apparent differences are due to trial design, the power of the trials to show an effect on disability, or to differences between the behaviour of the placebo groups in these trials, remains to be seen.

Whether short-term trials can demonstrate long-term benefit also awaits confirmation. Overall, there is a trend towards benefit with these agents, but further evidence is required before definitive claims can be made on this

Side-Effects and Antibody Issues

Few medicines are free from adverse effects, and despite much effort to develop such drugs, it is accepted that side-effects and effects on biochemical parameters are likely to occur. This is, therefore, a major contributor to the compliance of, and ultimately the long-term benefit from, drug regimens.

In multiple sclerosis (MS), the perceived safety profile of the two classes of agents currently approved for use is defined principally by the side-effects reported during three clinical trials. However, the observed safety profile can be influenced by many factors. The side-effect profile of the three agents currently approved will be reviewed, and the implications for clinical practice will be discussed.

The Side-Effect Profile of Interferon Therapy

Interferons are natural immune modulators that are finding a role for the treatment of many disorders. Consequently, clinical experience of their side-effects and tolerability is increasing. A review of the accumulated clinical experience with interferons demonstrated that acute side-effects are manageable and seldom treatment-limiting.²⁸ Acute adverse events include 'flu-like' symptoms – fever, malaise, tachycardia, chills, arthralgias and myalgias – which occur 4–8 hours after administration and diminish rapidly. This syndrome may limit dose but rarely contributes to discontinuation. Sustained treatment leads to tachyphylaxis, a decline in adverse events after 7–10 days treatment that is most pronounced in people receiving interferon via the subcutaneous route.²⁸ Symptomatic treatments to reduce the flu-like symptoms include paracetamol, prostaglandin inhibitors or corticosteroids, although individual circumstances determine the most appropriate therapy. Chronic adverse effects of interferon treatment are diverse yet relatively rare and related to dose.²⁸

Although clinical experience with alpha and gamma interferons is extensive, detailed information on adverse events related to beta interferon derives primarily from clinical trials, and post-marketing monitoring, of this agent in MS.

The Side-Effect Profile of Glatiramer Acetate

Prior clinical experience with glatiramer acetate was limited to one preliminary trial and two pilot studies of the agent in people with MS.²⁹ In these studies, injection-site reactions were notable, but only in a minority of cases were other side-effects a persistent problem. Of interest, however, was the occurrence of a transient systemic reaction characterised by flushing, sweating, palpitations, chest tightness, difficulty breathing and anxiety. Although the reaction is rare and self-limiting, its aetiology is unclear.

Adverse Events in the Three Clinical Trials

Although the reasons for patient discontinuation are varied, the results from the three trials at 2 years indicate that only a small proportion of participants found the treatments intolerable for the duration of the trial (table 18).^{1,2,4}

The adverse events described in the three trials fall into four groups:

- interferon-related (but not necessarily interferon-specific)
- injection-site or skin reactions
- general side-effects
- laboratory abnormalities.

However, the relative side-effect profile of these agents, like the efficacy profile, is difficult to compare due to differences in definition, reporting and concomitant medication.



	Interferon beta-1a ¹		Interferon beta-1b ²			Glatiramer acetate ⁴	
	Treated	Placebo	8 MIU	1.6 MIU	Placebo	Treated	Placebo
Total discontinuation	8.9%	6.3%	20.8%	16.2%	20.5%	15.2%	13.5%
Discontinuation for side-effects	4.4%	1.4%	8.7%	4.5%	0.9%	3.2%	0.8%

Table 18: Study discontinuation in the three trials

Interferon-related side-effects were, as expected, observed in both beta interferon trials.^{1,2} Flu-like symptoms, myalgia, fever and chills were significantly associated with treatment. None of these side-effects were reported in the glatiramer acetate trial.⁴ Injection-site reactions were more common in the treatment arms of the interferon beta-1b and glatiramer acetate trials, compared with their respective placebo groups.^{2,4} Good injection technique, however, can minimise these reactions. A rare, but important reaction to injection is skin necrosis. This was observed in 1–3% of individuals at some time during the interferon beta-1b trial⁵ and requires careful management.

General side-effects were varied, but rarely related significantly to treatment. Depression and suicide attempts were reported in the beta interferon trials,^{1,2} but the relationship between drug treatment and these side-effects is, *at best*, unclear. Depression itself is multifactorial and common in people with MS³⁰ and may be exacerbated by many factors. Finally, laboratory anomalies, particularly neutropaenia, anaemia, thrombocytopaenia and liver enzyme abnormalities – known to be dose-related – were significantly correlated with high-dose interferon beta-1b treatment.² However, these were never clinically significant events.

Interpreting Side-Effect Findings

All three agents can be considered to be reasonably well tolerated, and – given the goals of treatment – are comparable with other long-term therapies, such as anti-hypertensives for stroke prevention, in terms of compliance and drop-out rates. The low drop-out rate due to side-effects supports this viewpoint.^{1,2,4,5} Nevertheless, several points should be considered when interpreting the trial results:

- interferon-related side-effects are anticipated with beta interferons, so it is possible to prepare patients to expect them, and to highlight the simple techniques, like dose-escalation at the start of treatment, to minimise their impact
- the interferon beta-1a trial protocol explicitly required concomitant paracetamol to minimise side-effects.¹ Such agents were prohibited in the interferon beta-1b⁵ and glatiramer acetate⁴ trials. Thus, fewer side-effects were expected to be reported in the interferon beta-1a trial
- interferon-related side-effects are dose-related. Interferon beta-1a was administered once per week at a low dose,¹ whereas interferon beta-1b was administered every other day at a higher dose.² Thus dose and frequency of administration may influence the perceived side-effect profiles of the beta interferons
- reporting of side-effects in these trials has limitations. Each side-effect is recorded if a person experiences it only once; frequency, severity and changes over time were not reported
- short-term trials may not highlight side-effects related to long-term treatment.

Antibodies to Treatment

All the agents investigated in these trials are polypeptides, and therefore potential targets for an immune response. Antibodies to these agents have been observed – indeed, beta interferon antibodies are found in people with no prior beta interferon treatment – but their clinical significance is unknown. Antibodies may be binding, such as those measured against glatiramer acetate, and may have no direct effect on drug function; or they may be neutralising (NAB), which interfere with normal drug function.

Interpreting Antibody Findings

Antibodies are an issue because little is known about their frequency, significance or impact on management. It remains a priority, therefore, to investigate antibodies and to elucidate their role in MS treatment. The incidence of NAB in the three trials *cannot* be compared since the assays, definitions of NAB-positivity and assessment intervals differed substantially (table 19).^{1,31,32} For example, only binding antibody to glatiramer acetate was monitored,⁴ and it is unclear how NAB to this agent may meaningfully be measured. NAB to interferon beta-1a was assessed using an unspecified assay at 6-monthly intervals.¹

	Interferon beta-1a ¹	Interferon beta-1b ³¹	Glatiramer acetate ³²
Assay	Not specified	Screening ELISA with follow-up viral cytopathic effect reduction assay for neutralising activity if appropriate	Validated semi-quantitative solid-phase ELISA ^a
Definition of positivity	Positivity in treated group at a titre at which no placebo patient tested positive	Two consecutive titres 3 months apart ≥ 20 NU/ml	Not stated

^a – assay designed to measure binding antibody only

Table 19: Antibody assay and definition of positivity in the three trials

Preliminary analysis of the interferon beta-1b trial suggested that NAB-positivity coincided with loss of efficacy. However, these analyses were cross-sectional, and ignored the changing profile of NAB in individuals over time.³¹ When the data were analysed longitudinally, the results are equivocal.³³ Perhaps the most relevant information on this issue comes from long-term studies in which it is seen that the majority of patients who are antibody-positive eventually revert to antibody-negative status in the presence of continued beta interferon administration.³⁴

An international workshop convened to discuss the clinical relevance of NAB emphasised that many questions remain to be answered.³⁵ However, there was a strong recommendation that treatment decisions should be made on clinical assessment, rather than NAB status, since the relationship between NAB and clinical outcome remains uncertain.

Summary

All three agents were well tolerated in the trials. Glatiramer acetate appeared to have a particularly good safety profile, but injection-site reactions and a rare systemic reaction of unknown aetiology were noted. The safety profile of the beta interferons was reported to be similar, and any difference can be attributed to the dose used, concomitant medication and the route of administration. Interferon-related side-effects were to be expected, but in clinical practice they are relatively straightforward both to prepare for and to deal with.

Antibodies to all three agents were noted, but their clinical significance remains unclear. Comparisons between trials are impossible since different assays were used. A recent workshop recommended that no management decisions should be made on the basis of NAB status alone, because the relationship between NAB and clinical outcome remains unclear.

Concluding Remarks

Until recently there were no clearly effective long-term treatments for multiple sclerosis (MS). Today, however, three agents – interferon beta-1a, interferon beta-1b and glatiramer acetate – are available to offer some control of this disease. Ethically, therefore, there is a requirement to offer these drugs to people who can benefit from treatment. However, many factors influence the decision to treat, and the agent with which to treat.

Major considerations in this decision are efficacy, long-term benefit, tolerability and safety. Large, multicentre trials assessed these parameters for the three agents, and the trial outcomes are reviewed in this publication. Many issues have been revealed that can influence interpretation of the trial results, and alter the clinician's perception of the benefits of each agent.

In terms of efficacy, each trial addressed slightly different questions. Thus, although the interferon beta-1b and glatiramer acetate trials were not designed specifically to consider progression of disability as a primary outcome, this parameter was reported. Conversely, the interferon beta-1a trial was designed to show an effect on this outcome, and also reported on secondary measures. Enrolled populations, frequency and duration of follow-up, and many other factors all potentially affected the various outcomes.

Glatiramer acetate and interferon beta-1b offer a convincing reduction in relapse rate. The latter offered benefit over 5 years, and improved related outcomes including hospitalisation. The effect of interferon beta-1a was more modest. MRI outcomes, which remain secondary to clinical outcomes, were again substantial and sustained in the interferon beta-1b trial, but were less so in the interferon beta-1a trial. However, MRI evidence was not reported for the glatiramer acetate trial, leaving its effect on MRI-related disease parameters unanswered.

Perhaps the most important outcome is an impact on progression. All three agents show a trend towards benefit, significant in the interferon beta-1a trial. However, concerns have been raised about a poor outcome for participants in this trial, in which outcome was no better in the treated group than in the placebo group of other trials with similar entry criteria. This observation has implications for the power of the trial to show a treatment effect, and makes comparisons with other clinical trials difficult.

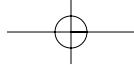
In terms of tolerability and safety, all three agents are comparable with any other long-term treatment. Adverse events do occur, but these usually can be dealt with effectively in the clinical situation.

Long-term benefit, however, remains an outstanding question. The extended follow-up of the interferon beta-1b trial, up to 5 years in many patients, suggests that the benefits of this agent are stable over time. Nevertheless, long-term efficacy needs to be monitored. Studies based on the Framingham, USA population may provide a model that can be adapted to monitor people with MS by long-term follow-up, stratified according to risk factors for long-term disability (age, sex, relapse rate, etc.). It is also important to consider assessing treatment effects on aspects of MS such as cognition, and it is with interest that results from secondary progressive MS trials are awaited.

Finally, regardless of future advances, the therapies available today have all demonstrated effects that will benefit people with relapsing/remitting MS. It is ethically required to offer these agents to people who will benefit, and it is hoped that the points highlighted in this publication will aid the clinician to make the appropriate drug choice for their patient.

References

1. Jacobs LD, Cookfair DL, Rudick RA, *et al.* Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996; **39**: 285–294.
2. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; **43**: 655–661.
3. Paty DW, Li DKB, the UBC MS/MRI Study Group, the IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomised, double-blind, placebo-controlled trial. *Neurology* 1993; **43**: 662–667.
4. Johnson KP, Brooks BR, Cohen JA, *et al.* Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 1995; **45**: 1268–1276.
5. The IFNB Multiple Sclerosis Study Group, The UBC MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomised controlled trial. *Neurology* 1995; **45**: 1277–1285.
6. Kurtzke JF. Rating neurological impairment in multiple sclerosis: An expanded disability rating scale (EDSS). *Neurology* 1983; **13**: 1444–1452.
7. Miller DH, Albert PS, Barkhof F, *et al.* Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. US National MS Society Task Force. *Ann Neurol* 1996; **39**: 6–16.
8. Design and interpretation of clinical trials in multiple sclerosis. Proceedings of the MS Forum Modern Management Workshop, Stockholm, 1996. Worthing: PPS Europe Ltd.
9. Rudick R, Antel J, Confavreux C, *et al.* Recommendations from the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force. *Ann Neurol* 1997; **42**: 379–382.
10. Noseworthy JH, O'Brien PC, The Mayo Clinic-Canadian Co-operative Study Group. The Mayo Clinic-Canadian Co-operative study of sulfasalazine in active multiple sclerosis: Preliminary report (Abstract). *Neurology* 1997; **48 (suppl)**: A340. S45.002.
11. Rice GP, Ebers GC. Interferons in multiple sclerosis: Do they prevent the progression of the disease? *Arch Neurol* 1998; in press.
12. Salman P, Le Cotonneq JY, Galazka A, *et al.* Pharmacokinetics and pharmacodynamics of recombinant human interferon beta in healthy male volunteers. *J Interferon Cytokine Res* 1996; **16**: 759–764.
13. Weinshenker BG. The natural history of multiple sclerosis. *Neurol Clin* 1995; **13**: 119–146.
14. Weinshenker BG, Bass B, Rice GPA, *et al.* The natural history of multiple sclerosis: A geographically based study. 2. Predictive value of the early clinical course. *Brain* 1989; **112**: 1419–1428.
15. Imaging in multiple sclerosis. Proceedings of the MS Forum Modern Management Workshop, Aylesbury, 1997. Worthing: PPS Europe Ltd.
16. van Walderveen MAA, Barkhof F, Hommes OR, *et al.* Correlating MRI and clinical disease activity in multiple sclerosis: Relevance of hypointense lesions on short-TR/short-TE (T₁-weighted) spin-echo images. *Neurology* 1995; **45**: 1684–1690.
17. Gass A, Barker GJ, Kidd D, *et al.* Correlation of magnetization transfer ratio with clinical disability in multiple sclerosis. *Ann Neurol* 1994; **36**: 62–67.
18. Koopmans RA, Li DK, Zhu G, *et al.* Magnetic resonance spectroscopy of multiple sclerosis: In-vivo detection of myelin breakdown products. (Letter). *Lancet* 1993; **341**: 631–632.
19. Filippi M, Paty DW, Kappos L, *et al.* Correlations between changes in disability and T2-weighted brain MRI activity in multiple sclerosis: A follow-up study. *Neurology* 1995; **45**: 255–260.
20. Simon JH, Jacobs LD, Campion M, *et al.* Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. *Ann Neurol* 1998; **43**: 79–87.
21. Stone LA, Frank JA, Albert PS, *et al.* Characterization of MRI response to treatment with interferon beta-1b: Contrast-enhancing MRI lesion frequency as a primary outcome measure. *Neurology* 1997; **49**: 862–869.
22. Stone LA, Frank JA, Albert PS, *et al.* The effect of interferon beta-1b on blood-brain barrier disruptions demonstrated by contrast-enhanced magnetic resonance imaging in relapsing-remitting multiple sclerosis. *Ann Neurol* 1995; **37**: 611–619.
23. Pozzilli C, Bastianello C, Koudriavtseva T, *et al.* Magnetic resonance imaging changes with recombinant human interferon beta-1a: A short-term study in relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1996; **61**: 251–258.
24. Magnetic resonance in multiple sclerosis. Miller DH, Kesseling J, McDonald I, *et al* (eds). Cambridge: University Press, 1997.
25. Weinshenker BG, Rice GPA, Noseworthy JH, *et al.* The natural history of multiple sclerosis: A geographically based study. 4. Applications to planning and interpretation of clinical therapeutic trials. *Brain* 1991; **114**: 1057–1067.
26. Rudick RA, Goodkin DE, Jacobs LD, *et al.* Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. *Neurology* 1997; **49**: 358–363.
27. Ellison GW, Myers LW, Leake BD, *et al.* Design strategies in multiple sclerosis clinical trials. *Ann Neurol* 1994; **36 (suppl)**: S108–S112.
28. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10**: 115–150.
29. Bornstein MB, Johnson KP. Treatment of multiple sclerosis with copolymer I. In: Rudick RA, Goodkin DE (eds). Treatment of multiple sclerosis: Trial design, results and future perspectives. Berlin/Heidelberg: Springer-Verlag, 1992.
30. Sullivan MJ, Weinshenker B, Mikhail S, Edgley K. Depression before and after diagnosis of multiple sclerosis. *Mult Scler* 1995; **1**: 104–108.
31. The IFNB Multiple Sclerosis Study Group, the UBC MS/MRI Analysis Group. Neutralizing antibodies during treatment of multiple sclerosis with interferon beta-1b: Experience during the first three years. *Neurology* 1996; **47**: 889–894.
32. Johnson KP, The US Phase III Copolymer I Study Group. Antibodies to copolymer 1 do not interfere with its clinical effect (Abstract). *Ann Neurol* 1995; **38**: 973.
33. Petkau J, White R. Neutralising antibodies and the efficacy of interferon beta-1b in relapsing-remitting multiple sclerosis (Abstract). *Mult Scler* 1997; **3**: 402.
34. Rice GPA, Lesaux J, Ebers GC. The evolution of neutralizing antibodies in patients taking beta interferon 1b (Abstract). Presented at ECTRIMS 97, Istanbul, Turkey, 3–7 November 1998.
35. Arnason BA. Neutralizing antibodies: Are they an issue? *Int MSJ* 1997; **4**: 40–42.



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