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# Key issues in the diagnosis and treatment of multiple sclerosis

## An overview

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## ▶ Introduction



Understanding of the etiology and pathogenesis of MS has improved significantly in recent years. In addition, important developments have occurred in the diagnosis and treatment of this disease. This review provides a concise, up-to-date overview of key issues relating to MS and its management. The review is divided into four main sections.

- ▲ [Top](#)
- [Introduction](#)
- ▼ [MS: THE DISEASE](#)
- ▼ [REVISED CRITERIA FOR THE...](#)
- ▼ [DISEASE-MODIFYING DRUGS IN MS](#)
- ▼ [MRI AS A SURROGATE...](#)
- ▼ [References](#)

1. A description of MS, covering symptoms and signs, natural history, epidemiology, etiology, and pathology and pathogenesis.
2. A critical analysis of the revised diagnostic criteria for MS that have recently been published by McDonald et al.<sup>1</sup>
3. A review of the key clinical studies that have been carried out with disease-modifying drugs for MS.
4. A discussion of the use of MRI as a surrogate measure in MS treatment trials, with commentaries on the specific MRI-oriented publications related to

the disease-modifying therapies.

## ▶ **MS: THE DISEASE**



### **Definition.**

MS is a chronic disease of the CNS, characterized by discrete areas of demyelination and axon injury associated with inflammatory activity. A key defining feature of MS is that lesions are disseminated in both space and time, i.e., they occur at more than one site and develop on more than one occasion. Additional information on the pathology of MS is provided below. Clinically, MS symptoms emerge between the ages of 20 and 40 years in approximately 70% of patients,<sup>2,3</sup> although changes visible on MRI are much more common than clinical activity and may well precede the latter.<sup>4-6</sup>

▲	<a href="#">Top</a>
▲	<a href="#">Introduction</a>
■	<a href="#">MS: THE DISEASE</a>
▼	<a href="#">REVISED CRITERIA FOR THE...</a>
▼	<a href="#">DISEASE-MODIFYING DRUGS IN MS</a>
▼	<a href="#">MRI AS A SURROGATE...</a>
▼	<a href="#">References</a>

### **Symptoms and signs.**

Because MS lesions can occur in many different parts of the CNS, they can cause a wide variety of symptoms and signs. An exhaustive list of clinical findings seen in MS clinics at the Universities of British Columbia and Western Ontario, Canada, is provided by Paty and Ebers,<sup>7</sup> together with estimates of the frequencies of each finding at onset and at any time. According to this list, initial neurologic symptoms and signs seen in 10% or more of patients include fatigue (20%, probably more common than this in many populations), optic neuritis (16%), internuclear ophthalmoplegia (17%), nystagmus (20%), vertigo (4–14%), gait disturbances (18%), sensory loss (30–50%, most commonly in the legs and implicating the posterior columns), increased deep tendon reflexes (20%), weakness in the legs (10%), spasticity (10%) and bladder disturbance (3–10%). Symptoms and signs seen in 50% or more of patients at any time include cognitive changes (70%), euphoria (10–60%), depression (25–54%), fatigue (80%, probably nearer 90% in many populations), optic neuritis (65%), optic atrophy (77%), retinal nerve fiber loss (80%), nystagmus (85%), vertigo (5–50%), dysarthria (50%), limb ataxia (50%), ataxia of the gait and trunk (50–80%), sensory loss (90%, again, most commonly in the legs and implicating the posterior columns), increased deep tendon reflexes (90%), weakness in the legs (90%), spasticity (90%), extensor or flexor spasms (50%), cramps (50%), amyotrophy (50%), bladder disturbance (80%), and sexual disturbance (50% in women, 75% in men).

### **Natural history.**

**Age of onset.** The mean age of onset of MS is about 30 years,<sup>8,9</sup> and the peak age of onset is 23–24 years.<sup>9</sup> Approximately 70% of cases arise between the ages of 20 and 40 years, with some 10% arising earlier in life and some 20% later.<sup>8</sup> Onset before the age of 15 years or after the age of 50 years is unusual.<sup>9</sup> However, MS has been recorded in children as young as 15 months,<sup>10</sup> and occasionally develops in individuals in their sixties or seventies.<sup>11</sup>

### **Disease course.**

The course followed by MS is highly variable. However, results from an international survey published in 1996 indicate that four main types of MS are generally recognized.<sup>12</sup> These include the following: (a) relapsing–remitting MS (RRMS), which is characterized by clearly

defined acute attacks followed by full or partial recovery to the pre-existing level of disability, and by a lack of disease progression in the periods between attacks; (b) primary progressive MS (PPMS), which is characterized by disease progression from onset, with or without occasional plateaus or temporary minor improvements; (c) secondary progressive MS (SPMS), which occurs after an initial relapsing–remitting phase and is characterized by disease progression with or without occasional relapses, minor remissions, and plateaus; and (d) progressive relapsing MS (PRMS), which is characterized by disease progression from onset punctuated by clear acute relapses that are followed by full or partial recovery to the pre-existing level of disability. Subsequent research has shown that the natural histories of PPMS and PRMS are much the same, raising questions about whether these are truly separate types of MS.<sup>13</sup>

Additional terms sometimes used to describe particular types of MS include benign, single-attack progressive, malignant or fulminant, and transitional. Benign MS is a subtype of RRMS distinguished by the fact that patients experience little or no progression of disability over a prolonged period of time (although significant disability does develop by the 25-year time point in a majority of cases). Although precise definitions vary, the term benign MS is generally applied to patients who have only minor disability [i.e., an Expanded Disability Status Scale (EDSS)<sup>14</sup> score of 3.0 or less] 10 years after the onset of disease.<sup>15</sup> Single-attack progressive MS is a rare condition in which a single initial attack is followed by the progressive phase; it is generally considered to be a subtype of SPMS. Malignant or fulminant MS is characterized by rapid disease progression that leads to significant disability or death within a few months of disease onset.<sup>12</sup> The term transitional MS refers to patients who are making the transition from RRMS to SPMS, and reflects the fact that this is often a gradual process.

Approximately 80–85% of patients with MS have RRMS at onset, and approximately 10–15% have PPMS.<sup>10</sup> A small minority (probably less than 5%) have PRMS. Results from a long-term population-based study carried out in London, Ontario, Canada, indicate that approximately 50% of patients with RRMS progress to SPMS during the first 10 years after disease onset, and approximately 90% make this transition within 25 years.<sup>2</sup>

At all stages of MS, physicians who perform patient assessments should note the presence or absence of relapses and/or progression because this information has important implications for treatment decisions.

#### **Relapse frequency.**

Relapse frequencies reported from population studies of MS vary widely. For example, the mean frequency in studies reviewed by Weinshenker and Ebers in 1987<sup>16</sup> ranged from 0.14 per patient per year to 1.1 per patient per year. At least part of this variation is probably due to the fact that relapse frequency is affected by both age and disease duration, being highest in young patients and during the early stages of MS.<sup>17</sup> Typical mean relapse frequencies are about 0.5 per patient per year for an entire MS population and 0.9–1.8 per patient during the year after disease onset.<sup>8</sup>

#### **Disability progression.**

As with relapse frequency, the rate at which disability progresses in patients with MS is highly

variable. However, data from a number of long-term studies suggest that it takes patients a median of approximately 10 years to reach the stage at which walking becomes impaired, a median of 15–20 years to reach the stage at which they need unilateral support while walking, and a median of approximately 30 years to reach the stage at which they can walk only a few steps.<sup>16,18,19</sup>

#### **Mortality.**

The effect of MS on life expectancy varies in different studies. Data from the Danish MS registry suggest that the disease reduces life expectancy by an average of 14 years.<sup>20</sup> In contrast, life table analysis of data from Vancouver, British Columbia, and London, Ontario, Canada, has shown that, for patients in most age groups, life expectancy is reduced by just 6–7 years.<sup>21</sup> Notably, the non-MS control group used in this latter analysis contained only individuals with health insurance, who are known to have a significantly better survival rate than those without insurance. If MS patients had been compared with a control population free from this bias, it is likely that the reduction in life expectancy would have been even smaller.

Approximately 50% of patients with MS eventually die of medical complications of the disease.<sup>17</sup> Other causes of death are similar to those in the general population, although the rate of suicide is several times higher in individuals with MS than in those without.<sup>17,22</sup>

#### **Prognostic factors.**

A number of clinical and demographic factors have been reported to affect the prognosis of MS.<sup>17,23</sup> It is generally accepted that an adverse prognosis is indicated if the following factors are present: (a) the patient is relatively old (>40 years) at disease onset (mainly because older-onset disease is much more likely to be progressive at onset); (b) the patient presents with motor, cerebellar, or sphincter symptoms, or with polyregional symptoms; (c) attacks are frequent during the early years of the disease; (d) the interval between the first two attacks is short; (e) remissions are incomplete; (f) disability progresses rapidly; or (g) MS is progressive from onset, or the time from onset to the start of the progressive phase is short.

Some of the most important data on clinical prognostic factors in MS come from a study from London, Ontario, Canada.<sup>24</sup> In this study, the median time taken for patients to reach a score of 6.0 on the Kurtzke Disability Status Scale (DSS; i.e., the level of disability at which they need a walking aid) correlated positively with the number of attacks during the 2 years after disease onset, with the length of the first interattack interval, and with the time taken to reach a DSS score of 3.0 (i.e., the level at which patients are moderately disabled but still fully ambulatory). In all three cases, however, the correlation coefficient was low.

Additional findings relating to the effects of relapses on the prognosis of MS have been published by Confavreux et al.<sup>25</sup> These findings show that, once a score of 4.0 has been reached on the EDSS (denoting the point at which the patient has limited ambulatory ability, but can still walk more than 500 m without aid or rest), the rate at which disability progresses is similar in patients who have progressive MS from onset and those who present with RRMS. In addition, these authors demonstrate that the rate of disability progression from an EDSS score of 4.0 is similar in patients with PPMS and those with PRMS. The findings of Confavreux et al. are interesting because they suggest that relapses, whether prior or concomitant, have little effect on the progression of disability after an EDSS score of 4.0 has been reached. They should be viewed with caution,

however, because approximately half of the patients involved in the study received pharmacologic treatment for MS, and many of the data were collected retrospectively. Moreover, these statements are generalizations based on populations of MS patients, which do not necessarily apply to the clinical behavior of individual patients.

In addition to clinical and demographic factors, MRI findings may be of prognostic value in patients with MS.<sup>4-6,26,27</sup> A long-term study based at the Institute of Neurology in London, UK, has shown that the number and total volume of brain MRI lesions in patients who present with clinically isolated syndromes (CIS) suggestive of MS are predictive of the probability of conversion to clinically definite MS (CDMS) and the rate of progression of disability over the next 14 years.<sup>4-6</sup> Of 109 patients who presented with a CIS, 71 were assessed after 14 years. CDMS developed in 44 of the 50 (88%) patients with an initially abnormal MRI, and in only 19% of those with an initially normal MRI. The median EDSS score in patients with MS at 14 years was 3.25 compared with only 2.0 in the group as a whole. Both of these EDSS scores are lower than the expected value of 6.0 at 15–20 years seen in other natural history studies.<sup>2,25</sup> This suggests that, in many cases, a CIS evolves slowly before CDMS supervenes. Follow-up EDSS scores were variable, with 31% of the MS patients having an EDSS score of 6.0 or more (including three deaths). The EDSS score at 14 years correlated moderately with MRI lesion volume at 5 years ( $r = 0.60$ ) and with change in lesion volume at 5 years ( $r = 0.61$ ), but less well with baseline lesion volume ( $r = 0.48$ ). The main point is that patients with a CIS and T2 lesions on MRI are very likely to develop further attacks in the future, although not necessarily immediately (i.e. they already have MS).

## Epidemiology.

**Geographic distribution.** The prevalence of MS varies widely in different geographic locations, from less than 1/100,000 to more than 100/100,000. A comprehensive list of prevalence rates recorded in different countries is provided by Ebers and Sadovnick.<sup>11</sup> For Canada, the values cited are 117/100,000 (British Columbia, 1982<sup>28</sup>), 134/100,000 (Saskatoon, 1977<sup>29</sup>), 94/100,000 (London, Ontario, 1984<sup>30</sup>), and 55/100,000 (Newfoundland, 1985<sup>31</sup>).

The pattern of geographic variation in the prevalence of MS is complex and non-random. If areas are classified as high risk ( $> 30/100,000$ ), medium risk ( $5\text{--}29/100,000$ ), or low risk ( $< 5/100,000$ ), as suggested by Kurtzke,<sup>32</sup> the pattern that emerges is as follows.<sup>11</sup> High-risk areas include northern and central Europe (except northern Scandinavia), Italy, the northern United States, Canada, southeastern Australia, parts of the former Soviet Union, and New Zealand. Medium-risk areas include southern Europe (excluding Italy), the southern United States, northern Australia, northern Scandinavia, other parts of the former Soviet Union, South Africa (white population only), and possibly Central America. Low-risk areas include other parts of Africa and Asia for which data are available, the Caribbean, Mexico, and possibly northern South America.

The geographic variation in the prevalence of MS appears to be due to both environmental and genetic factors.<sup>11,33</sup> Evidence for an environmental influence includes a trend for the prevalence of MS to increase with latitude, even in countries that are relatively racially homogeneous.<sup>34-37</sup> In addition, several instances have been described of immigrants to a country developing a prevalence rate similar to that of the indigenous population,<sup>38,39</sup> and there have been a number of reports of clusters and "epidemics" of MS.<sup>40-45</sup> Notably, the phenomenon in which the prevalence rate of immigrants changes to match the local rate has been found to occur in an



Australian study, regardless of the age of migration.<sup>46</sup> A role for genetic factors is suggested by the fact that certain racial groups have consistently low rates of MS. Examples include black Africans,<sup>38</sup> east Asians,<sup>35,47</sup> Sami,<sup>48</sup> Inuit,<sup>49</sup> native Americans,<sup>36,50</sup> Saudis,<sup>51</sup> and Maoris.<sup>37</sup> Moreover, major differences in the prevalence of MS may occur in populations of different ethnic backgrounds living in relatively close proximity, notwithstanding the general latitudinal gradient described above. For example, the prevalence rate on Malta is just 4.2/100,000, whereas that on the neighboring island of Sicily is 53.3/100,000.<sup>52,53</sup> The rate in Minnesota (the population of which is mainly of Scandinavian extraction) is markedly higher than that in other parts of North America lying at a similar latitude.<sup>11</sup>

#### **Sex ratio.**

Within a given population, the overall prevalence of MS is approximately twice as high in women as in men.<sup>11</sup> However, the sex ratio varies according to the type of disease. The prevalence of MS that is progressive from onset is approximately the same in men and women.<sup>11</sup> In contrast, the female:male ratio may be even greater than 2:1 for early-onset MS, familial MS, for twins, and for individuals who are positive for the human leukocyte antigen (HLA) DR2 allele.<sup>11</sup>

#### **Temporal changes.**

Most longitudinal surveys carried out to date have revealed an increase in the prevalence and/or incidence of MS over time.<sup>31,34,54-56</sup> However, it remains unclear whether this is because MS is genuinely becoming more common or because detection rates are improving.

#### **Etiology.**

As mentioned above, data on the geographic distribution of MS suggest that the disease is subject to both genetic and environmental influences. This conclusion is supported by a variety of other findings, the most important of which are summarized below. At present, the most widely accepted hypothesis for the etiology of MS is that susceptibility to the disease is genetically determined and that onset is triggered by an environmental factor.

#### **Genetic factors.**

Compelling evidence that genetic factors play an important role in MS has been obtained from the Canadian Collaborative Project on Genetic Susceptibility to MS and from a number of other family studies. This evidence can be summarized as follows. (a) There is clear familial aggregation in MS. In a large study conducted in Vancouver, British Columbia, Canada, approximately 20% of patients with MS had a first-, second-, or third-degree relative with the disease.<sup>57,58</sup> The lifetime risk for MS in first-degree relatives of patients with MS was 3–5%, and that in second- and third-degree relatives was 1.5–2.5%.<sup>57,58</sup> In contrast, the lifetime risk for MS in the Canadian population as a whole is approximately 0.2%.<sup>59</sup> (b) Population-based twin studies have demonstrated that the concordance rate for MS is much higher in monozygotic pairs (approximately 30%) than in dizygotic pairs (3–5%).<sup>60-64</sup> (c) The prevalence of MS in first-degree relatives by adoption of patients with the disease is similar to the prevalence in the general population, and is 25 times lower than would be expected for biologic first-degree relatives.<sup>65</sup> Finally, (d) the concordance rate for MS is similar in half-siblings raised together (1.2%) and apart (1.5%),<sup>66</sup> indicating that the increased risk for MS in half-siblings of patients with the disease is due to genetic factors rather than to a shared environment.

Detailed analysis of data from family studies strongly suggests that susceptibility to MS depends on at least two genes, and probably on several genes.<sup>59,67</sup> However, the question of exactly which genes are involved remains to be answered. It has long been known that a factor in the HLA class II region on the short arm of chromosome 6 plays a role in determining susceptibility to MS, and, more specifically, that the HLA-Dw2 haplotype is associated with a marked increase in risk for the disease.<sup>67</sup> However, much is still unclear about the association between HLA class II genes and MS, and research in this area continues. A number of other genes have been assessed for their contribution to MS susceptibility, including those coding for the T-cell receptor,<sup>68</sup> immunoglobulins (Igs),<sup>69,70</sup> tumor necrosis factor- $\alpha$  (TNF $\alpha$ ),<sup>71</sup> myelin basic protein (MBP),<sup>72,73</sup> and CTLA-4, a molecule expressed on the surface of activated T cells.<sup>74,75</sup> The results have mainly been negative or conflicting, but those for the CTLA-4 gene are more promising. Finally, additional insights into the genetics of MS have come from studies involving screening of the entire genome.<sup>76-79</sup> These studies have indicated that no single gene has a very large influence on MS. They have confirmed the importance of the HLA region, and they have suggested that certain loci on the short arms of chromosomes 2, 3, 5, and 7, and the long arms of chromosomes 2, 17, and 19 may contain relevant genes.

#### **Environmental factors.**

The hypothesis that environmental factors play a role in MS is supported not only by distributional data but also by the results of the twin studies mentioned above. The fact that monozygotic twins have a concordance rate of only about 30% indicates that the etiology of MS cannot be explained in genetic terms alone.

A wide variety of environmental factors have been suggested as triggers of MS, including certain foodstuffs,<sup>80</sup> certain toxins,<sup>81-83</sup> psychological stress,<sup>84</sup> anesthesia,<sup>85</sup> surgery,<sup>85</sup> and other forms of physical trauma.<sup>84</sup> Many of the data implicating these factors are retrospective or anecdotal, however, and none of the factors has yet been proved to have an effect. Recent work suggests an inverse relationship between the number of hours of sunlight per day and MS prevalence, even within racially homogeneous populations.<sup>46,86</sup> It has been proposed that this relationship may be mediated by vitamin D deficiency.<sup>87</sup>

Particular interest has been generated by the hypothesis that MS develops as a result of infection by a virus or other pathogen and by questions deriving from this hypothesis, e.g., whether MS might be triggered by infection in general or by infection with a specific agent, whether the tissue damage seen in MS might be a direct effect of a persistent infection or an indirect effect of a transient infection, and the possible role of retroviruses in MS. Evidence cited in support of the infectious hypothesis includes the following: (a) many infectious agents have been detected at elevated levels in the serum or CSF of patients with MS. Examples include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, the Epstein-Barr virus, and the viruses responsible for measles, mumps, influenza, rubella, and canine distemper<sup>88</sup>; (b) it is known that certain viruses can induce CNS demyelination in experimental animals<sup>89</sup>; and (c) certain human myelopathies similar to MS are caused by viral infection or consequent immune activity.<sup>90-93</sup>

None of this evidence is conclusive, and the role of infection in MS remains unclear. In particular, it is noteworthy that few of the findings of specific pathogens in patients with MS have proved to be reproducible, suggesting that at least some of these findings may have resulted from contamination

or adventitious infection.<sup>94</sup>

### **Pathology and pathogenesis.**

This section deals with the pathology and pathogenesis of "typical" MS. Variant pathologic forms such as Devic's syndrome, Baló's concentric sclerosis, and Marburg-type MS are beyond the scope of this supplement and are not discussed. Information on these variants can be found in standard accounts such as that by Moore.<sup>95</sup>

#### **Pathology.**

As explained above, MS is characterized by the presence in the CNS of discrete areas of demyelination and axon injury. These lesions can occur anywhere in the brain or spinal cord but tend to be most common in certain specific areas of white matter. The parts of the brain most commonly affected include the tissue bordering the lateral and fourth ventricles, periaqueductal tissue, the corpus callosum, the optic nerves, chiasma, and tracts, the corticomedullary junction, and the subpial section of the brainstem.<sup>96</sup> In the spinal cord, lesions are most often observed in the anterior columns flanking the median fissure, centrally in the dorsal columns, and subpially.<sup>96</sup> In short, there is a strong tendency for lesions to develop in white matter areas adjacent to CSF, for reasons that are as yet unclear.

MS lesions are conventionally divided into three main types: acute, chronic active, and chronic silent.<sup>97</sup> Acute lesions are of recent origin and are relatively uniform in appearance. They are characterized by ongoing demyelination and axon damage and by intense inflammatory activity. Chronic active lesions are longer-established and show a gradation of pathologic activity. Their borders are histopathologically similar to those of acute lesions, whereas their centers show little or no evidence of ongoing activity but extensive evidence of past activity. Chronic silent lesions are "old" lesions and bear a close histopathologic resemblance to the central parts of chronic active lesions.

Recent work by Lucchinetti et al.<sup>98,99</sup> indicates that, as well as differing in terms of age and disease activity, MS lesions vary in another important respect. This work suggests that actively demyelinating tissue has "profound heterogeneity in the structural and immunopathological patterns of demyelination and oligodendrocyte pathology between different MS patients." Therefore, it suggests that, rather than being a single disease with a uniform pathogenic mechanism, as is widely believed, MS may be a neurologic syndrome in which a variety of mechanisms lead to a common result. More specifically, Lucchinetti et al. propose that four different patterns of pathology exist, two of which are primarily inflammatory and spare oligodendrocytes, and two of which involve oligodendrocyte death.

The importance of axon injury in MS has only recently become fully apparent. Traditionally, MS has been viewed as a demyelinating condition in which there is relative sparing of axons, at least until the late stages of the disease. Using immunohistochemical staining and confocal microscopy, Trapp et al.<sup>100</sup> have shown that transected axons are a "consistent and abundant" feature of MS lesions, particularly acute lesions and the borders of chronic active lesions, even in patients who have had the disease for a short time. This finding is consistent with other results showing that amyloid precursor protein, a sensitive marker of axon damage, is expressed in many axons in acute lesions and the borders of



chronic active lesions,<sup>101</sup> that brain levels of *N*-acetyl aspartate (NAA), a putative marker of axon integrity, are significantly reduced in patients with early MS or mild MS,<sup>102</sup> and that brain atrophy can occur early in the course of MS.<sup>103</sup> Interestingly, studies measuring NAA have shown that levels of this marker may be reduced in normal-appearing white matter (NAWM) in the brains of patients with MS, as well as in lesions, and that a reduction in the level of NAA in a given area of NAWM may be a precursor to lesion formation.<sup>103</sup>

#### **Pathogenesis.**

MS is conventionally viewed as an autoimmune disease. More specifically, it is seen as an organ- or antigen-specific disease caused by immune-mediated injury to myelin, to its cell of origin in the CNS (the oligodendrocyte), and to the underlying axon. This view is hypothetical, however, because all that is known for certain about the pathogenesis of MS is that the demyelination and axon damage characteristic of the disease occur in the presence of immune cells and elevated levels of their products. It is even possible that MS is not primarily an inflammatory disease at all. The "altered target tissue" hypothesis holds that the primary event in MS is the development of a defect in the myelin sheath or in the axon itself, and that this event results in (rather than results from) inflammation.<sup>104</sup>

Notwithstanding the lack of firm evidence supporting the autoimmune paradigm, the most widely accepted hypothesis for the pathogenesis of MS is as follows. (a) T cells in the periphery that are specific for MBP or another myelin protein are activated as a result of interaction with a virus, another infective agent, or some other environmental stimulus. It is possible that survival of these cells is aided by a defect in apoptosis, which normally plays an important role in eliminating activated autoreactive T cells.<sup>105,106</sup> (b) The activated T cells migrate across the blood–brain barrier and enter the CNS. This process is mediated by a variety of molecules including adhesins, selectins, integrins, and matrix metalloproteinases (MMPs). (c) Once inside the CNS, activated T cells secrete immune mediators such as cytokines and chemokines, initiating an inflammatory cascade that leads to the death of oligodendrocytes, the destruction of the myelin sheath, and the degeneration of axons. Several lines of evidence suggest that oligodendrocyte death may be due at least in part to apoptosis.<sup>107,108</sup>

Research by Tuohy et al.<sup>109</sup> indicates that the autoimmune events presumed to underlie MS may include a process known as epitope spreading. The traditional view is that, throughout the course of MS, T-cell autoreactivity is directed predominantly against a single autoantigen (MBP or similar). However, Tuohy's group has found that, as MS advances, autoreactivity shifts in a defined way from the initial target to a progressively larger number of secondary autoantigens. This finding has potentially important implications for the management of MS because it suggests that the process underlying the disease may be considerably easier to disrupt at an early stage than at a late stage.

The data on the loss of axonal integrity in MS reviewed above have led to the postulation of an "axon hypothesis" for the disease, suggesting that axon damage is responsible for the permanent neurologic disability that eventually afflicts almost all patients with MS.<sup>110</sup> The available evidence indicates that axon damage begins early in the course of MS. The reason that permanent disability does not usually develop until later may be that the CNS is able to compensate for axon damage until the extent of this damage exceeds a certain threshold. An important corollary of the axon

hypothesis and the data from which it is derived is that treatment strategies for MS should be designed to minimize axon damage as effectively as possible from as early a stage as possible.

As with most other aspects of the pathogenesis of MS, the mechanism responsible for axon damage has not yet been fully elucidated. However, four main possibilities have been suggested: (a) axons may come under direct immune attack; (b) axons may suffer "bystander injury" because demyelination exposes them to an existing inflammatory milieu; (c) chronically demyelinated axons may degenerate because of the loss of trophic support from their myelin sheaths or the loss of a protective factor derived from those sheaths; or (d) axons, for reasons unknown, may degenerate primarily, eliciting a secondary inflammatory response.<sup>104,110</sup> It appears at present that the first of these mechanisms is of little or no importance in MS, that the second operates mainly during the early stages of the disease, and that the third is predominant in the later stages.<sup>110</sup> The importance of the fourth mechanism remains to be determined.

### Summary.

MS is a chronic disease of the CNS characterized by the presence of discrete areas of demyelination and axon injury. It is highly variable in symptoms, signs, and natural history. The mean age of onset is approximately 30 years, and about 50% of patients eventually die from complications of the disease. Most of the remainder suffer significant disability, although this may take many years to develop. It is believed that susceptibility to MS is genetically determined but that the onset of disease is triggered by an environmental factor. Although MS has traditionally been viewed as a demyelinating condition, an increasing body of evidence indicates that the permanent neurologic disability that eventually afflicts almost all patients with the disease is due to axon damage. Moreover, it appears that this damage begins early in the course of MS. The pathogenesis of MS is believed to involve an organ- or antigen-specific autoimmune reaction, but this remains to be confirmed.

## ▶ **REVISED CRITERIA FOR THE DIAGNOSIS OF MS: A CRITIQUE OF THE McDONALD CRITERIA**

□ Revised criteria for the diagnosis of MS were published in 2001 by the International Panel on the Diagnosis of Multiple Sclerosis.<sup>1</sup> These criteria are likely to be highly influential, and it is therefore important that they are subjected to critical analysis. The purpose here is to show how the use of these criteria may change the perception of MS, including diagnosis and treatment.

▲	<a href="#">Top</a>
▲	<a href="#">Introduction</a>
▲	<a href="#">MS: THE DISEASE</a>
▪	<a href="#">REVISED CRITERIA FOR THE...</a>
▼	<a href="#">DISEASE-MODIFYING DRUGS IN MS</a>
▼	<a href="#">MRI AS A SURROGATE...</a>
▼	<a href="#">References</a>

### Background.

The International Panel on the Diagnosis of Multiple Sclerosis was convened in July of 2000 under the auspices of the National MS Society of the USA and the International Federation of MS Societies.<sup>1</sup> The overall aim of the Panel was to review existing diagnostic criteria, particularly those published by Poser et al. in 1983,<sup>111</sup> and to recommend changes where necessary. The specific goals of the panel were as follows: (a) to create up-to-date diagnostic criteria that could be used by practicing physicians and that could be adapted, as necessary, for

use in clinical trials; (b) to integrate MRI into the overall diagnostic scheme; (c) to include a scheme for the diagnosis of PPMS; (d) to clarify the definition of certain terms used in the diagnosis of MS; and (e) to simplify the diagnostic classification of MS and related descriptions.

### General comments.

A genuine need exists for revised diagnostic criteria for MS, and the work done by the International Panel is highly valuable. Although we agree with many of the recommendations made by the Panel, comments can be made about a number of specific issues that are of practical importance to the neurologist. These comments are listed below, under the relevant headings from the paper by the International Panel.

### Specific comments.

**Introduction.** In the first of the general conclusions listed in the introductory section of the paper, the Panel states that "obtaining objective evidence of dissemination in time and space of lesions typical of MS is essential in making a secure diagnosis." However, it fails to specify exactly what it means by "objective." A precise definition of this term is required, particularly because it is used in a similar context in many other places in the paper. Are sensory or visual changes "objective"?

In the second general conclusion, the Panel states that "historical accounts of symptoms may lead to a suspicion of the disease but cannot be sufficient on their own for a diagnosis of MS." It is certainly true that MS should not be diagnosed on the basis of an historical account alone, even if the account includes descriptions of two or more attacks affecting two or more systems (i.e., suggests dissemination of lesions in time and space). However, it is equally true that an historical account can often be used as evidence of *one* lesion and that a firm diagnosis of MS can usually be made on the basis of an historical account combined with current evidence of a second lesion. Whether or not this approach is appropriate in a particular instance is a decision for the examining neurologist, and depends to a large extent on the nature of the historical account. Detailed descriptions of attacks typical of MS clearly have greater diagnostic value than vague accounts of less typical attacks. Confusingly, it is implied that any given attack requires objective verification, yet in [table 3](#) in the paper (Diagnostic Criteria), it is clear that an individual can have "two or more attacks" but "objective evidence of 1 lesion." This indicates that dissemination in time can be established partly on a subjective basis.

**View this table:** [Table 3 Key results from the study of early treatment with IM interferon \(IFN\)  \$\beta\$ -1a \(Avonex®\)<sup>117</sup>](#)  
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### What constitutes an "attack"?

In the discussion of what constitutes an attack, the Panel states that "an 'attack' (exacerbation, relapse) refers to an episode of neurologic disturbance of the kind seen in MS, when clinicopathologic studies have established that the causative lesions are inflammatory and demyelinating in nature." However, the phrase "neurologic disturbance of the kind seen in MS" is vague and, owing to the heterogeneous nature of MS, encompasses virtually all kinds of neurologic disturbance.

**Table 3** Key results from the study of early treatment with IM interferon (IFN)  $\beta$ -1a (Avonex®)<sup>117</sup>

	Placebo (n = 190)	IFN $\beta$ -1a 30 $\mu$ g IM once weekly (n = 193)	<i>p</i>
Cumulative probability of developing clinically definite MS over 3 years (unadjusted) (%)	50	35	0.002
Median increase in T2 lesion volume from baseline to 18 months (%)	16	1	<0.001
Mean number of new or enlarging T2 lesions per patient at 6, 12, and 18 months	2.8	1.5	0.001
	4.0	2.1	<0.001
	5.0	2.1	<0.001
Mean number of gadolinium-enhancing lesions per patient at 6, 12, and 18 months	1.5	0.9	0.03
	1.6	0.7	0.02
	1.4	0.4	<0.001

The Panel goes on to state that "for general diagnostic purposes, an attack ... should last for at least 24 hours." This statement is not incorrect, but physicians should exercise caution with attacks lasting less than 48 hours.

Finally, the Panel states that "single paroxysmal episodes (e.g., a tonic spasm) do not constitute a relapse, but multiple episodes occurring over not less than 24 hours do." This principle is correct and should apply to intermittent symptoms of all kinds, including Lhermitte's symptom, trigeminal neuralgia, and neurogenic bladder (but should exclude nonspecific sensory symptoms, such as tingling and numbness, that are unsupported by objective evidence). Separate bouts of a given intermittent symptom should not be viewed as separate relapses, even if they last for more than 24 hours and occur more than 30 days apart (see below).

#### **How is the time between attacks measured?**

The Panel states that "in defining what constitutes separate attacks, for the purposes of documenting separation in time of such events, it was agreed that 30 days should separate the onset of the first event from the onset of a second event." In addition, it explains that "this interpretation has the advantage of being less ambiguous than considering the interval from the beginning of recovery from the first event to initiation of the second event, as suggested in the definition of the 'Poser Committee'." Although we endorse both the revised definition of separation and the rationale behind it, the 30-day criterion is purely arbitrary and is in no way evidence-based.

#### **How is "abnormality" in paraclinical tests determined?**

**MRI.** The Panel recommends that, for the purposes of diagnosing MS, MRI abnormality should be defined using the criteria proposed by Barkhof et al. in 1997.<sup>112</sup> The reason given for this is that, although these criteria may be somewhat less sensitive than those suggested previously by Fazekas et al.<sup>113</sup> and Paty et al.,<sup>114</sup> they have been found to provide greater specificity. It is appropriate to favor specificity over sensitivity in this context. However, it should be noted that the criteria suggested by Barkhof et al. have certain important drawbacks. These drawbacks are as follows. The evidence in favor of the criteria derive from just two studies, both of which were concerned not with the diagnosis of MS but with predicting conversion to MS in patients who present with neurologic CIS suggestive of MS.<sup>112,115</sup> Both of the studies supporting the criteria have methodologic weaknesses. For example, patient numbers were relatively low, follow-up was relatively short, and the MRI techniques used were relatively unsophisticated. Much larger placebo patient cohorts are now available as a result of the CHAMPS and ETOMS studies.<sup>116,117</sup> In addition, the 14-year follow-up of CIS patients by Brex et al.<sup>6</sup> suggests that, whether the lesion number on presentation is 1–3 or >10, the risk for CDMS is the same (89% and 88%, respectively). Moreover, Barkhof et al. do not address the issue of spinal lesions sufficiently clearly. Their statement that "one spinal cord lesion can be substituted for one brain lesion" is ambiguous. Another drawback is lack of emphasis on the potential importance of spinal lesions. Such lesions can be equally or more valuable compared with brain lesions in the diagnosis of MS. It is unclear from the paper whether a single spinal lesion substitutes for one lesion or one line in the dissemination in space criteria. No mention is made of the fact that lesions in the corpus callosum



are particularly suggestive of MS. Finally, the remark that "lesions will ordinarily be larger than 3 mm in cross section" is ambiguous, because it does not specify whether this measurement refers to the shortest or the longest diameter.

MRI criteria for the dissemination of lesions in time are provided in [table 2](#) of the paper by the International Panel. The final sentence of these criteria reads: "However, if no further enhancing lesion is seen at this second scan, a further scan not less than 3 months after the first scan that shows a new T2 lesion or an enhancing lesion will suffice." The second clause of this sentence is potentially subject to misinterpretation regarding exactly when a new T2 lesion "counts" as dissemination in time, and how and when MRI scans should be performed in this context. A post-attack T2 lesion is new (i.e., shows dissemination in time) only if it first appears in a scan subsequent to a scan performed 3 months after the start of an attack. T2 lesions occurring within 3 months of an attack are not considered new T2 lesions for the purposes of showing dissemination in time.

**View this table:** [Table 2 Grading of studies<sup>121</sup>](#)  
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#### *CSF analysis.*

Discussing CSF analysis, the International Panel states that "for the purpose of diagnosing MS, CSF abnormality is defined (preferably using isoelectric focusing) by the presence of oligoclonal IgG bands different from any such bands in serum and/or the presence of an elevated IgG index." In addition, it requires that "lymphocytic pleocytosis should be less than 50/mm<sup>3</sup>." Finally, it emphasizes that "it is the practitioner's obligation, when including results of [CSF] analyses, to ensure that they are being done in the most reproducible fashion, with state-of-the-art technology." Although we are in general agreement with these recommendations, the following comments can be made. No data are cited to support the recommendation that isoelectric focusing should be the method of choice. It would be valuable to know the extent to which this statement is evidence-based. The Panel does not state how many oligoclonal IgG bands should be present. In the context of diagnosing MS, oligoclonal banding is usually defined by "the presence of two or more distinct IgG bands in the gamma region of the electrophoresis."<sup>9</sup> Furthermore, the figure of 50/mm<sup>3</sup> for lymphocytic pleocytosis should be expressed in SI units (i.e.,  $5 \times 10^7/L$ ). More importantly, this figure should not be treated as an absolute threshold. A lymphocyte count slightly greater than  $5 \times 10^7/L$  may make a diagnosis of MS less likely but should not exclude it completely.

#### *Visual evoked potentials.*

The Panel states that "abnormal VEPs [visual evoked potentials], typical of MS ... can be used to supplement information provided by a clinical examination to provide objective evidence of a second lesion provided that the only clinically expressed lesion did not affect the visual pathways." Comments are as follows. The Panel provides no guidance about the technical parameters that should be used to measure or interpret the VEP. Such guidance would be useful. The Panel implies through the wording it uses that VEP analysis cannot be employed to obtain

**Table 2** *Grading of studies*<sup>121</sup>**Class I**

Randomized, blinded, controlled trial carried out in a representative population and meeting all of the following criteria:

- a. Primary outcome(s) is/are clearly defined
- b. Exclusion/inclusion criteria are clearly defined
- c. There is adequate accounting for drop-outs and crossovers, and numbers of these are sufficiently low that there is minimal potential for bias
- d. Relevant baseline characteristics are presented and are substantially equivalent among groups, or there is appropriate statistical adjustment for differences

**Class II**

Prospective, matched-group cohort study in a representative population with masked outcome assessment that fulfills a–d above

OR

Randomized, controlled trial in a representative population that meets all but one of a–d above

**Class III**

All other controlled trials (including those with well-defined natural history controls or in which patients serve as their own controls) in a representative population, where outcome assessment is independent of patient treatment

**Class IV**

Evidence from uncontrolled studies, case series, case reports, or expert opinion

objective confirmation of a first lesion. This is arguable. Finally, the Panel makes no mention of somatosensory evoked potentials (SEPs), implying that VEPs are superior. Although we are in general agreement with this implication, SEP analysis should probably not be used on a widespread basis until the techniques involved are properly standardized.

#### **The diagnostic scheme.**

Comments about the diagnostic scheme recommended by the International Panel fall into two categories: comments about the scheme in general and comments about the recommendations for patients who present with "insidious neurologic progression suggestive of MS" (i.e., patients with suspected PPMS).

Comments about the scheme in general are as follows. (a) The scheme incorporates MRI in many places but does not require its use in all situations. However, it appears appropriate that all patients with suspected MS should undergo MRI if at all possible, because this technique is highly valuable in ruling out alternative diagnoses. (b) Four of the five categories of clinical presentation discussed are defined using the phrase "objective clinical evidence of [one or several] lesion(s)." As noted above, a precise definition of the term "objective" is needed. (c) For two of the five presentation categories, the Panel states that dissemination of lesions in space must be demonstrated before MS can be diagnosed, using either the MRI criteria developed by Barkhof et al. or a finding of "two or more MRI-detected lesions consistent with MS plus positive CSF." It would be interesting to know the extent to which the latter option (and particularly the requirement for just two lesions) is evidence-based; studies in support of this recommendation are not apparent. (d) A need exists for guidance to physicians on when and how they should re-investigate patients who become their responsibility after they have been diagnosed with MS. Specifically, it is unclear to what degree such patients require repeat investigation.

With respect to the recommendations for patients with suspected PPMS, comments are as follows. (a) One of the criteria that must be fulfilled for such patients to be diagnosed as having MS is "positive CSF." Rigid application of this criterion is likely to lead to underdiagnosis because it has been shown that some patients with PPMS do not demonstrate oligoclonal banding. (b) A number of ways are specified in which dissemination of lesions in space can be shown, all of which involve brain and/or spinal MRI. Although we support the implication that all patients with suspected PPMS should undergo MRI, the decision as to which region(s) should be scanned (brain or spinal cord) should depend on the presumed location of the clinically manifest lesion(s). (c) The recommendations favor specificity over sensitivity. They are based on criteria for "definite PPMS" developed by Thompson et al.,<sup>118</sup> who found in a preliminary assessment that these criteria were fulfilled by only 64% of patients enrolled in a natural history study of PPMS. The emphasis on specificity is appropriate at present because no effective treatment is available for PPMS. If such a treatment is developed, however, more sensitive criteria will be required. (d) The recommendations do not adequately address the issue of progressive cognitive dysfunction ("cerebral MS presenting with dementia").

#### **Discussion.**

In the Discussion, the International Panel expresses its hope that the recommendations "will encourage greater uniformity and reliability in the use of [paraclinical] technologies." However, it makes very few detailed suggestions regarding the ways in which these technologies should be

applied. The need for standardization is particularly acute for MRI because this is the most important paraclinical technique and can be performed in many different ways. Furthermore, wide variation exists in the way in which MRI results are reported. It would be extremely valuable if the radiologic community could generate evidence-based guidelines for the use of MRI in the diagnosis of MS, covering both acquisition protocols and interpretation and reporting methods. There is a similar need for standardized CSF and VEP performance and interpretation.

### Implications of the revised criteria.

The revised criteria have a number of important implications for patients with suspected MS and the physicians who care for them.

The key difference between the revised criteria and the previous Poser criteria<sup>111</sup> is that MS can now be readily diagnosed in individuals who have had a single clinical attack suggestive of the disease. This change might at first seem to be entirely beneficial for patients, because it allows earlier diagnosis and initiation of treatment. However, it should be remembered that early diagnosis of MS may have a negative impact on patient quality of life and that early initiation of treatment has not yet been proved to be advantageous from a long-term perspective, although it is helpful in the short term. Furthermore, the revised criteria may lead insurance companies to increase premiums for people who have had a single attack, or to refuse to insure them at all, even if medical investigation following the attack reveals no additional evidence of MS, and the discrimination that many people with MS suffer in the workplace may be extended to individuals who have had a single attack. In this vein, the median EDSS score of 2.0 at 14 years in individuals with CIS should be kept in mind, if not the median EDSS score of 3.25 in the subgroup of patients that actually developed CDMS after a CIS (48 of 71 patients).<sup>6</sup>

Acceptance of the revised criteria will not affect many patients adversely with respect to reimbursement, because most patients who are currently eligible for treatment will remain so. However, the revised criteria are likely to fuel the debate on whether treatment should be offered to patients who have had a single attack. This debate has intensified recently since the publication of data showing that treatment of such patients with interferon-beta (IFN $\beta$ ) can delay conversion to CDMS.<sup>116,117</sup>

From the neurologist's point of view, the revised guidelines have four key advantages. First, they require cases to be classified into just three categories—MS, possible MS, or not MS—and explain clearly how these categories are defined. Second, the MRI criteria they incorporate are highly rigorous and favor specificity over sensitivity. Therefore, the guidelines have the potential to counter the tendency toward overinterpretation of MRI findings that has recently caused concern.<sup>119</sup> Third, an obligation is placed on radiologists to standardize the way in which MRI is carried out and interpreted in the diagnosis of MS. Finally, by emphasizing the importance of MRI in the diagnosis of MS, the guidelines may facilitate access to this technology.

## DISEASE-MODIFYING DRUGS IN MS

□ During the past decade, major advances have been made in the development of disease-modifying therapies for MS, and

▲ [Top](#)  
▲ [Introduction](#)  
▲ [MS: THE DISEASE](#)

clinical trials (referenced below) have shown that IFN $\beta$ , glatiramer acetate (GA), and probably mitoxantrone have beneficial effects on certain measures of disease activity.

Indeed, five disease-modifying drugs are now licensed in the United States and Canada for use in the treatment of MS, presenting the prescribing physician with the need to make an informed decision about therapeutic choices for an individual patient.

▲ [REVISED CRITERIA FOR THE...](#)  
 • [DISEASE-MODIFYING DRUGS IN MS](#)  
 ▼ [MRI AS A SURROGATE...](#)  
 ▼ [References](#)

This section compares the scientific quality of the major studies of anti-inflammatory, immunomodulatory, and immunosuppressive therapies in MS, using a standard methodology. Each clinical trial was assessed on the basis of answers to the eight questions listed in [table 1](#) (after Sackett<sup>120</sup>) and was graded according to the definitions in [table 2](#).<sup>121</sup> The clinical application of each drug was then rated on the following scale: A, established as effective; B, probably effective; C, possibly effective; and D, unproved (data conflicting).

**View this table:** [Table 1 Guidelines for assessing randomized clinical trials](#)  
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A summary of the conclusions on each study is presented here divided according to the disease stage (early MS, RRMS, and SPMS), followed by some information on recent comparative studies of disease-modifying drugs. The information provided is brief, and for further detail the reader is referred to the original publications. The aim is not to provide recommendations on treatment but rather to enable some comparison of the clinical utility of these disease-modifying drugs in MS.

### Early treatment of suspected MS.

Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis (the CHAMPS Study).<sup>117</sup> In this randomized, blinded study, patients with a first demyelinating event and evidence of prior subclinical demyelination on brain MRI were treated with IFN $\beta$ -1a (Avonex®, Biogen, Cambridge, MA) 30  $\mu$ g IM once weekly, or placebo for 3 years. The primary end point of the study was the development of CDMS. The study was terminated after an interim analysis showed results that were strongly in favor of IFN $\beta$ -1a therapy.

### Patients, randomization, and blinding.

Patients included in the study (n = 383) had a very recent first acute clinical demyelinating event, with onset of neurologic symptoms no more than 27 days before randomization and two or more clinically silent lesions on brain MRI. They were randomized to receive IV methylprednisolone for 3 days, followed by a prednisone regimen for 15 days and IFN $\beta$ -1a (Avonex®) 30  $\mu$ g IM once weekly, or placebo for 3 years. Randomization was carried out in an appropriate manner and the study was well designed with respect to blinding. Because of the different side-effect profiles seen with active treatment and placebo, however, it is likely that patients and treating physicians were not completely blinded. Because treating physicians could be involved in deciding whether a patient was referred for evaluation of a possible disease-defining second attack, a lack of blinding



**Table 1** *Guidelines for assessing randomized clinical trials (after Sackett<sup>120</sup>)*

<p>Were patients really randomized?</p> <p>Was blinding performed? Was its effectiveness measured?</p> <p>Were all clinically relevant outcomes measured?</p> <p>Were the study patients recognizably similar to your own?</p> <p>Were both clinical and statistical significance considered?</p> <p>What is the number needed to treat?</p> <p>Is the treatment feasible in your practice?</p> <p>Were all patients who entered the trial accounted for at its conclusion?</p>
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among these physicians might conceivably have resulted in a degree of referral bias. No formal assessment of the effectiveness of blinding was performed. Final decisions on whether patients had developed CDMS were made by a separate blinded Examining Neurologist Committee.

**Clinical and statistical significance.**

Key results from the trial are summarized in [table 3](#). Outcome variables were chosen and measured appropriately but were few in number.

*Disability-related outcomes.*

This point is not applicable. The only clinical end point was the development of CDMS, defined as the occurrence of a new neurologic event or progressive neurologic deterioration. IFN $\beta$ -1a therapy reduced the probability of reaching this end point by about one-third compared with placebo without covariate adjustment, and by one-half with adjustment.

*Relapse-related outcomes.*

This point is also not applicable (see above).

*MRI.*

MRI was performed only at baseline and after 6, 12, and 18 months. It would have been desirable for all patients to have undergone an MRI scan on withdrawal from the trial, and for MRI scanning to have continued for the full duration of the trial. No information is provided about the effect of treatment on brain atrophy.

*Tolerability and drop-outs.*

Tolerability was satisfactory. The only adverse events with an incidence of five or more percentage points higher in the IFN $\beta$ -1a group than in the placebo group were an influenza-like syndrome (54% versus 26%;  $p < 0.001$ ) and depression (20% versus 13%;  $p = 0.05$ ). Patients were withdrawn from the study when they converted to CDMS and were not followed up, nor did they receive an exit MRI scan after this point. This is unfortunate because it reduces knowledge of the effect of IFN $\beta$ -1a on this subgroup of patients (the "converters"). Follow-up was discontinued early for a reason other than conversion to CDMS in 14% of the patients receiving placebo and 16% of those receiving active treatment. This means that the cumulative probability of converting to CDMS or dropping out was 64% in the placebo group and 51% in the treated group. The CHAMPIONS study, now under way, will attempt to follow all original CHAMPS study patients for 7 years after their first attack. Patients will be treated with IFN $\beta$ -1a (Avonex®) and the effects of early versus late onset of therapy will be assessed.

*Number needed to treat.*

The results of this study suggest that it is necessary to treat 6.7 patients to prevent one conversion to CDMS over a 3-year period.

**Conclusions.**

*Methodology: class I.* This trial meets the criteria for a class I study.

*Clinical application: category A.*

This study establishes that IFN $\beta$ -1a (Avonex®) 30  $\mu$ g IM once weekly delays conversion to CDMS in patients with a first acute clinical demyelinating event and MRI evidence of subclinical demyelination in the brain. It does not allow conclusions to be drawn about the effect of early

treatment on long-term prognosis. Because most patients in both the placebo and treatment groups developed new MRI T2 lesions during the trial, the effect of the drug is to delay rather than prevent MS, as defined by the new McDonald criteria.<sup>1</sup>

**Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study (the ETOMS Study).<sup>116</sup>**

This randomized, blinded study compared IFN $\beta$ -1a (Rebif®, Serono, Geneva, Switzerland) 22  $\mu$ g SC once weekly with placebo in a similar (although not identical) population to that in the CHAMPS Study.<sup>117</sup> Important differences in the ETOMS Study included the lack of standardized steroid therapy at study entry, much longer post-event entry eligibility (3 months versus 27 days in the CHAMPS Study), and the inclusion of polysymptomatic patients. The primary end point was conversion to CDMS.

*Patients, randomization, and blinding.*

The patient population in this study was reasonably representative of the "suspected MS" population as a whole. Patients (n = 308) with a first episode of neurologic dysfunction suggesting MS that had occurred within the previous 3 months and with strongly suggestive brain MRI findings were randomized to receive IFN $\beta$ -1a (Rebif®) 22  $\mu$ g SC once weekly, or placebo for 2 years. An appropriate randomization procedure was used, although complete stratification within centers was not possible because of the small numbers of patients at some centers.

Both patients and physicians were blinded. However, as in all studies of IFN $\beta$ , it is likely that at least some patients and treating physicians were aware of which treatment was being used, owing to the distinctive side-effects of this medication. The effectiveness of blinding was not formally assessed. Whereas all patients in the CHAMPS Study<sup>117</sup> had a true CIS, 39% of patients in the ETOMS Study had a multifocal onset.

*Clinical and statistical significance.*

The results of the study are summarized in [table 4](#). The chosen outcome variables were generally appropriate, as were the methods used to evaluate them.

**View this table:** **Table 4** *Key results from the study of early treatment with SC interferon (IFN)  $\beta$ -1a (Rebif®)<sup>116</sup>*  
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Disability-related outcomes. No differences were seen between IFN $\beta$ -1a and placebo groups with respect to the median change in EDSS score from baseline to year 2.

Relapse-related outcomes. The primary end point of conversion to CDMS, defined by the occurrence of a second relapse, was reached by significantly fewer patients in the IFN $\beta$ -1a group compared with the placebo group. The annual relapse rate was significantly lower.

MRI. The median number of T2 active lesions per patient per scan and the T2 lesion volume were significantly lower with IFN $\beta$ -1a compared with placebo.

**Table 4** Key results from the study of early treatment with SC interferon (IFN)  $\beta$ -1a (Rebif®)<sup>116</sup>

	Placebo (n = 154)	IFN $\beta$ -1a 22 $\mu$ g SC once weekly (n = 154)	<i>p</i>
Proportion of patients converting to clinically definite MS over 2 years (%)	45	34	0.047
Mean annual relapse rate	0.43	0.33	0.045
Median change in EDSS score from baseline to year 2	0	0	NS
Median change in SNRS score from baseline to year 2	0	0	NS
Median number of T2 active lesions per patient per scan	3	2	<0.001
Median number of enhancing lesions per patient per scan	0	0.5	NS
Median change in T2 lesion volume from baseline to year 2 (%)	8.8	-13.0	0.002
EDSS = Expanded Disability Status Scale; NS = not significant; SNRS = Scripp's Neurologic Rating Scale.			

Tolerability and drop-outs. Several adverse events occurred more frequently with IFN $\beta$ -1a than with placebo. These included injection-site reactions (60% versus 12%), fever (28% versus 12%), myalgia (17% versus 9%) and chills (11% versus 5%). The number of patients who withdrew prematurely was 13 (8%) in the IFN $\beta$ -1a group and 18 (12%) in the placebo group. However, only four (3%) patients in each group withdrew before conversion to CDMS. Changes in liver function tests and antibody rates were not reported.

Number needed to treat. A calculation based on the results of this study indicates that 9.1 patients must be treated to prevent one conversion to CDMS over a 2-year period.

*Conclusions.*

*Methodology: class I.* This trial meets the criteria for a class I study.

*Clinical application: category A.*

The results of this study demonstrate that IFN $\beta$ -1a (Rebif®) 22  $\mu$ g SC once weekly delays conversion to CDMS in patients who have had a first episode of neurologic dysfunction suggestive of MS and brain MRI findings strongly suggestive of MS. As with the CHAMPS Study,<sup>117</sup> no conclusion can be drawn about the effect of very early therapy on long-term prognosis. The annualized relapse rate of 0.43 among placebo-treated patients in this study is much lower than that of about 1.0 observed in the pivotal trials of IFNs in RRMS. The "single-attack" population is therefore much less clinically active than patients with established RRMS, and this must be considered when therapy is recommended. The ideal dose of IFN in this setting is unclear, and results from dose trials in active RRMS populations cannot necessarily be extrapolated to this group of patients. Note that the IFN $\beta$ -1a dose of 22  $\mu$ g once weekly used in the ETOMS Study is much lower than the 22 or 44  $\mu$ g three times weekly used in RRMS.

## **Relapsing–remitting MS.**

Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial.<sup>122</sup> This was the first large, multicenter, placebo-controlled study to show effectiveness of a disease-modifying agent in patients with MS and the first to use MRI as a surrogate end point. The primary end points were annual relapse rate and the proportion of relapse-free patients.

### **Patients, randomization, and blinding.**

Patients (n = 372) with RRMS, an EDSS score of 0.0–5.5, and at least two relapses in the previous 2 years were randomized to treatment with IFN $\beta$ -1b (Betaseron®, Berlex Laboratories, Montville, NJ) 1.6 or 8 MIU SC every other day, or placebo for 2 years. Randomization and blinding were appropriate but blinding was not formally assessed.

### **Clinical and statistical significance.**

The results of the study are summarized in [table 5](#).



**View this table:** [Table 5 Summary of the results of the initial 2-year study with SC interferon \(IFN\)  \$\beta\$ -1b \(Betaseron®\) in relapsing–remitting MS<sup>122</sup>](#)  
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*Disability-related outcomes.*

High-dose IFN $\beta$ -1b was found to have no significant beneficial effect on disability over 3 years.

*Relapse-related outcomes.*

The higher dose of IFN $\beta$ -1b had a significant beneficial effect over 2 years on relapse rate, the proportion of patients remaining relapse-free, and the median time to the first relapse. In addition, it reduced the number of moderate or severe relapses and the need for hospitalization.

*MRI.*

After 2 years, mean total lesion area had increased by 20% in the placebo group and by 10.5% in the low-dose IFN $\beta$ -1b group but had decreased by 0.1% in the high-dose group.

*Tolerability and drop-outs.*

Neither adverse events nor drop-outs are described in detail in the paper. No serious laboratory abnormalities were observed, but a number of adverse events were seen more commonly with IFN $\beta$ -1b than with placebo. These included fever, chills, myalgia, sweating, malaise, and injection-site reactions. A total of 65 (17%) patients discontinued treatment during the first 2 years of the study. Of these, 23 were in the placebo group, 18 were in the low-dose IFN $\beta$ -1b group, and 24 were in the high-dose group. The study was originally planned to last for 2 years, and 122 patients failed to take part in the study extension. Neutralizing antibody activity was recorded in the serum of 11% of placebo-treated patients and in 47% and 45% of those receiving IFN $\beta$ -1b 1.6 and 8 MIU, respectively. Mild or moderate changes in serum glutamate pyruvate transaminase occurred in five (4.1%) patients receiving placebo, in seven (5.6%) receiving low-dose IFN $\beta$ -1b, and in 14 (11.3%) receiving the higher dose.

*Number needed to treat.*

From the results of this study, it can be calculated that 2.3 patients must be treated with high-dose IFN $\beta$ -1b 8 MIU every other day to prevent one relapse per year in this actively relapsing population; 5.6 patients must be treated to keep one patient relapse-free for 2 years; and 4.5 patients must be treated to prevent one moderate or severe attack per year. This study appeared to show a dose–response relationship for a number of end points, including relapse rate and MRI lesion area.

**Conclusions.**

*Methodology: class I.* This trial meets the criteria for a class I study.

*Clinical application: category A for relapses and MRI activity.*

This study establishes that IFN $\beta$ -1b (Betaseron®) 8 MIU SC every other day is effective in reducing relapses and on measures of MRI activity. No statistically significant effect was seen on delaying disease disability, as measured by a confirmed 1.0-point change in EDSS score.

**Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial.**<sup>123</sup>

Patients involved in the pivotal Phase III trial of IFN $\beta$ -1b had the option of continuing in the study

**Table 5** Summary of the results of the initial 2-year study with SC interferon (IFN)  $\beta$ -1b (Betaseron®) in relapsing–remitting MS<sup>122</sup>

	Placebo (n = 123)	IFN $\beta$ -1b 1.6 MIU SC every other day (n = 125)	IFN $\beta$ -1b 8 MIU SC every other day (n = 124)
Annual relapse rate over 2 years	1.27	1.17 ( $p = 0.01$ vs. placebo)	0.84 ( $p = 0.0001$ vs. placebo; $p = 0.0086$ vs. 1.6 MIU)
Proportion of patients relapse-free at 2 years (%)	18	23	36 ( $p = 0.007$ vs. placebo)
Median time to first relapse (days)	153	180	295 ( $p = 0.015$ vs. placebo; $p < 0.05$ vs. 1.6 MIU)
Mean change in MRI lesion area from baseline to year 2 (%)	20	10.5	-0.1

for up to 5 years. Evaluation procedures were similar to those reported for the initial 3 years. Primary end points for the extension study were the time to sustained (3 months) worsening by at least 1.0 point on the EDSS in each treatment group and mean change in confirmed EDSS score from baseline.

*Patients, randomization, and blinding.*

These parameters were as for the initial study. Blinding was not formally addressed.

*Clinical and statistical significance.*

The results of the 5-year study are summarized in [table 6](#).

**View this table:** [Table 6 Summary of the final outcome of the 5-year study with SC interferon \(IFN\)  \$\beta\$ -1b \(Betaseron®\) in relapsing–remitting MS<sup>123</sup>](#)  
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Disability-related outcomes. High-dose IFN $\beta$ -1b had no significant effect on time to progression of disability over the 5 years, although a trend in favor of treatment was identified ( $p = 0.096$ ). Although defined as one of the two primary end points of the extension study, data on mean change in confirmed EDSS score are not provided.

Relapse-related outcomes. Both doses of IFN $\beta$ -1b had a significant beneficial effect on the pooled annual relapse rates for the entire study. Although annualized relapse rates for each year of the study were lower in the 8 MIU treatment group than with placebo, the differences did not reach statistical significance after year 2. However, fewer patients completed years 3, 4, and 5, indicating that this lack of significance may be a type II (false-negative) error. No information is provided on the defined secondary end points of the proportion of exacerbation-free patients. However, it is stated that the rate of moderate and severe attacks was significantly lower in both treatment arms compared with placebo ( $p = 0.012$  8 MIU versus placebo;  $p = 0.023$  1.6 MIU versus placebo).

MRI. At the end of 4 years, the median percentage change in MRI lesion area compared with baseline was an increase of 18.7% in the placebo group compared with a 0.8% decrease in the IFN $\beta$ -1b 8 MIU group. At the end of 5 years there was an increase of 30.2% in the placebo group and of 3.6% with high-dose IFN $\beta$ -1b although the patient numbers were very small by this stage of the study.

Tolerability and drop-outs. Adverse events are not described in detail in the paper, although the reasons for study withdrawal are. Laboratory abnormalities were slightly more common in the IFN $\beta$ -1b 8 MIU group than in the placebo arm in the later phases of the study. By the end of the study, there had been 154 drop-outs and this may have influenced the overall outcome of the study. This number is difficult to reconcile with the numbers provided in [table 1](#) in the paper. The text states that the number of patients in any given year is identical to those completing the previous year and, according to [table 1](#), 166 patients completed year 4 and thus went into year 5. If 372 patients entered the study, 166 started year 5, and 154 dropped out, there are

**Table 6** Summary of the final outcome of the 5-year study with SC interferon (IFN)  $\beta$ -1b (Betaseron®) in relapsing–remitting MS<sup>123</sup>

	Placebo (n = 123)	IFN $\beta$ -1b 1.6 MIU SC every other day (n = 125)	IFN $\beta$ -1b 8 MIU SC every other day (n = 124)
Median time to progression of disability (years)	4.18	3.49	4.79 ( $p = 0.096$ vs. placebo)
Pooled annual relapse rate	1.12	0.96 ( $p = 0.0057$ vs. placebo)	0.78 ( $p = 0.0006$ vs. placebo)
Rate of moderate and severe relapses	Data not provided	Data not provided ( $p = 0.023$ vs. placebo)	Data not provided ( $p = 0.012$ vs. placebo)
Median change in MRI lesion area from baseline to year 5 (%)	30.2	10.6	3.6 ( $p = 0.0363$ vs. placebo)

52 patients unaccounted for. In the placebo group, there was a significant difference in annual exacerbation rate between those who completed the study (0.98) and those who withdrew (1.6;  $p = 0.006$ ). This was also true for the median annual percentage change in MRI lesion area in this group: 4.6% among completers versus 13.7% among those who withdrew ( $p = 0.012$ ). By contrast, there was no significant difference between completers and those who withdrew in the two IFN $\beta$ -1b groups. Therefore, the placebo group may have become biased toward those less likely to progress, which would tend to reduce the apparent effect of the drug.

Number needed to treat. This parameter was not calculated.

*Conclusions.*

*Methodology: class II.* There were many drop-outs from the extension study, and small numbers of patients, particularly in year 5.

Clinical application: category B for relapses. This study establishes that IFN $\beta$ -1b (Betaseron®) 8 MIU SC every other day is probably effective in reducing relapses. No proven effect on disability was shown, but a trend in this direction was evident.

**Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis.**<sup>124</sup>

The primary end point of the study was a comparison of the time to confirmed EDSS progression (sustained for 6 months) between patients treated with IFN $\beta$ -1a (Avonex®) 30  $\mu$ g IM once weekly and the control group. Unlike the other trials with IFN, effects on relapse rates were secondary end points in the study design.

*Patients, randomization, and blinding.*

Patients ( $n = 301$ ) had RRMS with at least two relapses in the 3 years before study entry but were a mildly affected group with an EDSS score of 1.0–3.5. Patients were randomized to treatment with IFN $\beta$ -1a (Avonex®) 30  $\mu$ g IM once weekly, or placebo for 2 years. Randomization was appropriate. Questionnaires used at weeks 6, 52, and 104 indicated that medical personnel remained blinded throughout the study and that patients were more likely to correctly guess their treatment assignment than their examining physicians. Patient visits occurred at baseline and at every 6 months. The dose of IFN $\beta$ -1a was apparently chosen on the basis that it was the maximal dose that could be readily masked with acetaminophen.<sup>125</sup>

*Clinical and statistical significance.*

The results of the study are summarized in [table 7](#). Their clinical significance is reduced by the fact that only 57% of the 301 patients who were enrolled completed 2 years of treatment. Moreover, a subsequent analysis requested by the FDA showed that there was a strong cohort effect. Patients who enrolled early enough in the study to complete 2 years did considerably better than those who enrolled later.<sup>126</sup> Specifically, there was a reduction of approximately 30% in relapse rates at both year 1 and year 2 among those who completed 2 years in the study. Among the 43% who were non-completers, the relapse rate was actually higher in the treated group than in the placebo group. The reason for this is unclear.



**View this table:** [Table 7 Summary of the results from the 2-year study of IM interferon  \$\beta\$ -1a \(Avonex®\) in relapsing–remitting MS<sup>124</sup>](#)  
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**Disability-related outcomes.** The proportion of patients showing sustained progression of disability (defined as a deterioration of at least 1.0 point on the EDSS persisting for at least 6 months) was estimated from a Kaplan–Meier analysis to be 21.9% with IFN $\beta$ -1a and 34.9% with placebo ( $p = 0.02$ ). The robustness of this finding is questionable because, in patients with mild disability (such as those involved in this study), EDSS scores can show considerable variation over time owing to minor changes in the neurologic examination. A subsequent paper by Rudick et al.<sup>127</sup> demonstrated that few of the progressions were in cerebellar or motor functional systems and that many of the 6-month sustained progressions subsequently improved, suggesting that many of these disability changes had not necessarily been permanent.

**Relapse-related outcomes.** Mean relapse rate was reduced by 18% over the course of the study ( $p = 0.04$ ) with active treatment. Among the subset of patients who had completed 2 years of treatment, the corresponding figure was 32% ( $p = 0.002$ ).

**MRI.** At year 1, the proportion of gadolinium-enhancing lesions was 29% with IFN $\beta$ -1a and 42.3% with placebo ( $p = 0.05$ ), and it is stated that this group difference persisted at year 2. At year 2, the mean number of gadolinium-enhancing lesions per patient was reduced by approximately 50% with active treatment ( $p = 0.05$ ). Notably, however, the number of patients for whom MRI data were available at this time point was just 165 (of a total study population of 301). Treatment had no significant effect on the accumulation of T2 burden of disease over the 2 years of the study.

**Tolerability and drop-outs.** Active treatment was generally well tolerated, and the only symptoms that were reported more often with IFN $\beta$ -1a than with placebo were influenza-like symptoms (e.g., muscle aches, asthenia, chills, and fever). Twenty-three patients (9 in the placebo group and 14 in the IFN $\beta$ -1a group) discontinued injections early. However, only five patients were lost to follow-up before the primary outcome variable could be evaluated. Neutralizing antibodies were seen in approximately 14% of treated patients at week 52, 21% at week 78, and 22% at week 104. Fifteen treated patients tested positive for neutralizing antibodies when a cut-off value was used at which no placebo patient tested positive.

**Number needed to treat.** According to the results of this trial, it is necessary to treat 7.7 patients for 2 years to prevent progression by at least 1.0 point on the EDSS.

#### *Conclusions.*

**Methodology: class I.** This study was methodologically sound and the number of patients who withdrew was low. However, given its short duration and the fact that it was stopped early, the long-term relevance of these observations is indeterminate. Other difficulties include the restricted MS population studied (EDSS score of 1.0–3.5) and the unexpected, and unexplained, apparent "time of enrollment" effect.

**Clinical application: category A.**

**Table 7** Summary of the results from the 2-year study of IM interferon (*IFN*)  $\beta$ -1a (Avonex®) in relapsing–remitting MS<sup>124\*</sup>

	Placebo (n = 143)	IFN $\beta$ -1a 30 $\mu$ g IM once weekly (n = 158)	<i>p</i>
Annual relapse rate (all patients)	0.82	0.67	0.04
Annual relapse rate (subset who completed 2 years)	0.90	0.61	0.002
Proportion of patients showing sustained progression of disability (all patients) (%) <sup>†</sup>	34.9	21.9	0.02
Proportion of MRI scans showing gadolinium-enhancing lesions at year 1 compared with baseline (%)	42.3	29.9	0.05
Change in T2 lesion volume from baseline to year 2 (%)	-13.2	-6.5	NS
NS = not significant.			
* Only 57% of patients completed the full 2 years of treatment.			
<sup>†</sup> Defined as an increase of at least 1.0 point on the Expanded Disability Status Scale that persisted for at least 6 months.			

The study provides good evidence that IFN $\beta$ -1a (Avonex®) 30  $\mu$ g IM once weekly is effective in prolonging the time to disability and reducing the relapse rate in patients with low-disability RRMS. In contrast to the pivotal trials of SC IFN $\beta$ -1a and IFN $\beta$ -1b in RRMS, however, there was no significant effect of treatment on T2 burden of disease over the course of the study. A subsequent re-analysis of the T2 data using different methodology did show an effect over 2 years on T2 lesion number<sup>128</sup> (see below).

**Randomised double-blind placebo-controlled study of interferon  $\beta$ -1a in relapsing/remitting multiple sclerosis (the PRISMS Study).**<sup>129</sup>

This study of IFN $\beta$ -1a (Rebif®) administered SC three times weekly in patients with RRMS showed effectiveness in reducing relapses and delaying disability progression and major beneficial effects on MRI outcome measures. The primary end point was the relapse rate.

*Patients, randomization, and blinding.*

RRMS patients with at least two relapses in the preceding 2 years and an EDSS score of 0.0–5.0 (n = 560) were randomized to treatment with IFN $\beta$ -1a (Rebif®) 22 or 44  $\mu$ g SC three times weekly, or placebo. Randomization and blinding were appropriate but no data on the effectiveness of blinding were presented.

*Clinical and statistical significance.*

The results of the study are summarized in [table 8](#).

**View this table:** [Table 8 Summary of the key results of the 2-year study of SC interferon \(IFN\)  \$\beta\$ -1a \(Rebif®\) in relapsing–remitting MS](#)<sup>129</sup>  
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*Disability-related outcomes.*

Active treatment with IFN $\beta$ -1a significantly increased the time to confirmed progression of disability and reduced the probability of progression. In addition, it reduced the median Integrated Disability Status Scale score (the area under the EDSS curve),<sup>130</sup> the mean increase in EDSS score, and (at the higher dose) the mean increase in Ambulation Index.

*Relapse-related outcomes.*

The mean number of relapses per patient was significantly reduced with both doses of IFN $\beta$ -1a, as were the number of moderate and severe relapses, the number of steroid courses, and (with the higher dose) the number of hospitalizations. In addition, the proportion of patients who remained relapse-free was significantly increased.

*MRI.*

Burden of disease increased by more than 10% with placebo but decreased with both doses of IFN $\beta$ -1a. Similarly, the number of T2 active lesions was significantly reduced with both doses of IFN $\beta$ -1a.

*Tolerability and drop-outs.*

Patient disposition throughout the trial is well described in the paper. However, additional information on tolerability would be desirable. IFN $\beta$ -1a given SC three times weekly was generally

**Table 8** Summary of the key results of the 2-year study of SC interferon (IFN)  $\beta$ -1a (Rebif®) in relapsing–remitting MS<sup>129</sup>

	Placebo (n = 187)	IFN $\beta$ -1a 22 $\mu$ g SC three times weekly (n = 189)	IFN $\beta$ -1a 44 $\mu$ g SC three times weekly (n = 184)
Relapses per patient over 2 years	2.56	1.82*	1.73*
Proportion of relapse-free patients over 1 year (%)	22	37*	45*
Proportion of relapse-free patients over 2 years (%)	16	27 <sup>†</sup>	32*
Mean number of moderate/severe relapses over 2 years	0.99	0.71*	0.62*
First quartile time to progression of disability (months) <sup>§</sup>	11.9	18.5 <sup>‡</sup>	21.3 <sup>‡</sup>
Mean change in EDSS score over 2 years	0.48	0.23 <sup>‡</sup>	0.24 <sup>‡</sup>
Ambulation Index (2-step increase sustained for 3 months) (%)	13	12	7 <sup>‡</sup>
Median change in T2 MRI burden of disease (%)	10.9	-1.2**	-3.8**
Reduction in T2 active lesions compared with placebo (%)		-67**	-78** ( $p = 0.0003$ vs. 22 $\mu$ g)
Mean number of steroid courses over 2 years	1.39	0.97 <sup>†</sup>	0.75*
Mean number of hospitalizations over 2 years	0.48	0.38	0.25*

EDSS = Expanded Disability Status Scale.

\*  $p < 0.005$  compared with placebo.

<sup>†</sup>  $p \leq 0.05$  compared with placebo.

<sup>‡</sup>  $p < 0.05$  compared with placebo.

<sup>§</sup> Defined as an increase of at least 1.0 point on the EDSS that persisted for at least 3 months.

\*\*  $p < 0.0001$  compared with placebo.

well tolerated, although adverse events previously seen with this agent (such as influenza-like symptoms) were common. No significant intergroup differences in rates of depression were observed. Of the 560 patients randomized, 502 (90%) completed 2 years of treatment and 533 (95%) were followed-up for 2 years. At 2 years, neutralizing antibodies were seen in approximately 24% of patients who received the low dose of IFN $\beta$ -1a and in 15% of patients who received the higher dose.

*Number needed to treat.*

Numbers needing to be treated that can be derived from this study include the following: (a) 2.4 (high-dose) and 2.7 (low-dose) patients to prevent one relapse per year; (b) 4.3 (high-dose) and 6.7 (low-dose) patients to render one patient relapse-free over 1 year; (c) 6.3 (high-dose) and 9.1 (low-dose) patients to render one patient relapse-free over 2 years; (d) 2.7 (high-dose) and 3.6 (low-dose) patients to prevent one moderate–severe relapse over 2 years; and (e) 9 (high-dose) and 12 (low-dose) patients to prevent sustained progression of 1.0 EDSS point over 2 years.

*Conclusions.*

*Methodology: class I.* This trial meets the criteria for a class I study.

*Clinical application: category A.*

This study establishes that IFN $\beta$ -1a (Rebif®) 22 or 44  $\mu$ g SC three times weekly is effective in reducing relapses and delaying the progression of disability in patients with RRMS.

**PRISMS-4: long-term efficacy of interferon- $\beta$ -1a in relapsing multiple sclerosis.**<sup>131</sup>

After starting the 2-year study, the PRISMS investigators and Serono (Geneva, Switzerland) decided to extend it for an additional 2 years. The primary end point was the relapse rate per patient over 4 years, with the primary comparison being high-dose IFN $\beta$ -1a versus placebo.

*Patients, randomization, and blinding.*

Of the 560 patients initially enrolled in PRISMS, 506 (90%) entered the extension phase described in the paper. Patients originally on active treatment continued with the same dose for a further 2 years. Patients who had originally received placebo were re-randomized to receive IFN $\beta$ -1a (Rebif®) 22 or 44  $\mu$ g SC three times weekly, using an appropriate procedure that is adequately described. Blinding was maintained throughout the extension phase, but its effectiveness was not formally assessed.

*Clinical and statistical significance.*

The results of the study are summarized in [table 9](#). In general, the beneficial effects seen with IFN $\beta$ -1a during the first 2 years of the study persisted during the extension phase. Patients were assessed every 3 months during years 1–3 and every 6 months in year 4.

**View this table:** **Table 9 Summary of the key 4-year data from the PRISMS Study of SC**  
[\[in this window\]](#) **interferon (IFN)  $\beta$ -1a (Rebif®) in relapsing–remitting MS**<sup>131\*</sup>  
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*Disability-related outcomes.*

**Table 9** Summary of the key 4-year data from the PRISMS Study of SC interferon (IFN)  $\beta$ -1a (Rebif®) in relapsing–remitting MS<sup>131\*</sup>

	Crossover groups (n = 172)	IFN $\beta$ -1a 22 $\mu$ g SC three times weekly (n = 167)	IFN $\beta$ -1a 44 $\mu$ g SC three times weekly (n = 167)
Mean number of relapses per patient per year	1.02	0.80 ( $p < 0.001$ vs. crossover)	0.72 ( $p < 0.001$ vs. crossover)
Proportion of relapse-free patients (%)	6.7	14.4 ( $p = 0.016$ vs. crossover)	19.0 ( $p < 0.001$ vs. crossover)
Time to first confirmed progression of EDSS (months; 40th percentile) <sup>†</sup>	24.2	35.9	42.1 ( $p = 0.047$ vs. crossover)
Number of confirmed progressions per patient per year <sup>†</sup>	0.24	0.22	0.17 ( $p = 0.005$ vs. crossover; $p = 0.03$ vs. 22 $\mu$ g)
Median number of new T2 lesions per patient per scan	2.0 (placebo/22 $\mu$ g) 2.7 (placebo/44 $\mu$ g)	1.3 ( $p < 0.001$ vs. placebo/22 $\mu$ g)	0.5 ( $p < 0.001$ vs. 22 $\mu$ g and placebo/44 $\mu$ g)
Change in MRI burden of disease (%)	7.2 (placebo/22 $\mu$ g) 9.7 (placebo/44 $\mu$ g)	3.4	-6.2 ( $p = 0.009$ vs. 22 $\mu$ g; $p = 0.003$ vs. placebo/44 $\mu$ g)

EDSS = Expanded Disability Status Scale.

\* After the first 2 years of the study, patients taking active treatment continued with the same dose. Those on placebo were re-randomized to receive IFN $\beta$ -1a (Rebif®) 22 or 44  $\mu$ g SC three times weekly for an additional 2 years, and are described in the table as "crossover."

<sup>†</sup> Defined as an increase of at least 1.0 point on the EDSS that persisted for at least 3 months.



An important aim of the study was to determine whether the efficacy of IFN $\beta$ -1a was dose-dependent. Time to confirmed progression did not differ between doses over 4 years but was longer than that observed for placebo. However, a dose–effect relationship for disability progression in years 3 and 4 was identified.

*Relapse-related outcomes.*

The 4-year data confirm that relapse rate was significantly reduced with both doses of IFN $\beta$ -1a compared with the placebo crossover group, although no difference was seen over 4 years between the groups receiving the high and low doses. The higher dose was significantly more effective than the lower dose with respect to the time to the second relapse and the need for steroids. A significant dose–effect relationship on relapse rate was seen during years 3 and 4 only.

*MRI.*

Patients who switched from placebo to IFN $\beta$ -1a showed reductions in MRI activity during the second 2 years of the study, but their overall MRI findings were worse than in patients who received IFN $\beta$ -1a throughout. A dose–effect relationship was seen for several MRI variables. Treatment appeared to have an immediate effect on MRI, making it impossible for the placebo patients to recapture what was lost in the first 2 years.

*Tolerability and drop-outs.*

Adverse events during the extension phase were similar to those observed during the first 2 years of the study, and most were mild. A total of 73 patients stopped treatment prematurely during the extension phase, of whom 45 were receiving high-dose IFN $\beta$ -1a and 28 were receiving the low dose ( $p = 0.043$  for the intergroup difference). Interestingly, placebo patients switched to active treatment developed neutralizing antibody levels in excess of 20% (28% for placebo/IFN $\beta$ -1a 22  $\mu$ g and 24% for placebo/IFN $\beta$ -1a 44  $\mu$ g) irrespective of dose (data provided by Serono, Geneva, Switzerland). The development of neutralizing antibodies was associated with a significantly higher number of relapses (in both dose groups), and a greater increase in MRI burden of disease and T2 active lesions over 4 years.

*Number needed to treat.*

This parameter was not calculated.

*Conclusions.*

**Methodology:** *class I.* This trial meets criteria for a class I study.

*Clinical application: category A.*

This trial establishes that IFN $\beta$ -1a (Rebif®) 22 or 44  $\mu$ g SC three times weekly is effective in reducing relapses and delaying the progression of disability, as well as positively affecting a number of MRI markers of disease activity (change in MRI burden of disease, median number of new T2 lesions per patient per scan). The primary end point showed a difference between active treatment and placebo but not between low- and high-dose IFN $\beta$ -1a.

**Copolymer 1 reduces relapse rate and improves disability in relapsing–remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial.**<sup>132</sup>

The primary end point of this study was the number of relapses in GA (copolymer 1; Copaxone®, Teva Marion Partners, Kansas City, MO)-treated patients versus placebo-treated patients over 2 years. Relapses had to be accompanied by changes on neurologic functional systems. The paper

states that a priori adjustment of the relapse rate for certain prognostically significant variables was planned.

*Patients, randomization, and blinding.*

Patients (n = 251) with RRMS, at least two relapses in the previous 2 years, and a baseline EDSS score of 0.0–5.5 were randomized to receive GA 20 mg SC once daily, or placebo for 2 years. Randomization was carried out centrally and the two patient groups were similar at baseline. As in the pivotal IFN $\beta$  trials, treatment and evaluation were carried out by separate blinded physicians. The success of blinding was not formally tested.

*Clinical and statistical significance.*

The results of the trial are summarized in [table 10](#).

**View this table:** [Table 10 Summary of the results from the pivotal phase III trial of SC glatiramer acetate \(GA; Copaxone®\) in relapsing–remitting MS<sup>132</sup>](#)  
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Disability-related outcomes. Using the standard measure of disability progression (change in EDSS score by 1.0 point, sustained for 3 months), GA showed no significant effect.

Relapse-related outcomes. GA reduced relapse rate by 29% compared with placebo. This effect was statistically significant ( $p = 0.007$ ) when an ANCOVA analysis was performed using gender, duration of disease, baseline EDSS score, and relapse rate during the 2 years before study entry as covariates, but was not quite significant ( $p = 0.055$ ) when subsequently re-assessed using a  $t$ -test, without controlling for these covariates.<sup>133</sup>

MRI. No MRI data are presented because only a small subset of patients at one site (n = 27) underwent MRI assessment.

Tolerability and drop-outs. Tolerability was generally good, and the most common adverse events were injection-site reactions. A transient, self-limiting systemic reaction, consisting of brief chest tightness, flushing, dyspnea, palpitations, and anxiety, occurred after treatment in 15.2% of patients receiving GA and 3.2% of those receiving placebo. The proportion of patients who withdrew from the study was 15.2% in the GA group and 13.5% in the placebo group.

Number needed to treat. On the basis of the results of this study, 2.7 patients must be treated with GA to prevent one relapse over 2 years.

*Conclusions.*

*Methodology: class I.* This trial meets criteria for a class I study.

Clinical application: category A for relapses. This study establishes that GA (Copaxone®) 20 mg SC once daily is effective in reducing the relapse rate. No proven effect on disability was shown using a standard predetermined measure, such as sustained change in EDSS score of at least 1.0 point.

**Table 10** Summary of the results from the pivotal phase III trial of SC glatiramer acetate (GA; Copaxone®) in relapsing–remitting MS<sup>132</sup>

	Placebo (n = 126)	GA 20 mg SC once daily (n = 125)	<i>p</i>
Mean number of relapses over 2 years (covariate adjusted)	1.68	1.19	0.007*
Proportion of relapse-free patients at 2 years (%)	27.0	33.6	NS
Median time to first relapse (days)	198	287	NS
Proportion of patients with confirmed progression <sup>†</sup>	N/A	N/A	NS
Mean change in EDSS score <sup>‡</sup>	0.21	-0.05	0.023
Proportion of patients with ≥ 1.0-point improvement in EDSS score (%) <sup>‡</sup>	15.2	24.8	0.037
Proportion of patients with ≥ 1.0-point deterioration in EDSS score (%) <sup>‡</sup>	28.8	20.8	0.037
Mean Ambulation Index	0.28	0.27	NS
EDSS = Expanded Disability Status Scale; N/A = not available; NS = not significant.			
* ANCOVA analysis ( <i>t</i> -test, <i>p</i> = 0.055).			
<sup>†</sup> Defined as an increase of at least 1.0 point on the EDSS that persisted for at least 3 months.			
<sup>‡</sup> EDSS scores unsustained.			

**Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years.**<sup>134</sup> At the end of the placebo-controlled study with GA,<sup>132</sup> all patients were offered entry into an open-label trial. Patients were assessed every 6 months rather than every 3 months as in the initial pivotal trial. In the absence of a concurrent control group and blinding, it is difficult to evaluate the results of this study.

*Patients, randomization, and blinding.*

Of the 251 patients involved in the pivotal Phase III trial of GA in RRMS, 208 (83%) chose to enter the extension study described in this paper. Of these patients, 101 (group A) had received GA during the pivotal trial and 107 (group B) had received placebo. The patients who entered the extension study had been in the pivotal trial for various lengths of time, and some had dropped out of the pivotal trial before re-entering this trial. Moreover, the patients who entered the extension study had done significantly better during the pivotal trial, on average, than the patients who did not enter the extension phase, irrespective of their original treatment allocation. In group A, the annual relapse rate during the pivotal trial among those who stayed in the study was 0.61 compared with 1.05 among those who dropped out. In addition, 63% of the drop-outs versus 33% of those who remained in the study had progressed by 1.5 EDSS points ( $p = 0.003$ ). This suggests that the results of the extension study may be biased in favor of GA, because the group that entered the extension study had done better during the initial pivotal study. There were no randomization and no blinding in the extension study, as all patients received GA on an open-label basis.

*Clinical and statistical significance.*

The main results from the paper are summarized in [table 11](#).

**View this table:** **Table 11** Key results from the open-label extension of the pivotal phase III trial of SC glatiramer acetate (GA; Copaxone®) in relapsing–remitting MS<sup>134\*</sup>

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Disability-related outcomes. The proportion of patients in group A who experienced confirmed progression of disability (sustained over 90 days) was 40.6% compared with a figure of 77% derived from a large natural history study. It was concluded that many fewer patients had progressed than would have been expected in the absence of treatment. This approach is inappropriate because the population involved in the natural history study included not only patients with RRMS but also those with PPMS and SPMS.

Relapse-related outcomes. In group A, the mean annual relapse rate over the entire duration of the study (i.e., both double-blind and open phases) was 0.42. It is stated in the paper that this represents a 72% reduction in relapse rate compared with the 2 years before study entry. This statement is misleading, however, because the 0.42 figure is derived from only 83 patients and no account is taken of regression to the mean in relapse rates, a phenomenon seen in all pivotal trials in MS (i.e., relapse rates always go down with time, even in placebo groups). In addition, visits occurred every 6 months as opposed to every 3 months in the pivotal trial. Increasing the time between visits may reduce the likelihood of reporting/detecting a relapse.

**Table 11** *Key results from the open-label extension of the pivotal phase III trial of SC glatiramer acetate (GA; Copaxone®) in relapsing–remitting MS<sup>134\*</sup>*

Variable	Value
Mean annual relapse rate during year 6	0.23 (c.f. prestudy rate of 1.49 and rate of 0.61 during double-blind phase)
Mean annual relapse rate over the entire study	0.42 ( <i>p</i> = 0.0001 vs. prestudy rate)
Proportion of patients showing confirmed progression of disability (%) <sup>†</sup>	40.6
Proportion of patients showing a deterioration of ≥ 1.5 points on the EDSS (%) <sup>‡</sup>	49.5

EDSS = Expanded Disability Status Scale.

\* All data are for the subset of patients (n = 101) who received GA from the start of the trial.

<sup>†</sup> Defined as an increase of at least 1.0 point on the EDSS that persisted for at least 90 days.

<sup>‡</sup> Worsening not required to be sustained.

MRI. No MRI data are presented.

Tolerability and drop-outs. In general, tolerability was good. The most common adverse events were injection-site reactions, which occurred after 2.4% of injections in group A and 0.9% of injections in group B (double-blind and open phases combined). A total of 27% of patients (56/208) dropped out of the extension phase before the time of analysis; 24 from group A and 32 from group B. This high drop-out rate reduces the clinical significance of the study results.

Number needed to treat. This parameter is not applicable.

#### *Conclusions.*

*Methodology: class III.* The extension phase is difficult to interpret because the results were compared with natural history data. These comparisons are inherently flawed, as they amount to an "apples to fruitbasket" comparison, particularly when relapsing–remitting disease is compared with mixed natural history populations.

Clinical application: category C. GA (Copaxone®) 20 mg SC once daily may possibly have had a sustained beneficial effect on relapse rates, at least in the subset of patients in group A, but the data do not prove this. The study has important methodologic weaknesses, including the lack of a concurrent control group and a selection bias for the cohort of patients who did relatively well during the double-blind, placebo-controlled phase of the original study.

#### **Randomised, placebo-controlled trial of monthly**

intravenous immunoglobulin therapy in relapsing–remitting multiple sclerosis.<sup>135</sup> This is the largest study of IVIg in RRMS, with a comparison of mean change in EDSS score between treated and control groups as its primary end point. The ESIMS Study of IVIg in SPMS (presented at the European Charcot Foundation Symposium in Vienna, Austria, in October 2001) was negative on all three major end points; disability, relapses, and MRI changes, and is not further reviewed here.

#### *Patients, randomization, and blinding.*

Patients with RRMS and two relapses in the previous 2 years who were included in this study (n = 148) had baseline EDSS scores of 1.0–6.0, which differs slightly from the other major clinical trials in RRMS. Allocation to a once-monthly dose of IVIg (Sero-Merieux, Vienna, Austria) 0.15–0.20 g/kg body weight, or placebo was computer-generated, and baseline characteristics of patients in the two groups were similar. Treatment lasted for 2 years. Separate treating and evaluating physicians were used and, although the treating physician was aware of the treatment allocation, the evaluating physician was not. Blinding was not formally tested.

#### *Clinical and statistical significance.*

The results of the trial are summarized in [table 12](#).

**View this table:** [Table 12 Summary of the results of the clinical trial with IV immunoglobulin \(IVIg\) in relapsing–remitting MS<sup>135</sup>](#)  
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**Table 12** *Summary of the results of the clinical trial with IV immunoglobulin (IVIg) in relapsing–remitting MS<sup>135</sup>*

	Placebo (n = 73)	IVIg 0.15–0.20 g/kg body weight once monthly (n = 75)	<i>p</i>
Change in EDSS score <sup>*</sup>	0.12	-0.23	0.008
Proportion of patients with $\geq 1.0$ -point improvement in EDSS score at 2 years (%) <sup>*</sup>	14	31	
Proportion of patients with $\geq 1.0$ -point deterioration in EDSS score at 2 years (%) <sup>*</sup>	23	16	0.041
Number (%) of relapse-free patients at 2 years <sup>†</sup>	26 (35)	40 (53)	0.03
Mean annual relapse rate <sup>†</sup>	1.26	0.52	0.0037
Mean time to first relapse (days) <sup>†</sup>	151	237	NS
Mean time between relapses (days) <sup>†</sup>	362	720	0.026

EDSS = Expanded Disability Status Scale; NS = not significant.

\* EDSS scores unsustained.

† A relapse was confirmed only if the patient's symptoms were accompanied by objective changes of at least 1 grade in the score for one of the eight functional systems of the EDSS.

**Disability-related outcomes.** Beneficial effects were reported on a number of disability-related outcomes. All of these analyses, however, compared mean changes in EDSS scores from baseline to the end of treatment. Because the EDSS is an ordinal scale and not a true random variable, mean changes in EDSS scores are viewed as statistically dubious and of uncertain meaning. There was no 3–6-month follow-up to confirm that the observed changes in EDSS scores were sustained rather than relapse-related. No information was provided on time to change in EDSS score (giving an indication of deterioration rate) or the number of 1.0-point changes in the EDSS score per patient per group (which would demonstrate whether there was a disproportionate contribution by a small number of patients to the apparent response or lack of response). Neither is there a breakdown of the data according to baseline EDSS score, which would provide an indicator of the efficacy of IVIg in patients with different levels of disability.

**Relapse-related outcomes.** IVIg reduced the rate of confirmed relapses and the annual relapse rate, and increased the number of relapse-free patients compared with placebo. Although the time from baseline to first relapse did not differ significantly between the groups, the time between relapses was significantly longer with IVIg ( $p = 0.026$ ). No direct information is provided on the severity of relapses, steroid use, or hospitalizations, but it was implied that there was no difference in the severity of relapses, because relapse-related change in EDSS score was similar in the two groups.

**MRI.** There was no MRI analysis.

**Tolerability.** At the dose used in this study, IVIg was well tolerated. Among patients given IVIg, 85% completed the study compared with 77% of placebo-treated patients. This was a high drop-out rate, particularly among the placebo group, from which 17 patients withdrew (in 8 cases due to lack of efficacy).

**Number needed to treat.** The number needed to treat is 14 for the prevention of a 1.0-point worsening in EDSS score over 2 years, and 1.3 patients treated for preventing one relapse over 2 years. The apparently high efficacy of IVIg in preventing relapses in patients with RRMS is difficult to reconcile with the much lower effect on the proportion showing disease progression (17% with IVIg versus 23% with placebo;  $p = 0.06$ ). One contributory factor may be that the relapse rate among placebo-treated patients was higher than would be expected, at least during the first year.

#### *Conclusions.*

**Methodology: class II/III.** This study is of insufficient quality to be categorized as class I because the patient numbers were relatively small ( $n = 148$ ), patients were recruited from 13 centers, enrollment took 3 years, and the mean change in EDSS score (unsustained) was a suboptimal primary end point in this type of study. In addition, the drop-out rate was fairly high (30/148).

**Clinical application: category C.** This fairly small study indicates that IVIg 0.15–0.20 g/kg body weight may have an impact on relapse rate. The high placebo relapse rate with a low (23%) placebo proportion showing progression is puzzling. Moreover, the evidence of benefit on progression of disability is uncertain because, among the group of patients who completed the trial, the proportion showing progression did not differ significantly between the IVIg and placebo groups (17% versus 23%;  $p = 0.06$ ) despite the results with mean changes in EDSS

scores. A larger clinical trial is needed to confirm the efficacy of IVIg in patients with RRMS, using more conventional EDSS outcome measures and the addition of MRI, which was not included in this study.

**Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria.**<sup>136</sup>

This randomized MRI-blinded (but not clinically blinded) study with mitoxantrone was conducted in patients with aggressively active MS, who were treated once monthly with mitoxantrone and methylprednisolone or with methylprednisolone alone. The primary end point was the proportion of patients developing new gadolinium-enhancing lesions.

*Patients, randomization, and blinding.*

This study was conducted in a selected group of patients ( $n = 42$ ) with an EDSS score of 6.0 or less, with aggressive, frequently relapsing MS. In particular, the patient population was enriched with respect to MRI activity, because all patients were required to have at least one enhancing lesion during the 2 months before study entry, during which time they received monthly injections of methylprednisolone, 1 g IV. Randomization to 6 months of treatment with mitoxantrone 20 mg IV and methylprednisolone 1 g IV, or to methylprednisolone alone, was carried out appropriately and is described in detail in the paper. However, the male:female ratio was substantially higher in the control group than in the mitoxantrone group. This may have influenced the results because MS tends to be more aggressive in males. The study was blinded for MRI but not clinical outcomes.

*Clinical and statistical significance.*

The results of the study are summarized in [table 13](#).

**View this table:** **Table 13** *Summary of the results from the 6-month study of IV*

[\[in this window\]](#) *mitoxantrone in active MS*<sup>136\*</sup>  
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Disability-related outcomes. The mean EDSS score was no better in the mitoxantrone group than in the control group, except at month 4. However, the mean change (i.e., decrease) in EDSS score over the 6 months of the study was 1.1 points with mitoxantrone and 0.1 points without ( $p < 0.05$ ).

Relapse-related outcomes. The mean annualized relapse rate per patient during the study was 0.7 in the mitoxantrone group and 3.0 in the control group ( $p < 0.01$ ). The proportion of patients remaining relapse-free was 67% with mitoxantrone and 33% without ( $p < 0.05$ ).

MRI. The proportion of patients without new enhancing lesions (the primary outcome variable) was significantly higher in the mitoxantrone group than the control group at months 2, 3, 5, and 6. The number of new enhancing lesions and total number of enhancing lesions decreased progressively throughout the study in the mitoxantrone group but remained high in the control group.

Tolerability and drop-outs. No serious side effects were seen with mitoxantrone. Seven patients developed mild alopecia, and 8 of 15 women developed amenorrhea. As expected,

**Table 13** *Summary of the results from the 6-month study of IV mitoxantrone in active MS<sup>136\*</sup>*

	Mitoxantrone and methylprednisolone (n = 21)	Methylprednisolone alone (n = 21)	<i>p</i>
Proportion of patients without new enhancing lesions in month 6 (%)	90.5	31.3	<0.001
Median number of new enhancing lesions per scan over 6 months	0	2	
Median total number of enhancing lesions per scan over 6 months	0	3	
Median number of new T2 lesions	1	3	<0.05
Mean EDSS score at month 6	3.4	4.3	NS
Mean change in EDSS score	-1.1	-0.1	<0.05
Mean annualized relapse rate per patient	0.7	3.0	<0.01
Proportion of patients free from relapses (%)	67	33	<0.05
EDSS = Expanded Disability Status Scale; NS = not significant.			
* Patients were randomized to receive mitoxantrone 20 mg and methylprednisolone 1 g by monthly IV injection, or methylprednisolone alone for 6 months. Unless otherwise stated, data are for the entire study period.			

pronounced leukopenia developed about 2 weeks after injection in all patients given mitoxantrone, and diminished or disappeared within a few days. No patients withdrew from the study prematurely.

Number needed to treat. Three patients need to be treated to render one patient relapse-free, and treatment of 1.7 patients will result in one patient being free of enhancing lesions after 6 months.

#### *Conclusions.*

*Methodology: class II for MRI and class III for clinical outcomes.* This study is graded II/III because there was no blinding for clinical outcome variables, the sample size in each treatment arm was small (21 patients), the sex ratio differed in the two treatment arms, the patient population was highly selected, and the follow-up period was short.

Clinical application: category B for MRI and category C for clinical outcomes. Although the results of this study (particularly the impressive MRI results) are generally supportive of the use of monthly injections of mitoxantrone 20 mg IV in actively relapsing MS, the methodologic problems mentioned above suggest the need for caution with respect to this study. The drug does appear to reduce relapse rates and new MRI lesions in this select patient population. Long-term cardiotoxicity at doses > 100–140 mg/m<sup>2</sup> limits the drug's usefulness, as does the risk for leukemia.<sup>137</sup>

#### **Randomized placebo-controlled trial of mitoxantrone**

in relapsing–remitting multiple sclerosis: 24-month clinical and MRI outcome.<sup>138</sup> The primary end point of this study was the proportion of patients with confirmed progression of disability (defined as an increase in EDSS score > 1.0).

#### *Patients, randomization, and blinding.*

Patients (n = 51) were required to have had at least two relapses in the 2 years before study entry, and were otherwise typical of the general RRMS population. They were treated with mitoxantrone 8 mg/m<sup>2</sup> IV, or placebo by monthly infusion for 2 years. The study was randomized and double-blinded, but the effectiveness of blinding was not formally assessed. Given that mitoxantrone therapy is associated with significant side effects, such as nausea, patients may not have been blinded to their treatment. Clinical and MRI assessments were conducted at baseline and at years 1 and 2.

#### *Clinical and statistical significance.*

The results are summarized in [table 14](#). The organizers were unable to recruit their target number of patients (65 per arm), but nevertheless showed an effect on the primary outcome.

**View this table:** [Table 14 Summary of the results from the 2-year study of IV mitoxantrone in relapsing–remitting MS<sup>138</sup>\\*](#)  
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Disability-related outcomes. The proportion of patients who progressed by at least 1.0 point on the EDSS over the entire 2-year study period was significantly lower with mitoxantrone than with placebo (7% versus 37%;  $p = 0.02$ ). There was no significant difference between the two treatment

**Table 14** *Summary of the results from the 2-year study of IV mitoxantrone in relapsing–remitting MS<sup>138\*</sup>*

	Placebo (n = 24)	Mitoxantrone 8 mg/m <sup>2</sup> IV monthly (n = 27)	<i>p</i>
Proportion of patients showing confirmed progression of disability (%) <sup>†</sup>	37	7	0.02
Mean number of exacerbations per patient	2.62	0.89	0.0002
Proportion of exacerbation-free patients (%)	21	63	0.006
Median number of new T2 lesions	5	2	0.05
Median number of enlarging T2 lesions	3	3	1
* All data are for the entire 2-year study period.			
† Defined as an increase of at least 1.0 point on the Expanded Disability Status Scale (unsustained).			



groups in terms of mean change in EDSS score.

**Relapse-related outcomes.** The mean number of relapses per patient was significantly lower with mitoxantrone than with placebo over the 2 years of the study (0.89 versus 2.62;  $p = 0.0002$ ). Moreover, the proportion of relapse-free patients was significantly higher (63% versus 21%;  $p = 0.006$ ).

**MRI.** The MRI results were not encouraging. No significant difference was observed between the mitoxantrone and placebo groups with respect to the numbers of new and enlarging lesions at either the 12-month or the 24-month time point.

**Tolerability and drop-outs.** The most common side effect of mitoxantrone was nausea, which in most cases was mild. Five patients developed infections, none of which was serious, and five developed transient secondary amenorrhea. No adverse effects on cardiac function were detected. Nine (18%) of the 51 patients in the trial failed to complete MRI follow-up.

**Number needed to treat.** The results of this study suggest that 3.3 patients must be treated to prevent an increase of 1.0 point on the EDSS over 2 years, and 2.4 patients need to be treated for one to become relapse-free during the same period.

#### *Conclusions.*

**Methodology: class II/III.** A higher grade is not merited because of the small size of the study, the high drop-out rate from the MRI assessment, and the fact that the effectiveness of blinding was not assessed. With a medication such as mitoxantrone, patient blinding is a challenge, which would have made such a measure particularly interesting in this study.

**Clinical application: category C.** This study suggests that mitoxantrone 8 mg/m<sup>2</sup> IV by monthly infusion may be effective in the treatment of patients with RRMS. However, it has important methodologic flaws (as outlined above) and the MRI results are disappointing. In clinical trials with all other approved disease-modifying drugs in MS (IFN $\beta$ , GA), the effect on MRI was equal to or greater than the clinical effect. The risk for cardiac toxicity, in addition to significant common side effects such as nausea, alopecia, and leukopenia, limits the use of mitoxantrone in MS to patients with rapidly advancing disease in whom more conventional therapies have failed.

### **Secondary progressive MS.**

Placebo-controlled multicentre randomised trial of interferon  $\beta$ -1b in treatment of secondary progressive multiple sclerosis.<sup>139</sup> This was the first large published study of IFN in the treatment of patients with SPMS. By this time, MS investigators had learned their methodologic lessons from earlier trial errors. Therefore, the sample size was very large, the trial was continued for a full 3 years, and investigators were specifically trained in the performance of the primary end point, the change in EDSS score.

#### **Patients, randomization, and blinding.**

Patients with SPMS and EDSS scores of 3.0–6.5 ( $n = 718$ ) were treated with IFN $\beta$ -1b (Betaseron®) 8 MIU SC every other day, or placebo, for up to 3 years. SPMS was defined by the presence of a period of deterioration, independent of relapses, sustained for at least 6 months

before entry to the study. Nevertheless, some 70% of the patients enrolled had relapses in the 2 years before study entry, suggesting that the study population consisted largely of patients in transition from RRMS to SPMS. The study was randomized and treatment groups were similar at baseline, although there was a trend for those treated with IFN $\beta$ -1b to have lower EDSS scores. Blinding was maintained throughout the study, and its effectiveness was assessed by means of a questionnaire. It was found that approximately 50% of patients and treating physicians were able to guess correctly which treatment was being used (above the level expected by chance) but that blinding was much more effective for evaluating physicians.

**Clinical and statistical significance.**

The results of the study are summarized in [table 15](#).

**View this table:** [Table 15 Key results from the study of SC interferon \(IFN\)  \$\beta\$ -1b \(Betaseron®\) in secondary progressive MS<sup>139</sup>](#)  
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*Disability-related outcomes.*

After 33 months of treatment, the proportion of patients showing confirmed progression of disability (the primary outcome variable) was 49.7% with placebo compared with 38.9% with IFN $\beta$ -1b ( $p = 0.0048$ ). When patients were subdivided according to baseline EDSS score, it was found that IFN $\beta$ -1b had the same effect in all subgroups. Interestingly, however, analysis of the 36-month data required by the Canadian Health Protection Board showed that there was essentially no treatment effect at this time point in patients with high baseline EDSS scores (6.0 or 6.5) if those lost to follow-up were assumed to have progressed.<sup>140</sup> A second disability-related outcome variable, the time taken for patients to become wheelchair-bound (i.e., to reach an EDSS score of 7.0), was significantly increased with active treatment.

*Relapse-related outcomes.*

IFN $\beta$ -1b reduced the relapse rate during the study by approximately 30% ( $p = 0.002$ ).

*MRI.*

Over the course of the study, the mean total volume of T2 lesions increased by 8% with placebo but decreased by 5% with IFN $\beta$ -1b ( $p < 0.0001$ ). In the frequent-MRI cohort ( $n = 125$ ), patients receiving IFN $\beta$ -1b showed a 65% reduction in the number of newly active lesions from months 1 to 6 ( $p < 0.0001$ ) and a 78% reduction from months 19 to 24 ( $p = 0.0008$ ) compared with placebo.

*Tolerability and drop-outs.*

Neutralizing antibodies were detected in 27.8% of patients who received IFN $\beta$ -1b, most often in the first 6 months of treatment. They were found to have a significant impact on efficacy with respect to relapse rate but not with respect to the progression of disability. The adverse event profile of active treatment was similar to that seen in the pivotal trial of IFN $\beta$ -1b in patients with RRMS,<sup>122</sup> except that muscle hypertonia was found to be significantly associated with IFN $\beta$ -1b. Of the 718 patients who underwent randomization, 57 (7.9%) dropped out of the study, 31 (8.7%) from the placebo group and 26 (7.2%) from the IFN $\beta$ -1b group.

**Table 15** Key results from the study of SC interferon (IFN)  $\beta$ -1b (Betaseron®) in secondary progressive MS<sup>139</sup>

	Placebo (n = 358)	IFN $\beta$ -1b 8 MIU SC every other day (n = 360)	<i>p</i>
Patients with confirmed progression of disability over 3 years (%) <sup>*</sup>	49.7	38.9	0.0048
Mean annual relapse rate	0.64	0.44	0.002
Median time to first relapse (days)	403	644	0.003
Proportion of patients with moderate/severe relapses at 3 years (%)	53.1	43.6	0.0083
Change in mean MRI T2 lesion volume (%) <sup>†</sup>	8	-5	<0.0001
Reduction in newly active lesions compared with placebo (%) <sup>†</sup>		65 (months 1–6)	<0.0001
		78 (months 19–24)	0.0008

<sup>\*</sup> Defined as an increase of 1.0 point on the Expanded Disability Status Scale (EDSS) confirmed at 3 months or a 0.5-point increase if the baseline EDSS score was 6.0 or 6.5.

<sup>†</sup> In the frequent-MRI cohort (n = 125).

*Number needed to treat.*

Data from this study indicate that it is necessary to treat 9.2 patients with IFN $\beta$ -1b for 3 years to prevent a 1.0-point progression on the EDSS (for patients with an EDSS score of 5.5 or less) or to prevent a 0.5-point progression on the EDSS (for patients with an EDSS score of 6.0 or 6.5).

**Conclusions.**

*Methodology: class I.* This was a well-designed study with no major methodologic flaws.

*Clinical application: category A.*

This study suggests that IFN $\beta$ -1b (Betaseron®) 8 MIU SC every other day is effective in very modestly slowing progression in this specific group of patients with SPMS, i.e., a group in which 70% had prestudy relapses. The results of this study were not replicated in a subsequent North American trial of IFN $\beta$ -1b in patients with SPMS.<sup>141</sup> However, a post hoc analysis in the SPECTRIMS Study with IFN $\beta$ -1a also indicated that IFN therapy was more effective in patients with SPMS who had prestudy relapses than in those without prestudy relapses.<sup>142</sup> The large sample size in the European study raises a unique issue in MS trials. The observed difference in progression rate between those on active treatment and placebo is highly statistically significant (i.e., believable) but of questionable clinical significance (number needed to treat of 9 patients for 3 years is equivalent to 27 patient-years of treatment to prevent a 1.0-point progression on the EDSS).

**Randomized controlled trial of interferon-beta-1a in secondary progressive MS (the SPECTRIMS Study).**<sup>142</sup>

This large, randomized, double-blind, placebo-controlled study of IFN $\beta$ -1a by the SPECTRIMS Study Group in patients with SPMS did not meet its primary end point of significantly delaying the time to confirmed progression in disability as measured on the EDSS.

*Patients, randomization, and blinding.*

Patients with SPMS, EDSS scores of 3.0–6.5, and pyramidal function score of > 2 (n = 618) were randomized to treatment with IFN $\beta$ -1a (Rebif®) 22 or 44  $\mu$ g SC three times weekly, or placebo for 3 years. SPMS was defined as progressive deterioration of disability for at least 6 months after an initial relapsing–remitting course, with an increase of more than 1.0 point on the EDSS over the last 2 years (0.5 points between EDSS scores of 6.0 and 6.5), with or without superimposed relapses. The study was double-blind and the effectiveness of blinding was assessed. It was found that evaluating physicians were able to guess the treatment used in 25–30% of cases (no better than chance).

*Clinical and statistical significance.*

The results of the study are summarized in [table 16](#).

**View this table:** **Table 16** *Key results from the study of SC interferon (IFN)  $\beta$ -1a (Rebif®)*  
[\[in this window\]](#) *in secondary progressive MS*<sup>142,143\*</sup>  
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Disability-related outcomes. The primary outcome variable, the time to sustained progression of

**Table 16** Key results from the study of SC interferon (IFN)  $\beta$ -1a (Rebif®) in secondary progressive MS<sup>142,143†</sup>

	Placebo (n = 205)	IFN $\beta$ -1a 22 $\mu$ g SC three times weekly (n = 209)	IFN $\beta$ -1a 44 $\mu$ g SC three times weekly (n = 204)
Time to confirmed progression, hazard ratio <sup>‡</sup>		0.88 ( $p = 0.305$ ) <sup>§</sup>	0.83 ( $p = 0.146$ ) <sup>§</sup>
		0.85 ( $p = 0.182$ ) <sup>**</sup>	0.78 ( $p = 0.046$ ) <sup>**</sup>
Relapse rate per person-year	0.71	0.50 ( $p < 0.001$ )	0.50 ( $p < 0.001$ )
Median time to first relapse (days)	281	476 ( $p = 0.237$ )	494 ( $p = 0.034$ )
Median time between first and second relapses (days)	279	572 ( $p < 0.001$ )	511 ( $p = 0.001$ )
Mean number of moderate/severe relapses per person per year	0.39	0.26 ( $p = 0.002$ )	0.27 ( $p = 0.003$ )
Mean number of steroid courses per person-year	0.52	0.31 ( $p = 0.001$ )	0.34 ( $p = 0.006$ )
Mean number of hospitalizations per person-year	0.22	0.14 ( $p = 0.006$ )	0.15 ( $p = 0.005$ )
Median number of T2 active lesions per patient per scan	0.67	0.20 ( $p < 0.001$ )	0.17 ( $p < 0.001$ )
Median number of CU active lesions per patient per scan	1.00	0.22 ( $p < 0.01$ )	0.11 ( $p < 0.001$ )
Change in MRI burden of disease over 3 years (%)	10.0	-0.5 ( $p < 0.001$ )	-1.3 ( $p < 0.001$ )

CU = combined unique.

\* The study lasted for 3 years.

† All  $p$ -values are vs. placebo.

‡ Defined as an increase of at least 1.0 point on the Expanded Disability Status Scale (EDSS) or a 0.5-point increase if the baseline EDSS score was  $\geq 5.5$ .

§ Based on protocol-defined analysis, adjusted for center.

\*\* Post hoc covariate-adjusted analysis (center, Scripps's Neurologic Rating Scale, duration of secondary progressive MS, rate of progression before study).

disability, was not significantly affected by IFN $\beta$ -1a when all patients were considered together. When female patients were analyzed separately, however, this variable was found to be significantly increased (i.e., improved) with both doses of IFN $\beta$ -1a. The reason for the difference between men and women in this respect is not clear. A post hoc analysis indicated that patients with prestudy relapses were more likely to benefit from therapy with respect to time to confirmed progression. The odds ratio for the proportion of patients progressing in the combined IFN $\beta$ -1a groups compared with placebo was 0.52 for patients with prestudy relapses ( $p = 0.027$ ) and 1.07 for patients without prestudy relapses ( $p = 0.802$ ). The hazard ratio for progression of the treated group as a whole was 0.74 ( $p = 0.055$ ).

**Relapse-related outcomes.** Both doses of IFN $\beta$ -1a had a highly significant beneficial effect on relapse rate. In addition, they had significant beneficial effects on the time between the first and second relapses, steroid use, and the need for hospitalization.

**MRI.** MRI data were collected and showed a beneficial effect on active lesions in treated patients. The data are the subject of a separate publication.<sup>143</sup>

**Tolerability and drop-outs.** Neutralizing antibodies were detected in 0.5% of patients who received placebo, 20.6% of patients who received low-dose IFN $\beta$ -1a, and 14.7% of patients who received the high dose. They had no effect on the primary outcome variable, but antibody positivity produced a significant negative impact on relapse rate in the high-dose IFN $\beta$ -1a group and on MRI in both groups. IFN $\beta$ -1a was well tolerated, and full data were available for 92.4% of the patients enrolled.

**Number needed to treat.** This parameter is not applicable, because treatment had no significant effect on the primary outcome variable.

#### *Conclusions.*

**Methodology:** *class I.* This study was well designed and well performed.

**Clinical application.** No clear effect of IFN $\beta$ -1a (Rebif®) 22 or 44  $\mu$ g SC three times weekly was demonstrated on disability progression. The significance of a lower relapse rate and less MRI progression of disease in the treated group is unclear, given the failure to slow disability progression.

#### **Mitoxantrone in progressive MS: clinical results of the MIMS trial.**<sup>144,145</sup>

The results of this clinical trial were presented at the 16th Congress of the European Committee for Treatment & Research in Multiple Sclerosis (ECTRIMS 1998) in Stockholm, Sweden. Additional information on the 3-year follow-up was presented at the 51st Annual Meeting of the American Academy of Neurology (AAN 1999) in Toronto, Ontario, Canada<sup>146</sup> and at the 17th ECTRIMS Congress (1999), Basle, Switzerland.<sup>147</sup> The primary end point was a composite of EDSS, Ambulation Index, number of relapses requiring steroids, time to first relapse requiring steroids, and Standard Neurologic Status. As of April 2002, the paper describing this trial has yet to be published, an unusually long delay.

#### *Patients, randomization, and blinding.*

This was a randomized clinical trial in patients ( $n = 194$ ) aged 18–55 years with "remittent–

progressive MS" or SPMS (mean baseline EDSS scores of 4.5–4.7; range 3.0–6.0) who had shown a deterioration of at least 1.0 point on the EDSS during the previous 18 months. Patients received mitoxantrone 5 or 12 mg/m<sup>2</sup> IV every 3 months, or placebo for 2 years. Relapses were treated for 5 days with IV methylprednisolone. Both patients and rating physicians were blinded. Because mitoxantrone therapy is associated with significant side effects, patients were probably not blinded to their treatment allocation. A follow-up examination was performed at 3 years.

*Clinical and statistical significance.*

The main results of the study are shown in [table 17](#). A significant treatment effect was reported with mitoxantrone 12 mg/m<sup>2</sup> on the primary multivariate, composite outcome measure ( $p < 0.0001$ ).

**View this table:** [Table 17 Summary of the results of the clinical trial with IV mitoxantrone in relapsing–progressive or secondary progressive MS<sup>145</sup>](#)  
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Disability-related outcomes. The higher dose of mitoxantrone significantly slowed disease progression compared with placebo, as shown by the change in EDSS and Ambulation Index scores and by the proportion of patients deteriorating on the EDSS, confirmed at 6 months.

Relapse-related outcomes. The mean number of treated relapses was dose-dependently reduced by mitoxantrone, with the higher dose being significantly superior to placebo. There was also a significant difference in time to first treated relapse ( $p = 0.0004$ ), percentage of patients with no relapse, total number of relapses, and number of hospitalizations.

MRI. A subset of 110 patients underwent non-enhanced and gadolinium-enhanced MRI at baseline and at months 12 and 24. Mitoxantrone reduced the number of new T2 lesions and the proportion of patients with new enhancing lesions compared with placebo.

Tolerability and drop-outs. A number of adverse events were more frequent in mitoxantrone-treated patients, including nausea, alopecia, urinary tract infections, and menstrual disorders. Dose-dependent leukopenia was reported in 19% of patients on the high dose of mitoxantrone and 9% of those on the lower dose. Of the 194 patients initially enrolled in the study, 149 completed study evaluations at month 24.

*Conclusions.*

*Methodology: class II.* This is a small Phase III study, with only 63–66 patients in each treatment group at randomization and even fewer completing the study.

Clinical application: category B. Mitoxantrone 12 mg/m<sup>2</sup> IV every 3 months probably reduces relapse frequency, EDSS progression, and MRI disease measures in this population of fairly rapidly worsening patients. A key point to consider in this study is the high proportion of patients (approximately 74%) with relapses in the 2 years before study onset. Therefore, the study population is more like the European<sup>139</sup> than the North American<sup>141</sup> IFNβ-1b SPMS study (i.e., a predominantly relapsing population in transition to SPMS). Potential cardiac and hematologic



**Table 17** Summary of the results of the clinical trial with IV mitoxantrone in relapsing–progressive or secondary progressive MS<sup>145</sup>

	Placebo (n = 65)	Mitoxantrone 5 mg/m <sup>2</sup> IV every 3 months (n = 66)	Mitoxantrone 12 mg/m <sup>2</sup> IV every 3 months (n = 63)	<i>p</i> <sup>*</sup>
Multivariate analysis (Wei–Lachin test)				<0.0001
Mean change in EDSS score at month 24 compared with baseline	0.23	-0.23	-0.13	0.0194
Mean increase in Ambulation Index from baseline to month 24	0.77	0.41	0.30	0.0306
Patients with an increase of 1.0 point on the EDSS confirmed over 6 months (%)	19	9.4	7	0.045
Mean number of treated relapses per patient (adjusted for discontinuation) from baseline to month 24	1.20	0.73	0.40	0.0002
Median time to first treated relapse (months)	14.2	NR by month 24	NR by month 24	0.0004
Mean SNS change from baseline to month 24	0.77	-0.38	-1.07	0.0269
Mean change from baseline in number of T2-weighted lesions <sup>†</sup>	1.94	0.68	0.29	0.0272
Proportion of patients with new gadolinium-enhancing lesions at month 24 (%) <sup>†</sup>	16	11	0	0.022
EDSS = Expanded Disability Status Scale; NR = not reached; SNS = Standard Neurologic Status.				
* <i>p</i> -values are mitoxantrone 12 mg/m <sup>2</sup> vs. placebo.				
† 110 patients also underwent MRI analysis, although MRI results are not available for all patients at all time points.				

toxicity limits the use of this therapy, particularly in patients with milder forms of the disease.

**Interferon beta-1b in secondary progressive MS: clinical and MRI results of a 3-year randomized controlled trial.**<sup>141</sup>

The full results of this blinded, placebo-controlled trial of IFN $\beta$ -1b in SPMS by the North American Study Group have not yet been published, but were presented at the 52nd Annual Meeting of the AAN (2000) in San Diego, CA. The study did not meet its primary end point of significantly delaying the time to confirmed progression of disability as measured on the EDSS.

*Patients, randomization, and blinding.*

Patients (n = 939) with SPMS were randomized to treatment with IFN $\beta$ -1b (Betaseron®) 8 MIU or 5 MIU/m<sup>2</sup> SC every other day (equivalent to 9 MIU for an average adult weighing 70 kg with a surface area of 1.8 m<sup>2</sup>), or placebo for 3 years. They had had CDMS for 2 or more years (EDSS score of 3.0–6.5), had a progressive course for at least 6 months, and an increase of at least 1.0 point on the EDSS during the 2 years before study entry. The study was blinded.

*Clinical and statistical significance.*

**Disability-related outcomes.** There was no significant difference between the treatments on disability progression.

**Relapse-related outcomes.** IFN $\beta$ -1b reduced the relapse rate during the study compared with placebo. It also reduced the need for steroid use.

**MRI.** During the course of the study, patients receiving IFN $\beta$ -1b had fewer new brain lesions than those receiving placebo.

**Tolerability and drop-outs.** No information is available.

**Number needed to treat.** This parameter is not applicable, because treatment had no significant effect on the primary outcome variable.

*Conclusions.*

**Methodology: class 1.** This trial meets criteria for a class I study.

**Clinical application: category D.** This study found no effect on disability progression for IFN $\beta$ -1b (Betaseron®) 8 MIU or 5 MIU/m<sup>2</sup> SC every other day, which disagrees with the results of the European study of IFN $\beta$ -1b in patients with SPMS.<sup>139</sup> However, compared with the European study, the North American trial included patients who were approximately 6 years older at the time of entry to the study and had had SPMS for twice as long (4 versus 2.1 years). In addition, 55% of participants in the North American study were relapse-free in the 2 years before study entry, compared with only 30% of the European participants. IFN $\beta$  therapy appears to be less effective in patients with non-relapsing SPMS compared with those in transition from a relapsing to a purely progressive course. To put this another way, the further along the EDSS, the longer the duration of SPMS and the greater the age of the patient (note that these variables are all correlated), the fewer the relapses, and the less effective are anti-inflammatory therapies such as IFN $\beta$ .

**Results of IMPACT, a phase 3 trial of interferon beta-1a in secondary progressive multiple sclerosis.**<sup>148</sup>

The results of this study of IFN $\beta$ -1a in patients with SPMS were presented at the 53rd Annual Meeting of the AAN (2001), in Philadelphia, PA. The primary outcome measure was the average change in disability in the MS Functional Composite (MSFC), a new measure of MS disability.<sup>149</sup>

*Patients, randomization, and blinding.*

This randomized, double-blind study included patients (n = 463) with CDMS, a secondary progressive course with or without recent relapses, and baseline EDSS scores of 3.5–6.5 (mean 5.2). Patients were randomized, in approximately equal numbers, to treatment with IFN $\beta$ -1a (Avonex®) 60  $\mu$ g IM once weekly (double the standard dose), or placebo for 2 years.

*Clinical and statistical significance.*

**Disability-related outcomes.** IFN $\beta$ -1a slowed the progression of disability as measured on the MSFC. This scale measures three functions: cognition, upper extremity function, and lower extremity function. Although worsening of disability was seen in both treated and placebo patients during the study, progression in treated patients was 27% less than in the control group ( $p = 0.033$ ). However, the majority of this benefit was derived from the results on the nine-hole peg test, a measure of arm function ( $p = 0.024$ ). On the timed 25-foot walk and the paced auditory serial audition test at 3-second intervals, there was no significant difference between patients receiving IFN $\beta$ -1a and those receiving placebo ( $p = 0.38$  and  $p = 0.061$ , respectively). Furthermore, there was no effect on time to sustained disability change on the EDSS ( $p = 0.9$ ), which was a secondary outcome measure.

**Relapse-related outcomes.** The number of relapses decreased with IFN $\beta$ -1a, with a mean annual relapse rate of 0.2 compared with 0.3 for placebo ( $p = 0.008$ ).

**MRI.** No information is available.

**Tolerability and drop-outs.** IFN $\beta$ -1a was well tolerated. No information on drop-outs is available.

*Conclusions.*

**Methodology: probably class I.** This trial probably meets criteria for a class I study; however, the full publication is not yet available.

**Clinical application: category B.** Although a credible effect of IFN $\beta$ -1a (Avonex®) 60  $\mu$ g IM once weekly on the MSFC is reported, it appears to apply only to manual dexterity. Furthermore, there is no beneficial effect of therapy on the EDSS, which is the most widely used clinical end point for measuring progression of disability. Finally, an unpublished study cannot receive a definite class or category rating.

**Comparative studies in relapsing–remitting MS. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN).**<sup>150</sup>

The 2-year results of this head-to-head study comparing IFN $\beta$ -1b with IFN $\beta$ -1a in patients with RRMS were published in April 2002. The primary end points were the number of relapse-free patients and the number of patients with no new T2 lesions on MRI.

**Patients, randomization, and blinding.**

Patients with RRMS, two relapses during the preceding 2 years, and EDSS scores of 1.0–3.5 ( $n = 188$ ) were treated with IFN $\beta$ -1b (Betaseron®) 250  $\mu$ g (8 MIU) SC every other day, or IFN $\beta$ -1a (Avonex®) 30  $\mu$ g (6 MIU) IM once weekly, for 2 years. Patient randomization to treatment arms was performed by independent statisticians with allocation concealment. The clinical evaluation was conducted on an open-label basis, and MRI scans were analyzed blind of the treatment used. Doses were those used in current standard clinical practice.

**Clinical and statistical significance.**

The results of the study at 2 years are shown in [table 18](#).

**View this table:** [Table 18 Summary of the 2-year results from the INCOMIN Study of SC interferon \(IFN\)  \$\beta\$ -1b \(Betaseron®\) vs. IM IFN \$\beta\$ -1a \(Axonex®\)<sup>150</sup>](#)  
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*Disability-related outcomes.*

Disease progression was defined as a worsening of at least 1.0 point on the EDSS, confirmed after 6 months and maintained until the end of follow-up. It was significantly slower with IFN $\beta$ -1b, with 13% of patients worsening during the study compared with 30% in the IFN $\beta$ -1a group ( $p = 0.005$ ).

*Relapse-related outcomes.*

The proportion of patients relapse-free at 2 years was 51% in the IFN $\beta$ -1b group versus 36% in those receiving IFN $\beta$ -1a ( $p = 0.03$ ).

*MRI.*

In patients who received IFN $\beta$ -1b over 2 years, 55% were free of new T2 lesions compared with 26% of those who received IFN $\beta$ -1a ( $p < 0.001$ ). IFN $\beta$ -1b also showed similar significant benefits over IFN $\beta$ -1a on other measures of MRI disease activity.

*Tolerability and drop-outs.*

Because of a lack of clinical response, treatment was discontinued by 3 patients receiving IFN $\beta$ -1b and by 10 patients receiving IFN $\beta$ -1a at 2 years.

*Number needed to treat.*

The number needed to treat with IFN $\beta$ -1b every other day to render one more patient relapse-free over 2 years compared with IFN $\beta$ -1a once weekly is 7.

**Conclusions.**

*Methodology:* class I for MRI and class III for clinical outcomes. This study is graded class I for the MRI outcome measures, which were assessed in a blinded fashion, but class III for clinical outcomes, which were unblinded.

The results of this study indicate that IFN $\beta$ -1b (Betaseron®) 8 MIU SC every other day is significantly more effective in reducing MRI disease activity than IFN $\beta$ -1a (Avonex®) 30  $\mu$ g IM once weekly. The data also suggest that high-dose and/or frequent therapy with IFN is superior to

**Table 18** Summary of the 2-year results from the INCOMIN Study of SC interferon (IFN)  $\beta$ -1b (Betaseron®) vs. IM IFN $\beta$ -1a (Axonex®)<sup>150</sup>

	IFN $\beta$ -1b 250 $\mu$ g (8 MIU) SC every other day (n = 96)	IFN $\beta$ -1a 30 $\mu$ g (6 MIU) IM once weekly (n = 92)	p
Proportion of relapse-free patients after 2 years (%)	51	36	0.03
Proportion of patients showing confirmed progression of disability (%) <sup>*</sup>	13	30	0.005
Proportion of patients free of new PD/T2 lesions (%)	55	26	<0.001
Proportion of patients free of enhancing lesions (%)	76	49	0.001
Proportion of patients with MRI disease activity (new PD/T2 or enhancing lesions) (%)	49	75	0.001
PD = proton density.			
<sup>*</sup> Defined as an increase of at least 1.0 point on the Expanded Disability Status Scale that persisted for 6 months and was confirmed at the end of follow-up.			

once-weekly dosing in terms of MRI and clinical outcomes in patients with RRMS during the time frame of these studies.

**The EVIDENCE Study: direct comparative study of IFN $\beta$ -1a in RRMS.** [151-154](#)

The results of this head-to-head study have been presented in preliminary form, most recently at the Annual Meeting of the AAN in Denver, CO, in April 2002. [153](#) The primary efficacy end point was the proportion of patients who remained relapse-free at 24 weeks. The study was continued and the results at 48 weeks are now available. [154](#)

*Patients, randomization, and blinding.*

Patients (n = 677) with RRMS and EDSS scores of 0.0–5.5 were randomized to treatment with IFN $\beta$ -1a (Rebif®) 44  $\mu$ g SC three times weekly, or IFN $\beta$ -1a (Avonex®) 30  $\mu$ g IM once weekly. Patients and treating physicians were aware of treatment allocation and that this study was designed by one company to demonstrate superiority over the product of another company. However, the evaluating neurologists and radiologists were blinded to study treatment.

*Clinical and statistical significance.*

The results of the study are summarized in [table 19](#).

**View this table:** **Table 19** *Summary of the key data from the EVIDENCE Study of interferon (IFN)  $\beta$ -1a (Rebif® and Avonex®)* [151-154\\*](#)  
[\[in this window\]](#)  
[\[in a new window\]](#)



Disability-related outcomes. There was no difference in disability-related outcomes at 6 months.

Relapse-related outcomes. After 24 weeks, significantly more patients given Rebif® three times weekly were relapse-free compared with those given Avonex® once weekly (74.9% versus 63.3%; adjusted odds ratio of being relapse-free on Rebif® was 1.9;  $p = 0.0005$ ). Rebif® was also significantly superior to Avonex® in reducing the mean number of relapses per patient, and the number of steroid courses per patient was 50% lower. The treatment effect seen at week 24 was also evident at week 48. [154](#) Relative risk for relapses at both time points was 1.18 (at 1 year, 52% of Avonex®-treated patients were relapse-free versus 62% for Rebif®).

MRI. The mean number of combined unique active lesions per patient per MRI scan (the main secondary outcome measure) was significantly reduced in patients receiving Rebif® compared with those receiving Avonex®. Similar significant benefits were seen on active T1 gadolinium-enhancing and active T2 lesions, the proportion of active scans per patient, and the proportion of patients with no new MRI activity. Analysis was adjusted for baseline active lesion number.

Tolerability and drop-outs. Some adverse events, such as injection-site reactions, elevated liver enzymes, and reduced white blood cell counts, were significantly more common in the Rebif® group than in the Avonex® group. The most common adverse events were injection-site reactions (reported in 80.5% of patients receiving Rebif® and 24.3% of those receiving Avonex®),

**Table 19** Summary of the key data from the EVIDENCE Study of interferon (IFN)  $\beta$ -1a (Rebif® and Avonex®)<sup>151-154\*</sup>

	IFN $\beta$ -1a (Rebif®) 44 $\mu$ g SC three times weekly (n = 339)	IFN $\beta$ -1a (Avonex®) 30 $\mu$ g IM once weekly (n = 338)
Proportion of relapse-free patients at 24 weeks (%)	74.9	63.3
Odds ratio (adjusted) = 1.9		
Mean number of relapses per patient during 24 weeks	0.29	0.40
Adjusted mean number of CU active lesions <sup>†</sup> per patient per scan <sup>‡</sup>	0.8	1.2
Mean proportion of scans per patient showing CU active lesions (%) <sup>†</sup>	24.0	37.3
Proportion of patients with no CU active lesions (%) <sup>†</sup>	48.3	33.2
Adjusted mean number of T1 active lesions per patient per scan <sup>‡</sup>	0.6	1.0
Adjusted mean number of T2 active lesions per patient per scan <sup>‡</sup>	0.3	0.6
Proportion of relapse-free patients at 48 weeks (%)	52	62
CU = combined unique.		
* Patients were randomized to either IFN $\beta$ -1a (Rebif®) 44 $\mu$ g SC three times weekly, or IFN $\beta$ -1a (Avonex®) 30 $\mu$ g IM once weekly, for 24 weeks.		
<sup>†</sup> CU active lesions were defined as active lesions on T2 or T1 post-gadolinium sequences.		
<sup>‡</sup> Means were adjusted to account for slightly different numbers of lesions in the two treatment groups at baseline.		



but most were mild. A total of 11 (3.2%) patients in the Rebif® group and 3 (1%) in the Avonex® group discontinued treatment because of adverse events. Neutralizing antibodies were seen in 24% of Rebif®-treated patients versus 2% of Avonex®-treated patients at 48 weeks, using 20 NU/ml as a cut-off point.

Number needed to treat. The number needed to treat with Rebif® to render one more patient relapse-free compared with Avonex® is 9 at 24 weeks and 10 at 48 weeks.

#### *Conclusions.*

*Methodology: probably class I.* This trial will probably be graded class I for both clinical and MRI outcome measures, but the study is not yet published.

Although this was an open-label study, both clinical and MRI outcome measures were assessed in a blinded fashion. The results indicate that IFNβ-1a (Rebif®) 44 μg SC three times weekly is more effective in preventing relapses and reducing MRI disease activity than IFNβ-1a (Avonex®) 30 μg IM once weekly. It appears that the dose, frequency of dosing, or both, have a significant impact on the clinical efficacy of IFNβ-1a in patients with RRMS during the first 6 months of treatment.

#### **Summary.**

On the basis of the two class I studies with IFNβ-1a in early MS, therapy with this agent at 22 or 30 μg once weekly appears to delay conversion from suspected MS to CDMS.<sup>116,117</sup> At this stage, it is not possible to draw conclusions about the effect of early treatment on long-term prognosis. The observed treatment effect was slightly greater for 30 μg IM versus 22 μg SC per week, suggesting a possible dose or route effect.

The initial 2–3-year studies with IFNβ-1b (Betaseron®), IFNβ-1a (Avonex®), and IFNβ-1a (Rebif®) in patients with RRMS were all well designed class I studies, providing support for the clinical efficacy of IFNβ on relapse-related outcome measures.<sup>122,124,129</sup> IFNβ-1b, however, did not significantly delay the development of disability over 3 years, and treatment with IFNβ-1a at a dose of 30 μg once weekly had no significant effect on the 2-year accumulation of T2 lesion volume, whereas IFNβ-1a 44 μg three times weekly provided a significant beneficial effect on relapse-, MRI-, and disability-related outcome measures. The initial 2-year class I study with GA (Copaxone®) also showed benefit for this agent on relapses, but a clear positive effect on disability was not demonstrated.<sup>132</sup> IVIg may be helpful in patients with RRMS, although this remains to be established,<sup>135</sup> and mitoxantrone appears to work in what could be termed "aggressive transitional" MS.<sup>136,144</sup>

The benefit of disease-modifying therapies in patients with SPMS is less clear. The results obtained in the European study with IFNβ-1b (Betaseron®) in patients with SPMS showed a modest slowing of progression in a group with the higher proportion of relapsing patients.<sup>139</sup> By contrast, no effect of IFNβ-1b on disability progression was observed in the North American study, which included a greater proportion of patients who were not having relapses.<sup>141</sup> A post hoc analysis in the SPECTRIMS Study with IFNβ-1a (Rebif®) also indicated that therapy was more effective in patients with prestudy relapses than in those without.<sup>142</sup> These data appear to suggest that, for treatment to be effective in patients with MS, IFNβ should be given at a time when the patient is still having relapses. The efficacy of mitoxantrone in MS patients without relapses is

undetermined.<sup>144</sup>

It is important to bear in mind that the studies described here have lasted for a maximum of 5–6 years and therefore provide no information on the long-term benefit of therapy in a disease that typically spans decades. Long-term follow-up of patients treated with disease-modifying drugs is essential to compare their disability outcomes with those expected from natural history studies, although the appropriate choice of a comparator natural history control group remains a great practical challenge.

## ▶ **MRI AS A SURROGATE MEASURE IN MS TREATMENT TRIALS**



The new era of MS treatment trials commenced with the use of MRI as a surrogate measure for disease activity and burden, and this was undoubtedly a factor in the first-ever approval of disease-modifying therapies in MS in the early 1990s (Betaseron®). A large series of studies, some of which are reviewed below, have indicated that MRI is a sensitive measure of disease activity in patients with RRMS. This is less true in patients with SPMS.

- ▲ [Top](#)
- ▲ [Introduction](#)
- ▲ [MS: THE DISEASE](#)
- ▲ [REVISED CRITERIA FOR THE...](#)
- ▲ [DISEASE-MODIFYING DRUGS IN MS](#)
- [MRI AS A SURROGATE...](#)
- ▼ [References](#)

Perhaps surprisingly, however, there is a low correlation between clinical and MRI measures of disease activity. Published correlation coefficients for measures such as relapse rate and change in EDSS score compared with measures such as T2 lesion volume or area are generally in the range of 0.15–0.30. Helped by the large sample size from which these *r*-values are derived, these correlations can be considered statistically significant (i.e., believable) but, in a clinical sense, insignificant. It is not possible to predict from a cranial MRI scan what a patient's EDSS score is or what the recent relapse rate has been, and the reverse is also true. Nevertheless, MRI provides a unique biological window on the process of MS-associated disease activity, and has provided clinicians with the invaluable insight that MRI lesion accumulation exceeds clinical relapses by a factor of 5–10.<sup>155,156</sup>

There has yet to be a large clinical trial of disease-modifying therapy in MS in which clinical improvement has occurred in the absence of improvement in MRI. Relative MRI improvement is therefore a necessary, but not sufficient, precondition for success of drug therapy in patients with MS. Should there ever be a clinical trial in which MRI and clinical outcomes change in opposite directions, faith in this putative surrogate marker of disease activity will be shaken.

The Prentice criteria<sup>157</sup> for a surrogate marker require that the surrogate marker activity must closely mirror the "gold standard," which, in the case of MS, is the clinical activity. Moreover, the changes in the surrogate marker ought to "mediate" the changes in the clinical marker. The latter criterion has not been fulfilled in the case of MRI in MS, given the relatively low correlations described above. As is well known, the degree of suppression of MRI activity associated with IFN use far exceeds the degree of observable clinical benefit in all published IFN studies. In contrast, the degree of relative MRI improvement seen in patients treated with GA is the same for both

clinical and MRI measures.

The following commentaries look at specific MRI-oriented publications related to the IFN and non-IFN disease-modifying therapies, presented in order of date of publication. They provide information that is intended to complement the clinical study results rather than to replace them.

### **MRI-oriented publications.**

Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. II. MRI analysis results of a controlled multicentre, randomized, double-blind, placebo-controlled trial.<sup>158</sup> This paper presents the MRI results of the pivotal study of IFN $\beta$ -1b (Betaseron®) in patients with RRMS. At 2 years the placebo group showed a 20% increase in lesion area, compared with a 10.5% increase in the group receiving IFN $\beta$ -1b 1.6 MIU and a 0.1% decrease in the group receiving 8 MIU. These mean changes were similar to the median changes and were highly statistically significant. The median change in lesion area at 2 years was an increase of 305.1 mm<sup>2</sup> in the placebo group and 142.0 mm<sup>2</sup> in the 1.6 MIU group, and a decrease of 13.0 mm<sup>2</sup> in the 8 MIU group. Active lesions (defined as new, recurrent, or enlarging lesions) occurred at a median rate of 3.0 per year in the placebo group, 1.0 in the low-dose group, and 0.5 in the high-dose group. All differences described between treatment groups and placebo were highly statistically significant.

This paper also introduces the concept of active scans, defined as the proportion of scans showing new enlarging or recurring lesions (gadolinium was not used in this study). Over the course of the study, the median number of active scans was 29.4% for placebo-treated patients, 11.8% for patients receiving low-dose IFN $\beta$ -1b, and 5.9% for those receiving the high dose, with both treatment groups showing a statistically significant difference from placebo.

### **Magnetic resonance studies of intramuscular**

interferon  $\beta$ -1a for relapsing multiple sclerosis (the MSCRG Study).<sup>128</sup>

Dr. Simon, the lead radiologist for the MSCRG Study of IFN $\beta$ -1a (Avonex®) in patients with RRMS, published this re-analysis of the MRI data from the study. The key findings include the following.

The baseline number of gadolinium lesions was the strongest predictor of the change from baseline T2 lesion volume at year 1 and year 2 in the study population. The median number of new plus enlarging lesions at baseline compared with year 2 did not differ between groups in those patients who were gadolinium-negative at baseline in contrast to a significant difference ( $p = 0.008$ ) in favor of IFN $\beta$ -1a in patients who were gadolinium-positive at baseline.

Gadolinium positivity at baseline was not associated with a significant effect in favor of the drug at the end of year 2 in terms of change in T2 lesion volume, nor was a drug effect for the group as a whole observed for this end point. Correlations between MRI and clinical parameters, such as the relapse rate and change in EDSS score, are evident but modest ( $r = 0.02$ – $0.30$ ). It is contended by the authors that measures of actual lesion volume change are more meaningful than percentage changes in lesion numbers or volumes. However, actual lesion volume changes are difficult for clinicians to remember and use for comparisons between studies. In the following reviews, percentage change will therefore be used.

In conclusion, this paper suggests that IFN $\beta$ -1a (Avonex®) 30  $\mu$ g IM once weekly is associated with a modest reduction in the number of new plus enlarging lesions at year 2, and that this effect is driven by those patients who are gadolinium-positive at baseline. A drug effect on T2 lesion volume is not seen at year 2.

#### **Magnetic resonance imaging results of the PRISMS**

trial: a randomized, double-blind, placebo-controlled study of interferon  $\beta$ -1a in relapsing–remitting multiple sclerosis.<sup>[159](#)</sup>

In this paper, the MRI results from the randomized 2-year study in patients with RRMS treated with IFN $\beta$ -1a (Rebif®) 22 or 44  $\mu$ g SC three times weekly are reported. The median percentage increase in lesion area in the placebo group after 1 year is 6.4 compared with a decrease of 3.5 and 4.5, respectively, in the two treatment arms. At 2 years the median change in lesion area was an increase of 10.9% with placebo and decreases of 1.2 and 3.8%, respectively, with low- and high-dose IFN $\beta$ -1a. The median proportion of active scans was 44% in the placebo group, 12.5% in the low-dose group, and 11% in the high-dose group. Favorable treatment effects were identified in terms of number of T2 active lesions per patient per scan, T2 active scans, and proportions of patients with no T2 activity. The same measures were applied to combined unique activity scans, with the same results.

**European/Canadian multicenter, double-blind,**  
randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis.<sup>[160](#)</sup>

The original pivotal GA (Copaxone®) treatment trial in patients with RRMS did not have a major MRI component. This European/Canadian study was an attempt to address the lack of data regarding the efficacy of GA on MRI measures of disease activity in patients with RRMS.

Eligible patients (n = 239) were randomized to GA 20 mg SC once daily or to placebo. Importantly, patients were required to have had one or more relapses in the 2 years before study entry and at least one gadolinium-enhancing lesion on the screening MRI. This study therefore represents the first large trial of RRMS patients who were all gadolinium-positive on screening MRI. The primary outcome measure was the total number of enhancing lesions on T1-weighted images, and the placebo-controlled portion of the trial lasted 9 months.

At the end of this period, the mean cumulative number of enhancing lesions was 36.8 in the placebo group versus 26.0 in the treatment group, giving a relative reduction of 29% ( $p = 0.003$ ). Statistically significant differences first emerged after 5 months of continued therapy from randomization. The median percentage increase in T2 lesion volume from baseline to the end of the trial at 9 months was 20.6% in the placebo group and 12.3% in the GA group, with a relative reduction of 40% ( $p = 0.0011$ ). This is the only published clinical trial of an approved disease-modifying therapy in MS in which the degree of MRI effect paralleled the degree of clinical effect (approximately 30%). The proportion of patients with new gadolinium-enhancing lesions was not affected by treatment. T1 black hole number<sup>[161](#)</sup> was beneficially affected by treatment but the volume was not.

## Footnotes



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## References



[▲ Top](#)  
[▲ Introduction](#)  
[▲ MS: THE DISEASE](#)  
[▲ REVISED CRITERIA FOR THE...](#)  
[▲ DISEASE-MODIFYING DRUGS IN MS](#)  
[▲ MRI AS A SURROGATE...](#)  
 • [References](#)

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