Fourth Edition

# McAlpine's MULTIPLE SCLEROSIS


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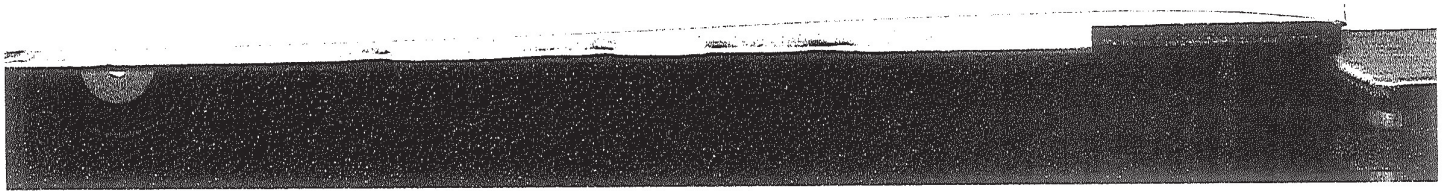

# McAlpine's MULTIPLE SCLEROSIS

FOURTH EDITION

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# 18 Disease-modifying treatments in multiple sclerosis

*John Noseworthy, David Miller and Alastair Compston*

## THE AIMS OF DISEASE-MODIFYING TREATMENT

There have been many developments since we last reviewed the role of disease-modifying treatments in multiple sclerosis. Collectively, these represent progress but fall well short of a solution to the problem. Results of the pivotal interferon and glatiramer acetate trials led to approval of these treatments by licensing bodies throughout the world. For the first time, patients with multiple sclerosis had a treatment. This was welcome and fuelled further efforts to improve on the evidence for efficacy and indications for the timing, dose and duration of therapy. Increasingly sensitive diagnostic criteria, bolstered by serial magnetic resonance imaging (MRI) studies (W.I. McDonald *et al* 2001), now allow more rapid diagnosis and hence – in our current climate – earlier exposure to treatment. However, further work is needed on many strategic issues and points of detail:

- Will early treatment make a difference?
- Can sensitive clinical and MRI measures detect early favourable trends that predict long-term benefit?
- Might the trials be made even shorter?
- How early in any study should a monitoring committee conclude with certainty that a trial is positive and recommend early termination with generalized access to the therapy?

It is axiomatic that doctors want to make their patients better. Patients want to lead normal lives unencumbered by any physical, psychological or life-style baggage related to multiple sclerosis. As clinical scientists, we need to structure that pastoral position around concepts of the pathogenesis and strategies for what realistically can be achieved. Patients with multiple sclerosis need treatment before the onset of fixed disability. Throughout, we have argued that the clinical manifestations of multiple sclerosis can be attributed to perivascular inflammation and the tissue injury with which it is inextricably linked. Since we last reviewed the subject in 1998, the diversity of mechanisms that injure nerve fibres throughout the illness and the contribution these processes make to the clinical course have been intensively studied. Concepts have been updated and revised. Thus, whilst we remain of the view that inflammation is pivotal to the destruction in parallel of axons and oligodendroglia, the inflammatory process also triggers biological processes that increasingly contribute to tissue destruction. What position should the prescribing physician take on how and when to treat the person with multiple sclerosis? Our stance is pragmatic but informed by the neurobiology and neuroimmunology, and by the evidence from clinical trials.

We structure this discussion around the formulation that, typically, the early clinical course of multiple sclerosis is marked by relapses from which symptomatic recovery is usually complete. Inflammation drives the process. Subsequent episodes may affect the same or different myelinated pathways. Before long, clinical deficits, which correlate with abnormalities in saltatory conduction of the nerve impulse, accumulate. These reflect loss of functional reserve in the adaptive capacity of the nervous system to make best use of surviving electrical activity, and the impoverished but detectable signals that reach the cortex or distant parts of major pathways. Then, inflammation wanes (without necessarily ceasing) and the relative contribution of cumulative axonal damage, amplified by loss of trophic support, makes an impact (Figure 18.1). Initially, the clinical course is intermittent in 80% of affected individuals but a high proportion do later enter the secondary progressive phase in which impairment, loss of ability, and impact on health-related quality of life are each affected. For these patients, disability is established in 40% by 10 years, in 60% by 15 years and in 80% (that is 50% of all patients) by 25 years. It is the onset of secondary progression that gives multiple sclerosis the frightening reputation it has amongst affected individuals. Progression is the main factor distinguishing mild from severe forms of multiple sclerosis. In 20% of patients, the disease progresses slowly from onset, most typically with predominant spinal involvement, and this form of multiple sclerosis is even more predictably disabling. The analysis that fully reversible deficits mainly result from inflammtion, oedema and the physiological action of cytokines whereas persistent symptoms and signs can be attributed to demyelination and the initial wave of axonal damage with failure of recovery mechanisms, and that chronic progression is attributable to cumulative axon degeneration, has obvious implications for treatment.

Immunological therapies are most likely to be effective in the inflammatory (relapsing–remitting and relapsing–persistent) phases. Conversely, it will be more difficult to influence progression with immunotherapy. Any treatment that reduces the accumulation of disability, and inhibits or delays time to onset of the progressive phase, is most likely to have a clinically useful disease-modifying effect whether or not that treatment also

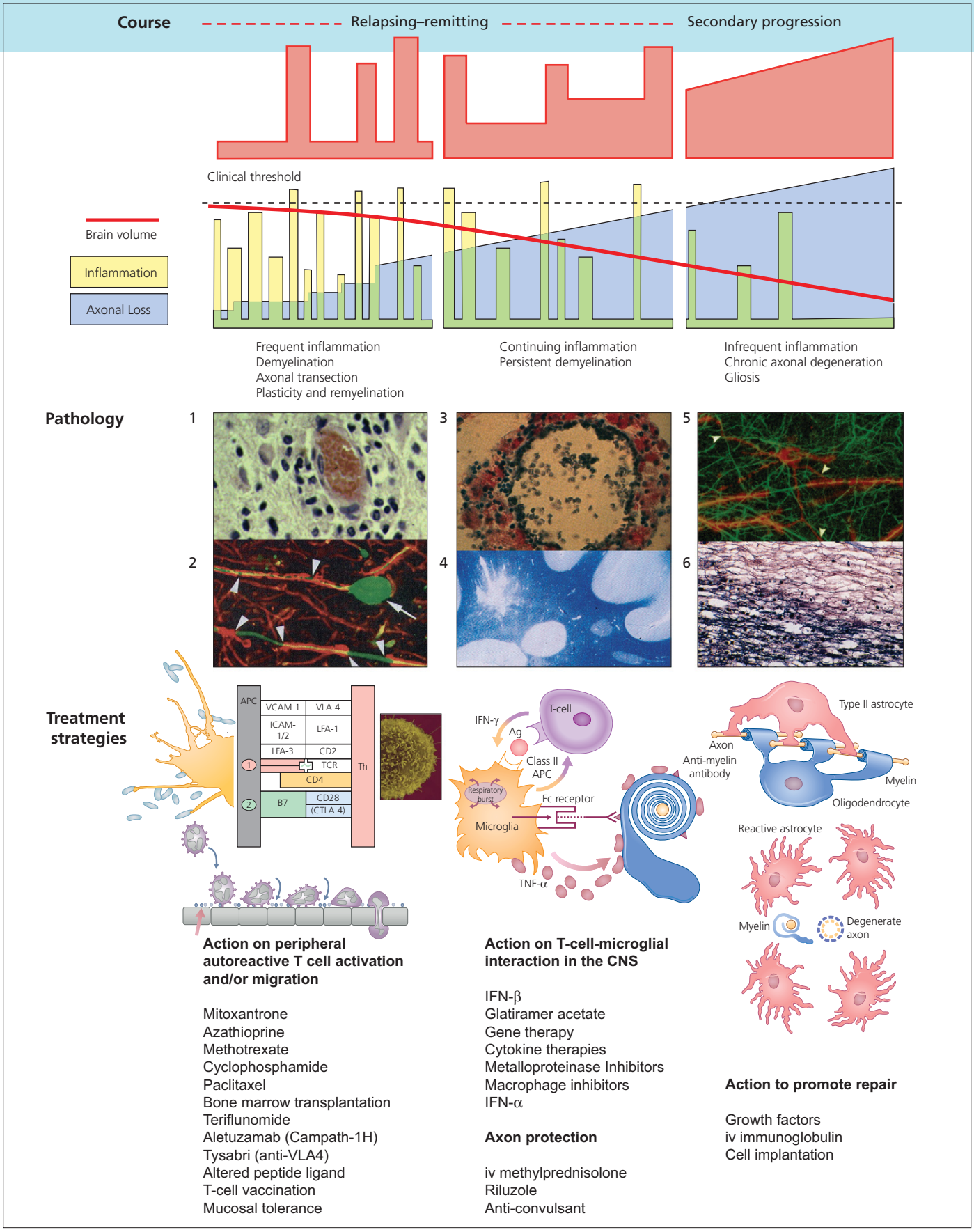



**Figure 18.1** The course, pathogenesis and treatment of multiple sclerosis. *Course*: the clinical phases of relapse with recovery, relapse with persistent deficits and progression depend mainly on the effect of inflammation, demyelination and axon degeneration, respectively. Disease activity is often presymptomatic and, later, not invariably expressed clinically. As inflammation wanes, brain volume reduces with accumulated axonal loss. *Pathology*: perivascular inflammation (panel 1) causes acute axonal transection (panel 2), and microglia-mediated removal of myelin (panel 3) with persistent demyelination despite some remyelination (panel 4); chronic lesions show further axonal loss (panel 5) and gliosis (panel 6). The scheme does not depict primary progressive multiple sclerosis in which there is significant axonal degeneration with or without a preceding inflammatory phase. *Treatment strategies*: target the phase of T-cell activation in the periphery or cell migration; interactions between the activated T cell and microglia in the central nervous system; and axon protection and remyelination. Adapted from Compston and Coles (2003). © 2003, with permission from Elsevier.

affects the number of new episodes or lesions detected by brain imaging. Therefore, it makes sense to deploy strategies for treatment that address this evolution of events – choosing those interventions that preferentially tackle (or, preferably, anticipate) the individual components so as to be maximially effective. Although much contemporary research in multiple sclerosis is appropriately directed at identifying disease-modifying treatments, many patients already make clear that merely aspiring to shape the future course of the disease is not sufficient. They want to get better. If repair is a matter of restoring structure and function, it follows that dealing with the rewriting of neurological history requires treatments that enhance plasticity and reconstruct the myelinated axon in its network of connectivity. Thus, repair involves applying the lessons of neurobiology to the problems of multiple sclerosis. It remains possible that enhanced remyelination will occur in an immunologically stable environment. The experimental evidence already hints at this possibility (see Chapter 10). Remyelination may protect injured axons from further damage resulting from loss of trophic support. Conversely, optimizing their growth factor environment may reduce the extent to which axons, already insulted, are affected by further exposure to inflammatory mediators. Conversely, it is logical to assume that sophisticated repair strategies will have a low dividend for success without first having available a treatment that reliably stabilizes the disease process. Just as the dichotomy of genes versus environment is a somewhat sterile aetiological debate, so too separating inflammatory and biological mechanisms of injury to the axon–glial unit is somewhat strained.

But to go back a step, in Chapter 1 we reviewed the development of ideas concerning disease-modifying treatments in multiple sclerosis. The era prior to 1980, summarized by W.I. McDonald (1983), was empirical and largely uncluttered by serious concern about disease mechanisms. This period of intellectual freedom concerning the nature of multiple sclerosis provided ample opportunity for wild, and at times frivolous, approaches to treatment, some of which (rightly) gave the disease the bad therapeutic name from which it has not yet fully recovered. An important development in the treatment of multiple sclerosis in the 1980s was the acceptance that therapeutic claims must adopt orthodox clinical trial methodology based on blinding (single or double), use of controls (preferably placebo but sometimes receiving best existing medical practice), matching groups at entry for potentially confounding variables, setting primary outcome measures at the outset of the study and not trawling for the best result on completion, and considering power calculations during the planning stage. Working groups were convened to issue guidelines (see, for example, J.R. Brown *et al* 1979; Weiss and Dambrosia 1983). The impact of papers laboriously listing trial design tactics encouraged journal editors and referees to flex their methodological muscles – factors which undoubtedly led therapists to conform and resulted in the steady demise of therapeutic generalizations based on anecdote. The rubric 'double-blind, randomized and placebo-controlled' became commonplace. Since progress in identifying useful treatments was disappointingly slow, through no fault of those who designed the studies, separate trials of many agents proliferated and none could be regarded as definitive. Patients violated protocols and left studies for open label treatments, making it necessary to sort those who completed studies from 'intention to treat' cohorts. Commentators struggled to put their thoughts in order by cataloguing published material and seeking a best position on disparate data. Faced with too few studies involving sufficient numbers of patients from which to draw firm conclusions, the meta-analysis emerged as a device for 'seeing the wood for the trees'. Considered by some as scientific sophistry, this analytical procedure exposed the criticism of mixing chalk with cheese and creating statistical noise, not least because outcome measures in multiple sclerosis are an integral of up to three independent clinical features – acute events, persistent deficits, and progression – which contribute to impairment, loss of ability, autonomy and participation (formerly referred to as impairment, disability and handicap).

Later, came the interim analysis – often used to stop trials either on the grounds of futility or issues of patient safety. Recent examples include studies of intravenous immunoglobulin designed to measure clinical recovery in multiple sclerosis and optic neuritis; trials of altered peptide ligands; the story of agents that have an impact on tumour necrosis factor-α (TNF-α); the glatiramer acetate study in primary progressive multiple sclerosis; and the use of oral glatiramer acetate (see below for more detailed discussion). However, the interim analysis has also recently been used increasingly to stop trials early on the basis of perceived efficacy, thereby allowing active treatment to be made immediately available for all patients without the disadvantaged controls waiting for completion of the protocol. We have seen this happen repeatedly, dating from the first wave of pivotal trials in relapsing–remitting multiple sclerosis [the North American IFNβ-1a trial (Avonex)] and, subsequently, with trials in possible (CHAMPS) and secondary progressive multiple sclerosis (the European trial, SPECTRIMS) – all discussed below. More recently, trials have been reported and widely accepted as valid with as little as 6 months follow-up (for example, EVIDENCE). The lesson from the failed Mayo Clinic Canadian Sulfasalazine Trial that early benefit may wane with further blinded follow-up seems often to have been forgotten (Noseworthy *et al* 1998; Rudge 1999). Hence, we now have to provide wise counsel to a generation of patients, some treated immediately after an inaugural clinical episode (clinically isolated syndromes), others when the illness has been established for only a few years (early relapsing–remitting multiple sclerosis), and many long into the illness with advanced secondary progressive disease – despite the lack of convincing evidence for protracted benefit – aiming to steer a course between managing their expectations and not shirking our responsibilities as clinical scientists.

The concentration of clinical research on the evaluation of therapies that target the immune response in multiple sclerosis itself represents something of an advance, displacing hypotheses for the pathogenesis finding their expression in less rational clinical trials. We hope that those who contributed to these studies will accept our decision to concentrate on contemporary immunotherapy and applied neurobiology. Of course, we accept that some (or indeed many) of the agents which we have selected for detailed discussion may in time join those which we have placed on the well-stacked shelves of therapeutic history in multiple sclerosis.

By the late 1980s, Noseworthy *et al* (1989b) were able to tabulate a large number of potential therapies which experienced investigators considered to be promising options for treatment. Many are still being evaluated but some degree of consensus on

the basis for treatment in multiple sclerosis has emerged in recent years. At first, physicians were cautious when considering the use of immunotherapy for multiple sclerosis even though many of the available medications had been used successfully in other inflammatory and autoimmune diseases. This caution was appropriate since a significant proportion of affected individuals remain free from disability despite having intermittent symptoms over several decades, and it is not possible to segregate individuals destined to have benign forms of multiple sclerosis early in the course. In our opinion, however, the focus on treating secondary progressive multiple sclerosis held up progress for a generation. Since the late 1990s, that lesson has been clear. Wait until late and the contribution of anti-inflammatory therapy is so small as to not be cost effective. For many affected individuals, this is a formula for disappointment leading to cynicism that, despite intense research, no useful progress is being made in understanding the disease. It seems clear that, in the context of disease progression, the focus should now be on neuroprotective and biologically motivated approaches – alone or in combination with immunotherapy. Treat early and the dividend may be greater but still the dilemma remains. Drugs that are partially effective may not sufficiently stabilize the disease processes whereas the more actively anti-inflammatories are likely to carry nontrivial adverse-effect profiles. As we wrote in the early 1990s, the comprehensive management of multiple sclerosis is about both limiting and repairing the damage.

Progress has been made in improving outcome measures in the assessment of treatments for multiple sclerosis. Totting up the number of acute events requires them to be reliably defined, but patients will understandably assign significance to transient alterations in symptoms, perhaps having explanations other than disease activity. Conversely, motivation and the hope of a therapeutic effect will lead others to ignore clinical changes even though these are biologically meaningful. Periods of disease activity measured by high relapse rates tend to oscillate and, overall, slow with time so that a reduction in relapse rate *per se* is not necessarily impressive unless the placebo group has behaved less well and in keeping with the known natural history of the disease. The problems are even greater for the assessment of disability. There have probably been more critiques of the Expanded Disability Status Scale of Kurtzke (EDSS) (Kurtzke 1983a)and related clinical outcome measures than clinical trials in multiple sclerosis. The problems are well known. The EDSS mixes activity with disability and ignores participation. It is excessively weighted towards the motor system. It is ordinal not linear. Patients tend to cluster in the lower and higher echelons and it is insensitive in the middle range. However, it survives and despite much squabbling has yet to be replaced by a better, fully validated and universally accepted system. In this context, we welcome the deliberations of a panel convened by the United States National Multiple Sclerosis Society to make recommendations for a comprehensive clinical outcome system applied universally to treatment trials in multiple sclerosis, so allowing more meaningful comparisons between studies of the same or different agents (Rudick *et al* 1996a). The original guidelines were subsequently updated with special emphasis on the need for advisory/steering (to comment on the rationale, design, protocol, accrual and ownership of the data) and safety committees (to monitor operational aspects of trials), and the involvement of a group to supervise publication (Lublin *et al* 1997). The panel derived the Multiple Sclerosis Functional Composite scale (MSFC; G.R. Cutter *et al* 1999; Rudick *et al* 1996a; 1997) specifically to resolve these matters. The MSFC integrates scores on a timed 25 foot (7.5 m) walk (T25FW), Nine-Hole Peg Test (9HPT) of upper limb function, and Paced Auditory Serial Addition Test (PASAT). Values are reported as a Z-score, derived from comparison with an index population from the National Multiple Sclerosis Society Task Force dataset (G.R. Cutter *et* al 1999). The scale awaits validation as an accepted outcome for clinical trials and the MSFC has yet to be embraced by practising and academic neurologists. In large part, this is because, using this metric, most do not understand what is meant by changes in the Z-score, whereas few have difficulty with a single or multiple step change in the EDSS.

The introduction of novel scales has been trivial by comparison with the introduction of surrogate MRI markers as indices of therapeutic efficacy. The apparently favourable impact of approved but, in the event, partially effective treatments on relapse rates and MRI appearance solidified the sense that trials could increasingly use surrogate markers to detect a treatment effect. Clearly, reduction in the initial frequency of relapse and MRI activity may genuinely predict prolonged benefit but this requires evidence and has yet to be demonstrated. Such a study design aims to push new and existing therapies over a very high hurdle, requiring huge investments of time and money. Only recently have investigator-led studies adopted this long-term view but attention to effects that last and shape the neurological future is in the interests of patients and should be seen as motivated by the highest principles of clinical science, with a real dividend for improvement from the investment of hope in treatment. Worried by the sustained use of imperfect instruments for assessing outcome, investigators have created and partially validated increasingly sensitive measures of disability (such as the MSFC) and shown that these may detect treatment differences between treated patients with secondary progressive multiple sclerosis and controls, when standard measures (the Kurtzke EDSS) do not. Is the problem that our measures of disease progression are too insensitive to recognize a favourable response to treatment? Rather, it seems increasingly likely that existing treatments are insufficiently effective, or are deployed too late, completely to inhibit advancing disability.

The essential yet daunting task of confirming that these sensitive measures matter clinically in the long term – and are thereby predictive of a meaningful long-term benefit – has yet to be established. Here, a difference in agenda exists between physicians and the pharmaceutical industry, spawning secondary tensions between doctor and patient. The clinical scientist has a responsibility to proselytize secure knowledge even if this is gathered slowly and is disappointing in its scope. Sponsors need an early return on investment. In the context of multiple sclerosis, *Big Pharma* can be caricatured as having avoided engaging investigators in a dialogue about the importance of establishing long-term disability benefits. In turn, licensing agencies have not required that industry, assisted by teams of clinical investigators, demonstrate continued benefit for these expensive drugs as the necessary qualification for a drug licence. We have seen a proliferation of extension trials designed to demonstrate continued benefit. However, as discussed below, most are degraded by bias resulting from the recurring reality that failing patients drop out at the completion of the proper trial. Conversely, responders are

better motivated to participate in the extension limb of the study. Although re-randomized, loss of the original 'treatment failures' introduces selective sampling that subsequently haunts the trial, thereby reducing confidence that any long-term benefit claims are real. The push to earlier treatment, and acceptance by patients and physicians of the need for prolonged use of the currently available drugs (even in the face of obvious ongoing disease activity dressed up around 'perhaps the treatments are helping a bit'), is bolstered by several factors. Sponsors of the approved agents have failed to press for clinical and laboratory biomarkers that characterize responder status. As a result, far more patients are being treated than might be appropriate given the partial benefits noted in the literature.

These recent changes in the attitudes of specialists in multiple sclerosis should not be seen as mulish obstruction to the pharmaceutical agenda. Investigators and sponsors share the sense of urgency in wanting to provide patients with effective drugs as soon as possible. More than $1 billion is spent annually on these agents, in the United States alone, with no funds invested to confirm sustained benefit. This hope that treatment with existing agents will provide an extended benefit, especially for patients treated early, remains just that – an unconfirmed, elusive concept without proof for patients and physicians. Meanwhile, little (if any) progress is being seen in creating a robust strategy to validate this goal. If we appear critical, it is in the spirit of prioritizing real not virtual progress. Our attitude is in the interests of people with multiple sclerosis and the advancement of clinical science, with personal reputation and commerce well down the motivation stakes.

## THE PRINCIPLES OF EVIDENCE-BASED PRESCRIBING IN MULTIPLE SCLEROSIS

As discussed in the preceding section, over the last decade clinical investigators have become increasingly familiar with the principles of clinical trial design and have adopted these structures in the evaluation of putative new treatments. Thus, practice has shifted from the extrapolation of anecdotal experience to a more evidence-based stance on prescribing (Sackett *et al* 2000). The concepts of levels of evidence and grades of recommendation are slowly becoming part of the clinical trials lexicon. The neurological community is increasingly demanding that published reports of clinical trials clearly state how each trial was conducted and wishes to know how the data were analysed and by whom. Prior to 1994 it was common to see trials that were neither randomized, blinded, nor adequately controlled. Patients with different disease courses (relapsing–remitting, and primary or secondary progressive) were often included in the same study; this latter concern is still rarely addressed. At that time, trials rarely performed an intention to treat analysis, often accounted incompletely for drop-outs, and rarely assessed the adequacy of efforts to blind patients and evaluators. Outcome measures were usually not validated (regrettably, this is still largely the case). Nor were the sensitivity and specificity of these measures provided in the reports. Sample size estimates and power calculations were often not stated, leaving open the possibility of type 2 ('false-negative') errors resulting from an underpowered sample size. Many authors did not state the predetermined primary outcome measure and post-hoc analyses were often not identified as such. Authors rarely corrected for multiple statistical comparisons (the Bonferroni correction).

With time, the clinical trials community in multiple sclerosis has become increasingly sophisticated about these essentials of trial design and conduct. Most of the design flaws already listed are now appropriately filtered during design of the protocol, and policed by the peer review process before a report is published. However, some problems remain. As emphasized repeatedly throughout this chapter, clinical trials in multiple sclerosis are rarely of sufficient duration to determine whether the intervention affects eventual outcome in terms of disability but there are many seemingly insurmountable obstacles that block the path to longer trials. These include the lack of 'equipoise' for selecting both the active treatment(s) and the control group, since many investigators have strong opinions about which treatments they consider to be superior. There is reticence by both the sponsor and patients to commit to long trials. To date, every treatment has proved incompletely effective and this regrettable truism results in an inevitable but variable degree of 'treatment failure' for most participants – most patients experiencing clinical or MRI evidence for worsening. Naturally, the disappointed patients who detect clinical worsening remain anxious to try another form of treatment and many options are now available. Whitaker (1993), on behalf of the Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis of the National Multiple Sclerosis Society (NMSS), argued against named patient prescribing (compassionate use of investigational drugs) since this bypasses or otherwise compromises the double-blind, randomized and placebo-controlled trial. His views are no less relevant today when patients have been given high expectations of drug treatment and efficacy has been proselytized through a combination of altruism and exploitation. Many doctor–patient relationships have been strained by these helter-skelter events. Agreement on trial design and protocol management and policing of methodology in treatment trials continues into the new millennium. With increasing duration, drop-outs accumulate and blinding of the patient and evaluator become increasingly difficult. Similarly, as discussed later in this chapter, extension trials are flawed by the late loss of protection from the initial randomization step that is so essential to reduce bias by balancing unknowable prognostic variables across each study group. Most reports of positive trials do not discuss the 'numbers needed to treat' analysis (see below), although independent editorials and correspondents frequently raise this matter; there remains a pressing need to establish that MRI measures can serve as reliable predictive biomarkers of disease course.

It is regrettable to acknowledge that few investigators participating in industry-sponsored trials yet have full access to raw data or the process of analysis. This continues to be a vexing problem in multiple sclerosis research despite requirement by major clinical journals for authors to confirm that an opportunity was provided to participate both in the collection of results and their analysis (Davidoff *et al* 2001). The academic community is gradually accepting the importance of so-called integrity policies that mandate full disclosure of competing interests with sponsors but greater transparency on this issue is still needed (Noseworthy *et al* 2003). The strong stance taken recently by major biomedical journals to require that trials be fully registered, if they are to be accepted for publication, may provide

much needed clarity within the clinical trials arena (De Angelis *et al* 2005).

With the proliferation of partially effective, disease-modifying treatments, fewer untreated patients are available to participate in clinical trials. In 1998, a small group of investigators decided to create a research centre independent of commercial influence and with the goal of hastening the search for therapeutic advances (Noseworthy *et al* 2003). The Sylvia Lawry Centre for Multiple Sclerosis Research at the Technical University of Munich (named in honour of the founder of the National Multiple Sclerosis Society of the United States and the International Multiple Sclerosis Society – see Chapter 1 – and directed by Albrecht Neiss and Martin Daumer) has amassed an impressive repository of data from natural history and completed clinical trials. In 2004, it had access to 43 data sets involving 14 700 cases and representing 62 000 patient years of follow-up. These data were primarily orientated towards controls since pharmaceutical sponsors had yet to donate information on individuals receiving study medications. Efforts are already under way to use this resource as the basis for understanding the contribution of demographic variables and laboratory measures (primarily MRI data) in identifying characteristic of the short- and long-term clinical course. The aim is to apply this knowledge in predicting the long-term course early in what is, for most affected individuals, almost invariably a chronic illness. Several countries (Denmark, Canada and Spain amongst others) have developed national registries to monitor the use of expensive therapies. Such databases will increasingly provide insights on long-term treatment efficacy with these drugs.

## THE ROLE OF MAGNETIC RESONANCE IMAGING IN CLINICAL TRIALS

Over the last decade, the application of a range of MRI outcome measures has become a standard means of assessing therapeutic efficacy in the context of controlled clinical trials. The potential to monitor both natural history and treatment interventions was quickly recognized when MRI was introduced into clinical practice in the 1980s. As a direct and sensitive surrogate measure of the evolving disease process, it promised outcome measures that were simultaneously more objective and efficient than the cumbersome clinical markers on which clinical trials exclusively depended at that time. In the first clinical trial of interferon-β (IFN-β), culminating in a drug licence, the unequivocal evidence that new lesions could be prevented was seen as strong supporting evidence to accompany the principal clinical effect of a reduction in relapse rate (Paty *et al* 1993).

### Individual magnetic resonance imaging lesions

The sensitivity of counting new MRI lesions in treatment monitoring has been amply confirmed. In relapsing–remitting or relapsing secondary progressive multiple sclerosis, serial monthly brain MRI reveals about ten new gadolinium enhancing or new $T_2$ lesions for every clinical relapse. It can thus be anticipated that the number of subjects and length of follow-up is reduced when using MRI lesions as the primary outcome measure (D.H. Miller *et al* 1991). Significant reduction in the number of new MRI lesions can be demonstrated in a matter of months using a relatively small number of patients and, as a result, MRI has been proposed – and is widely accepted – as the primary outcome measure in exploratory trials of potential new disease-modifying agents in relapsing multiple sclerosis (D.H. Miller *et al* 1996). This approach is biologically plausible when the treatment is intended to suppress inflammation, since gadolinium-DTPA (gadopentetate dimeglumine) enhancing lesions identify areas of active inflammation. Monthly $T_2$-weighted and gadolinium-DTPA enhanced (0.1 mmol/kg of a gadolinium chelate) brain MRI are usually performed in phase I/II studies. In relapsing–remitting multiple sclerosis, a parallel groups design with placebo requires about 40 patients per arm to show a 60% reduction in new enhancing lesions over 6 months (McFarland *et al* 1992; Sormani *et al* 1999; Tubridy *et al* 1998a). A single run-in scan at 1 month reduces the sample size by about 30% (Tubridy *et al* 1998a). Slightly larger numbers are needed in secondary progressive multiple sclerosis. Crossover designs are more powerful, because there is less intra- than inter-patient variability in MRI activity. A single crossover design with 6 months run-in followed by 6 months of treatment requires between 10 and 12 patients to show a 60% reduction in activity (McFarland *et al* 1992). Double crossover designs are even better, but there needs to be a wash-out period between the two phases. Both crossover designs are compromised by regression to the mean. If a safe and cheap drug shows only a moderate reduction in activity (c.50%) in a small crossover study, this might be sufficient evidence to justify going straight to a phase III trial using a clinical end point. However, if the drug has more side effects or is expensive, a parallel group design with the larger sample sizes (such as 2 groups of 40 individuals treated for 6 months) should first be undertaken to gain more certainty about the MRI effect. An important limitation of studies with this size and duration is that they will not detect infrequent, severe or delayed side effects. It is therefore still considered necessary for the definitive (phase III) trial to be longer, to involve larger cohorts and to have a primary clinical end point.

A major limitation in the interpretation of gadolinium enhancing or $T_2$ lesions as outcome measures in trials is that these do not strongly predict or correlate with the long-term clinical course. Although concordance of the treatment effect on MRI lesions and relapses has been observed with most (but not all) agents that have been investigated in placebo-controlled trials (Table 18.1), the magnitude of reduction on MRI has not reliably predicted the extent of any decrease in relapse rate. For example, IFN-β and glatiramer acetate both reduce relapse rate by about 30% but, whereas IFN-β reduces the new MRI lesion rate by 50–70%, glatiramer acetate is associated with only 30% reduction. More importantly, the extent of $T_2$ and gadolinium-DTPA enhancing lesions has consistently demonstrated little or no relationship with concurrent or future disability (Kappos *et al* 1999). This lack of a relationship may partly be the result of limited follow-up – most published studies have lasted no more than a few years and may not have allowed sufficient time for substantial changes in disability to be revealed. Two recently published cohorts of patients presenting with clinically isolated syndromes have been followed for 8.7 and 14 years, respectively. One study of 42 patients showed that infratentorial lesions at presentation are associated with greater disability after 8.7 years (Minneboo *et al* 2004). In the second, the number and

**Table 18.1: Treatment effects on active MRI lesions and relapses reported in parallel groups, placebo-controlled multiple sclerosis treatment trials**

| Therapy | Sub-group | Treatment duration | Patient number | MRI effect % | Relapse effect % | Reference |
|---|---|---|---|---|---|---|
| Beta interferon 1b SC | RR | 4 years | 372 | –60 to 75 | –33 | IFNB Study Group (1995) |
| Beta interferon 1a IM | RR | 2 years | 301 | –50 | –31 | Jacobs *et al* (1996) |
| Beta interferon 1a SC | RR | 2 years | 560 | –75 | –27 to 33 | PRISMS Study Group (1998) |
| Beta interferon 1b SC | SP | 3 years | 718 | –65 | –31 | D.H. Miller *et al* (1999) |
| Beta interferon 1a IM | CIS | 2 years | 383 | N/A | –44 | Jacobs *et al* (2000) |
| Beta interferon 1a SC | CIS | 2 years | 308 | –33 | –23 | Comi *et al* (2001) |
| Beta interferon 1a SC | SP | 3 years | 618 | –73 | –30 | SPECTRIMS Study Group (2001) |
| Beta interferon 1a IM | SP | 2 years | 436 | –46 | –33 | J.A. Cohen *et al* (2002) |
| Alpha interferon | RR | 6 months | 20 | –95 | None[a] | Durelli *et al* (1994) |
| Linomide | RR | 6 months | 31 | –70 | None[a] | Andersen *et al* (1996) |
| Linomide | SP | 6 months | 30 | –55 | None[a] | Karussis *et al* (1996) |
| Anti-CD4 antibody | RR/SP | 6 months | 71 | None | –41 | van Oosten *et al* (1996) |
| Mitoxantrone | RR/SP | 6 months | 42 | –90 | –77 | Edan *et al* (1997) |
| Lenercept | RR | 6 months | 168 | +30 to 60 | +50 to 68 | Lenercept MS Study Group (1999) |
| Tysabri | RR/SP | 2 months | 72 | –50 | None[a] | Tubridy *et al* (1999) |
| Cladribine | SP/PP | 1 year | 159 | –80 | None | G.P. Rice *et al* (2000) |
| Glatiramer acetate | RR | 9 months | 239 | –29 | –33 | Comi *et al* (2001) |
| Mitoxantrone | RR/SP | 2 years | 194 | –85 | –60 | Hartung *et al* (2002) |
| Oral beta interferon | RR | 6 months | 173 | None | None | Polman *et al* (2003) |
| Tysabri | RR/SP | 6 months | 213 | –90 | –50 | D.H. Miller *et al* (2003) |

*a Study too small to reliably evaluate relapses.*
*RR = relapsing–remitting; SP = secondary progressive; CIS = clinically isolated syndrome; PP = primary progressive.*
*– = decrease in activity rate treatment versus placebo.*
*+ = increase in activity rate treatment versus placebo.*
*SC = subcutaneous; IM = intramuscular.*
*N/A = not possible to assess because of patient censoring on developing clinically definite multiple sclerosis.*

volume of $T_2$ lesions in 71 patients at presentation correlated modestly with EDSS after 14 years (Brex *et al* 2002). The increase in $T_2$ volume during the first 5 years correlated somewhat more strongly with disability at year 14 ($r = 0.61$), suggesting that early accumulation of an increased lesion load does partially relate to long-term outcome. These studies are, however, quite small and the strength of the relationship between lesions and disability remains modest, suggesting that it is not sufficient to rely on MRI lesions *per se* (or their modification by treatment) to predict long-term disability (or its prevention by treatment).

The poor predictive value for disability of $T_2$ and gadolinium-DTPA enhancing lesions is that they are neither specific nor sensitive to axonal loss – the major pathological substrate for irreversible disability in multiple sclerosis. These markers do not reflect axonal attrition within lesions, or the loss that occurs more widely in normal-appearing white and grey matter. As a result, increasing attention has been placed on surrogate MR measures of axonal loss to study disease progression in multiple sclerosis and its modification by treatment.

It has been suggested that axonal loss in MRI lesions may be inferred by the presence of $T_1$ hypointensity. Such lesions (colloquially described as $T_1$ black holes) account for 20–30% of all $T_2$ visible lesions and have been found in post-mortem studies to indicate a greater extent of axonal loss than lesions that remain $T_1$ hypointense (van Walderveen *et al* 1998b). However, the use of $T_1$ hypointense lesions as a surrogate marker for axonal loss has important limitations. First, not all such lesions are irreversible – acute enhancing lesions frequently display transient hypointensity, and their resolution with follow-up may simply imply that reversible mechanisms such as oedema contribute significantly to the appearance. Secondly, $T_1$ hypointensity is a subjective assessment that is less reproducible than $T_2$ lesion identification and is highly dependent on MR sequence parameters. Thirdly, $T_1$ hypointense lesions are almost never seen in the spinal cord, yet axonal loss in this location is crucially related to locomotor disability. Fourthly, being a subset of visible lesions, assessment of $T_1$ hypointensity provides no indication of the axonal loss occurring in normal-appearing tissues.

It has been useful in placebo-controlled clinical trials to follow the evolution of acute inflammatory gadolinium enhancing lesions through to areas of persistent $T_1$ hypointensity. The frequency of such an evolution is reduced in patients treated with glatiramer acetate compared to the placebo group (Filippi *et al*

2001a) and Tysabri (Dalton *et al* 2004a) but not IFN-β (Brex *et al* 2001b). This outcome could be considered as the MR equivalent of an incomplete recovery from relapses. However, given the abundant evidence for neuronal and axonal loss in the white matter and grey matter beyond MR visible lesions, attention is being focused on global MR measures as a more plausible surrogate marker of irreversible and progressive disability.

## Global magnetic resonance measures of neuronal and axonal loss: atrophy

Tissue loss (atrophy) is the most widely used measure of neuroaxonal loss in treatment trials. Axons contribute 45% to white matter volume, followed by myelin (25%) and other tissue elements (glial and vascular tissues and water: D.H. Miller *et al* 2002). Neuronal cell bodies and axons constitute the bulk of grey matter volume although myelin is also present, albeit to a lesser extent than in white matter. Atrophy of white or grey matter in multiple sclerosis in large part reflects axonal and neuronal loss. In a study of the spinal cord of five people with multiple sclerosis, marked atrophy and axonal loss were both observed (Bjartmar *et al* 2000). However, neuroaxonal loss is not the only cause of atrophy. Loss of myelin, variations in glial bulk, inflammation and tissue water content also affect global or regional volume measures in multiple sclerosis. Pertinent to treatment trials, it should be noted that anti-inflammatory therapies (such as high-dose corticosteroids or IFN-β) reduce brain volume without axonal loss having occurred. We recommend that a period of 3 months should elapse after receiving such therapy before inferring that atrophy is measuring axonal loss.

The optimal technique for detecting atrophy should be reproducible, sensitive to change, accurate and pragmatic. The two distinct methodological aspects involved in measuring tissue volumes are data acquisition and data analysis. The ability to reduce partial volume errors with high resolution scans means that 3-D acquisitions are attractive, although 2-D sequences (Molyneux *et al* 2000) have also been used successfully to derive cerebral volume measures. Segmentation of the brain is necessary for whole brain atrophy measurements, and suppression of cerebrospinal fluid helps to generate a sharp distinction in signal between cerebral and extracerebral matter. The most widely used 3-D sequence is a $T_1$-weighted gradient echo. Specific study of white or grey matter requires good contrast at the cortical boundaries and interfaces both with cerebrospinal fluid and the individual lesions. It is aided by multiple contrast acquisitions (e.g. $T_1$, $T_2$ and proton density).

Manual outlining provides the simplest approach to measuring changes in volume and is useful in small structures or regions such as the third ventricle, where significant atrophy occurs in multiple sclerosis. Disadvantages of manual segmentation include operator bias, long analysis time and poor reproducibility when compared with automated techniques. Semi-automated methods improve speed and reproducibility. Regional segmentation algorithms are used to outline lesions, spinal cord, optic nerves and ventricles. Many automated methods exist for segmentation (and thus volume measurement) of the whole brain. Both single contrast (Chard *et al* 2002c) and multispectral data (Ge *et al* 2000) are utilized for whole brain segmentation. Usually, the difference in signal intensity between brain parenchyma and cerebrospinal fluid on a single contrast acquisition is enough to drive the segmentation process. Segmentation of grey and white matter may also be accomplished with either single contrast or multispectral data, although additional sophistication is required to separate the two tissue types. Methods include Statistical Parametric Mapping (SPM) based segmentation (Ashburner and Friston 2000) and the fuzzy C-means algorithm (Pham and Prince 2000). Masking of lesions is necessary to avoid misclassification.

Estimates of absolute volume at separate time points are not necessarily needed. Evidence for atrophy may be obtained by looking for differences between serial scans (S. Smith *et al* 2001). Nonlinear registration of such scans produces deformation fields that yield information concerning regional and global atrophy, and rigid body registration can be used to track displacement of the brain surface during atrophy (Freeborough and Fox 1997; 1998). Normalizing to head size reduces intersubject variations in brain volume. Relative volumes also remove variability due to scanner instability. The scalp, and the total intracranial capacity (determined by the sum of the volumes of grey matter, white matter and cerebrospinal fluid, or the sum of the brain and ventricular and sulcal cerebrospinal fluid) have all been used to adjust brain volumes for normalization. Atrophy is seen in both the brain and spinal cord in secondary and primary progressive multiple sclerosis. It is most marked in secondary progressive disease and correlates with disability (Kalkers *et al* 2001; Lin *et al* 2003; Losseff *et al* 1996b). In primary progressive multiple sclerosis, significant atrophy of brain and cord over 1 year was evident in a large cohort of primary progressive patients drawn from six European centres (Stevenson *et al* 2000). Change in cerebral volume over this period correlated only weakly with change in $T_1$ and $T_2$ brain load. More recently, progressive cerebral and cervical cord atrophy has been observed over a 5 year follow-up in a cohort of 41 primary progressive patients with multiple sclerosis (Ingle *et al* 2003). The rates of atrophy appeared relatively constant within individual patients but varied between subjects.

Atrophy, however, is not confined to advanced stages of the disease. Brain atrophy is also seen in established relapsing–remitting multiple sclerosis within 3 years of the onset of symptoms (Chard *et al* 2002a). Both white and grey matter atrophy are observed (Chard *et al* 2002a; de Stefano *et al* 2003). Even early follow-up of patients with clinically isolated syndromes has shown that significant brain atrophy emerges over 1–3 years in those subjects who later develop multiple sclerosis. This is most clearly seen in the grey matter and also as progressive ventricular enlargement (Dalton *et al* 2002b; 2004a). The apparent absence of progressive white matter tissue loss at this early stage of disease may reflect bulk tissue compensation by inflammation or gliosis (Fernando *et al* 2004). Possibly, grey matter atrophy will be a more sensitive measure of neuroaxonal loss because inflammation is less evident in this location (Bo *et al* 2003b; Petersen *et al* 2001). Atrophy of about 10–15% has also been observed in the optic nerve following a single attack of optic neuritis (Hickman *et al* 2001). We discuss later the evidence for atrophy as an outcome in the context of specific clinical trials.

From these data emerge a crucial lesson for the pathogenesis of multiple sclerosis and the timing of its treatment. The point is made repeatedly throughout this and other chapters. Despite effective suppression of inflammatory MRI lesions, treatments may not slow the rate of ongoing cerebral atrophy (Coles *et al*

1999a; Filippi *et al* 2000a; 2000b; Molyneux *et al* 2000) or have only a modest effect (Filippi *et al* 2004b). While differences in tissue loss from baseline can be detected in multiple sclerosis within 12 months, little work has been done to determine the optimal sample sizes and length of study required to demonstrate significant slowing of progressive atrophy as a result of therapeutic intervention. This is a priority area for further research, which should include consideration of the stage of disease, type of data acquisition, method of image analysis, region of the central nervous system being studied, frequency of scanning, and other potential confounding factors such as age or concomitant atrophy due to reduction of oedema.

## Magnetic resonance spectroscopy: *N*-acetyl aspartate (NAA)

The main peak in the proton MR spectrum from human adult brain is *N*-acetyl aspartate (NAA), an amino acid contained almost exclusively in neurons and axons. A reduction in NAA provides evidence for axonal dysfunction or loss, and has been consistently reported in lesions and normal-appearing white matter in multiple sclerosis (Fu *et al* 1998). A greater reduction of normal-appearing white matter NAA is observed in secondary and primary progressive than relapsing–remitting multiple sclerosis, and disability has been correlated with reduced NAA in both cerebral (Sarchielli *et al* 1999) and cerebellar (Davie *et al* 1995) tissue. Decreased NAA (by 7%) has also been observed in cortical grey matter in early relapsing–remitting multiple sclerosis, suggesting that early neuronal cell body damage is occurring (Chard *et al* 2002b). It is reduced by c. 20% in thalamic grey matter in secondary progressive multiple sclerosis and, in a post-mortem study, the decrease in NAA (accompanied by atrophy) was associated with reduced numbers of neurons (Cifelli *et al* 2002).

Two approaches have been used to measure NAA: an absolute measure of concentration using an external standard reference of known concentration; and a ratio of NAA : Cr which assumes that Cr (creatine and phosphocreatine) remains stable in pathological situations. Although both approaches have produced robust evidence that NAA is reduced in the lesions and normal-appearing tissues, abnormalities of Cr may also occur. Therefore absolute measures are preferable. A methodological approach of recent interest is the quantification of whole brain NAA (Gonen *et al* 2000). This has been reported as low in patients with clinically isolated syndromes, implying extensive axonal damage even at this very early stage of disease (Filippi *et al* 2003). However, the resonance for whole brain NAA is broad and requires manual delineation for quantification – its analysis is potentially subject to bias and poor reproducibility. In contrast, the narrow NAA resonances from small voxels, obtained as a single region or as part of a spectroscopic imaging slice, can be automatically identified and quantified with a model that uses as reference a solution with a known concentration of NAA (Provencher 1993). Using such an approach, the normal-appearing white matter in patients with clinically isolated syndromes does not reveal a significant reduction of NAA (Fernando *et al* 2004). The time of onset and location of neuroaxonal damage should therefore be considered as uncertain.

A limitation of spectroscopy is the low signal to noise ratio and modest reproducibility of the measured metabolite concentrations. For this reason, it has been little used in multicentre therapeutic trials. Highlighting the problem, two small single-centre studies of patients treated with IFN-β have produced conflicting results. One study showed an increase in NAA, suggesting that therapy induced reversal of axonal dysfunction (Narayanan *et al* 2001). The other showed a decrease in NAA indicating that progressive axonal loss continues despite treatment (Parry *et al* 2003). Nevertheless, more vigorous efforts to investigate NAA as a surrogate outcome in trials of neuroprotection in multiple sclerosis are warranted, given that it provides specific information on axonal survival and function.

## Diffusion tensor imaging

Diffusion tensor imaging offers potentially more specific access to the integrity of white matter tracts. Fractional anisotropy indicates the orientation of diffusion and is high along well-defined pathways such as the corpus callosum, pyramidal tracts and optic radiations. A reduction in such pathways is therefore a potential marker of axonal structural integrity. Algorithms have been developed for identifying individual white matter tracts. Diffusion tractography can be performed using several approaches (G.J. Parker *et al* 2002). Problems arise where pathways cross and there are sharp bends in the tract. However, tractography algorithms can quantify the size and fractional anisotropy of major pathways in the brain such as optic radiation and pyramidal tract (Ciccarelli *et al* 2000b; 2003a).

## Other global measures

Many other quantitative MR measures have been applied to the study of multiple sclerosis. These include magnetization transfer ratio (MTR), $T_1$ relaxation time, and the apparent diffusion coefficient. Such measures are sensitive in depicting subtle abnormalities in normal-appearing white and grey matter, and convincing evidence has emerged that increasing abnormality in these tissues is associated with clinical progression (Filippi *et al* 1999a; Traboulsee *et al* 2003). However, these subtle MR changes do not denote specific pathological findings and could potentially represent the effects of inflammation, gliosis or axonal loss, each of which occurs in normal-appearing white matter (D.H. Miller *et al* 2003b). MTR may be valuable for monitoring clinically relevant disease progression in clinical trials. In a recent placebo-controlled study of IFN-β in secondary progressive disease, there was a significant increase in whole brain MTR abnormality in both the treated and placebo arms but no beneficial effect of treatment (Inglese *et al* 2003). This finding is consistent with lack of efficacy in the context of progressive disability. However, it is important to remember that progressive MTR abnormality may not be specific for neurodegeneration.

The process of neuronal and axonal degeneration is diffuse throughout the central nervous system and becomes more prominent with increasing disability and the progressive phase of multiple sclerosis. The two most specific MR methods for detecting neuroaxonal loss are atrophy and decreased NAA. For several reasons, atrophy has emerged as the preferred method for monitoring the neurodegenerative process in multiple sclerosis. Robust methods for detecting tissue loss are available. It is progressive from onset and increases with disability, correlates

only modestly with inflammatory lesions, and thus provides additional information in therapeutic monitoring. Whereas a number of existing therapies have shown good suppression of inflammatory lesions, an effect on progressive atrophy has been less evident (for review, see D.H. Miller *et al* 2002). Although other MR markers of diffuse disease (such as MTR) are not specific for axonal loss, along with atrophy they provide sensitive measures of a diffuse, progressive underlying process that relates to clinical progression. MTR measurement in lesions may have a more specific role in therapeutic monitoring in that decreases and increases (which are larger than the subtle changes seen in normal-appearing tissues) may reflect demyelination and remyelination, respectively (Barkhof *et al* 2003; Schirmer *et al* 2004).

It is therefore recommended that atrophy should be measured in trials aiming to prevent disability at all stages of disease (clinically isolated syndromes, relapsing–remitting, primary and secondary progressive) and, where feasible, NAA should also be measured along with other techniques (such as MTR) to monitor progressive normal-appearing white and grey matter. It is nevertheless important to remember that the MR surrogates for neuroaxonal loss and diffuse disease have not yet unambiguously been shown to predict future disability and its prevention by treatment. Long-term follow-up studies of well-characterized cohorts, including those participating in controlled clinical trials, are needed to clarify this relationship. Meanwhile, definitive trials should continue to measure an appropriate clinical end point.

## DRUGS THAT STIMULATE THE IMMUNE RESPONSE

In the past, attention was more or less equally divided between strategies designed to stimulate the immune system (initially, in the belief that immunological injury is sustained by persistent viral infection) or provide specific antiviral therapy, and those that suppress immunity. Now, it is clear that immune stimulants are either not effective or increase disease activity – perhaps as a result of increased expression of class II major histocompatibility complex (MHC) antigens on antigen-presenting cells. Some of these discarded treatments are briefly reviewed as part of the evidence that suppression of immunity and inflammation, not its stimulation, holds most promise for modifying the clinical course of multiple sclerosis.

### Isoprinosine

Isoprinosine is a physicochemical complex of inosine and the para-acetamidobenzoic acid salt of *N*,*N*-dimethylamino-2-propranolol, that enhances B-lymphocyte activity, perhaps through an effect on T helper cells. It also increases macrophage phagocytosis, release of cytokines that induce macrophage proliferation, including immune interferon and interleukin-1 (IL-1) and IL-2, and augments the action of T-cell mitogens (Hadden and Speafico 1985). Pompidou *et al* (1986) compared the clinical and immunological effects of isoprinosine, chlorambucil and a placebo preparation in a small cohort of patients with multiple sclerosis over 2 years. Relapses occurred in all patients treated with chlorambucil or placebo but in only a minority of those receiving isoprinosine. Relapses did not differ in severity between the three groups but the authors reported a reduction in disability associated with the use of isoprinosine. Immunological studies showed increased suppressor cell number and function in isoprinosine-treated cases, whereas cells with the T helper phenotype and delayed-type hypersensitivity were reduced in patients receiving chlorambucil.

Milligan and Compston (1994) used isoprinosine under double-blind, randomized and placebo-controlled conditions in 52 patients with relapsing–remitting or progressive multiple sclerosis. All patients initially received pulsed treatment with methylprednisolone. There was no significant effect of treatment on clinical disability or the accumulation of MRI abnormalities, after correction of results for multiple comparisons.

### Linomide

Linomide is an immunomodulator that appears primarily to affect natural killer cells without inducing the release of IFN-γ. It also increases T-cell proliferative responses, the proportion of the CD45-Ra-positive subpopulation and IL-2 production. Its use in multiple sclerosis arose from the apparent ability of linomide to prevent and reverse the clinical and histological manifestations of experimental autoimmune encephalomyelitis (see Chapter 11). Karussis *et al* (1996) evaluated linomide (2.5 mg/day for 6–12 months) in 24 patients with secondary progressive multiple sclerosis who had deteriorated by >1 EDSS point in the previous 2 years, and showed either three regular or one enhancing MRI lesions on a single screening scan. There were no major adverse effects although minor events were reported in a high proportion of all participants. On this evidence, linomide appeared safe. An increase in disability (EDSS) at 6 months occurred in three of the 15 linomide-treated patients, and in six of the 15 placebo-treated patients; five and two of the 15 cases improved, respectively. Active lesions were present in 16% of linomide-treated patients and 33% of the placebo group at onset. Subsequently, 11 of 33 (33%) and 24 of 32 (75%) had active scans, with a difference in mean number of new enhancing lesions of 0.2 and 0.4 per scan, respectively.

Andersen *et al* (1996) reported a somewhat greater range and prevalence of adverse effects (one requiring drug withdrawal and another a reduction in dose) in 28 patients with relapsing multiple sclerosis randomized to oral linomide (2.5 mg/day for 6 months). MRI showed a lower rate of active $T_2$-weighted lesions in treated patients (1.4 compared with 4.2 in the placebo group; 0.8 and 2.6 for new lesions, respectively; constituting a 68% reduction in activity) and this effect seemed to increase with the duration of treatment. Three patients on linomide had four relapses and six of the placebo group had nine new episodes. Whilst the placebo group showed no change in disability, patients on linomide had a modest reduction in EDSS (–0.4). The numbers who improved, remained unchanged or deteriorated were ten, one and three in the treated group, respectively, compared with five, one and eight in the placebo-treated patients.

Enthusiasm for the use of linomide in multiple sclerosis collapsed with the decision to terminate early the North American and European phase III trials after enrolling >1380 patients with relapsing–remitting and secondary progressive multiple sclerosis because of serious cardiopulmonary and other adverse effects in the treated groups (Noseworthy *et al* 2000c; I.L. Tan

*et al* 2000; Wolinsky *et al* 2000). Two linomide-treated patients died in the course of the trial from suspected cardio-pulmonary complications of linomide, but autopsies were not performed. An unacceptable number of patients treated with linomide developed pleuro-pericarditis (nine patients), chest pain, myocardial infarction (five patients), and possible pulmonary embolic disease as well as arthralgia, myalgia, bursitis and facial and peripheral oedema. These trials again emphasize that experimental treatments can place patients at risk of life-threatening adverse events. The importance of scrupulous surveillance by data-monitoring committees cannot be overstated. If there are safety concerns, immediate action may be needed to lessen risks to patients. Unless a preventable mechanism for these events becomes apparent, it looks as if linomide will join the ranks of drugs no longer to be used in patients with multiple sclerosis. However, Polman *et al* (2005) have recently studied the oral agent laquinimod (ABR-215062), a synthetic compound structurally related to roquinimex (linomide) in a randomized, double-blind, placebo-controlled trial of 209 patients with multiple sclerosis in three groups (laquinimod 0.1 mg or 0.3 mg, or placebo daily for 6 months). There were no serious adverse side effects (notably, no cardiopulmonary events or serositis; see above for linomide). High-dose laquinimod reduced the frequency of active MRI lesions significantly compared with placebo. These results, if confirmed in a larger controlled trial of sufficient duration and statistical power, suggest reasons for optimism in the search for oral agents that might one day simplify the management of relapsing–remitting multiple sclerosis.

## Interferon-γ

The clinical trial of IFN-γ reported by Panitch *et al* (1987a, 1987b) proved extremely influential because it made patients worse and so told an important story (Figure 18.2). The logic for using IFN-γ was based on the hypothesis that multiple sclerosis is caused by persistent viral infection or an immunoregulatory defect that requires stimulation. If the study had shown clinical benefit in such a small group of patients, replication would have been immediately demanded, but this result was readily accepted because, at the time of publication, knowledge of autoimmune processes had advanced to the stage where it could be predicted that disease activity would increase with promotion of class II MHC molecule expression. Panitch *et al* (1987a; 1987b) recruited 18 patients known retrospectively from case records to have had two or more relapses in the previous 2 years. All were in remission and ambulatory at the start of treatment. Follow-up was to be for 6–12 months after receiving three doses of IFN-γ (1, 30 and 1000 mg by intravenous injection) on eight occasions over 4 weeks. Within 1 month of treatment, seven of the patients had experienced a new relapse. Based on pretreatment rates, no more than two relapses were expected. Onset and severity were unrelated to the dose given. Recovery was complete and the relapse rate stabilized during follow-up at the former frequency with no overall change in disability. There was an increase in MHC class II-positive circulating lymphocytes. The implication of the study was that systemic IFN-γ had a rapid and causal effect on stimulating inflammatory processes within the central nervous system. In their discussion, the authors recommended others to assess treatments, including IFN-α and IFN-β, that specifically inhibit IFN-γ. Not surprisingly, this study is often cited as a clear example of clinical science in which lessons learned from the experience of treatment led to new concepts of disease mechanisms and, in turn, the development of more rational and effective therapies. Self-evidently, there are no subsequent studies on which to comment.

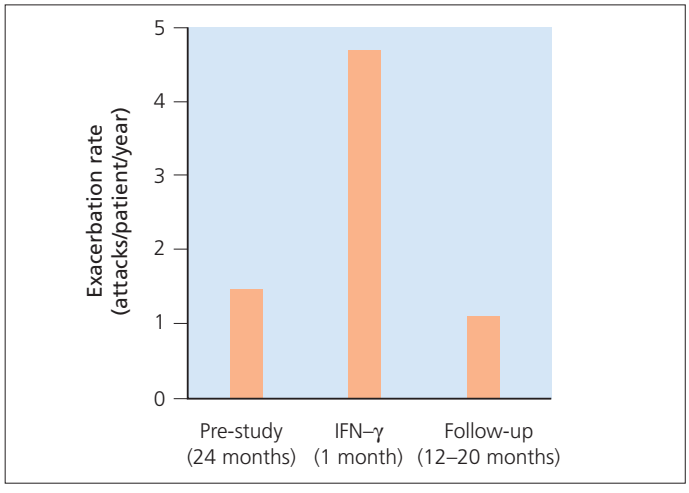



**Figure 18.2** Increase in exacerbation rate during treatment with IFN-γ compared with pretreatment and follow-up periods. Adapted from Panitch *et al* (1987b). © 1987, with permission from Elsevier.

## Interferon-α

The demonstration of a deficient interferon response in patients with multiple sclerosis stimulated the use of IFN-α at a time when the adverse effects of IFN-γ and the logic for using anti-inflammatory cytokines were not fully understood. Fog (1980) failed to show a beneficial effect on the disease course over 18 months in six patients with chronic progressive multiple sclerosis openly treated with intramuscular IFN-α. Next, Knobler *et al* (1984) reported fewer and shorter new episodes during IFN-α treatment in 24 patients with relapsing multiple sclerosis compared with retrospective assessment of relapse frequency over 2 years before starting the trial. Although the crossover design made for difficulties in judging the magnitude of this treatment effect, there was a reduction in relapse frequency with time in all participants. This was most apparent in patients receiving IFN-α after the placebo period. The reduction in relapse rate was maintained and improved in those patients showing a treatment effect over the initial 2 year period of observation in the subsequent 2 years, but the extent to which this could be attributed to treatment rather than to the natural history of the disease remained uncertain. Compared with the relapsing–remitting patients, those with relapsing progressive disease demonstrated evidence of mild to moderate symptom worsening during the prestudy period and they continued to have exacerbations during treatment (Figure 18.3). There was no effect on disability (Panitch 1987). Recombinant IFN-α, given by self-administered subcutaneous injection three times weekly for 1 year, was first used in a study of 98 patients with multiple sclerosis with at least two relapses during the previous 2 years. The results were not encouraging. All patients showed a reduction in relapse rate as part of the natural history of the

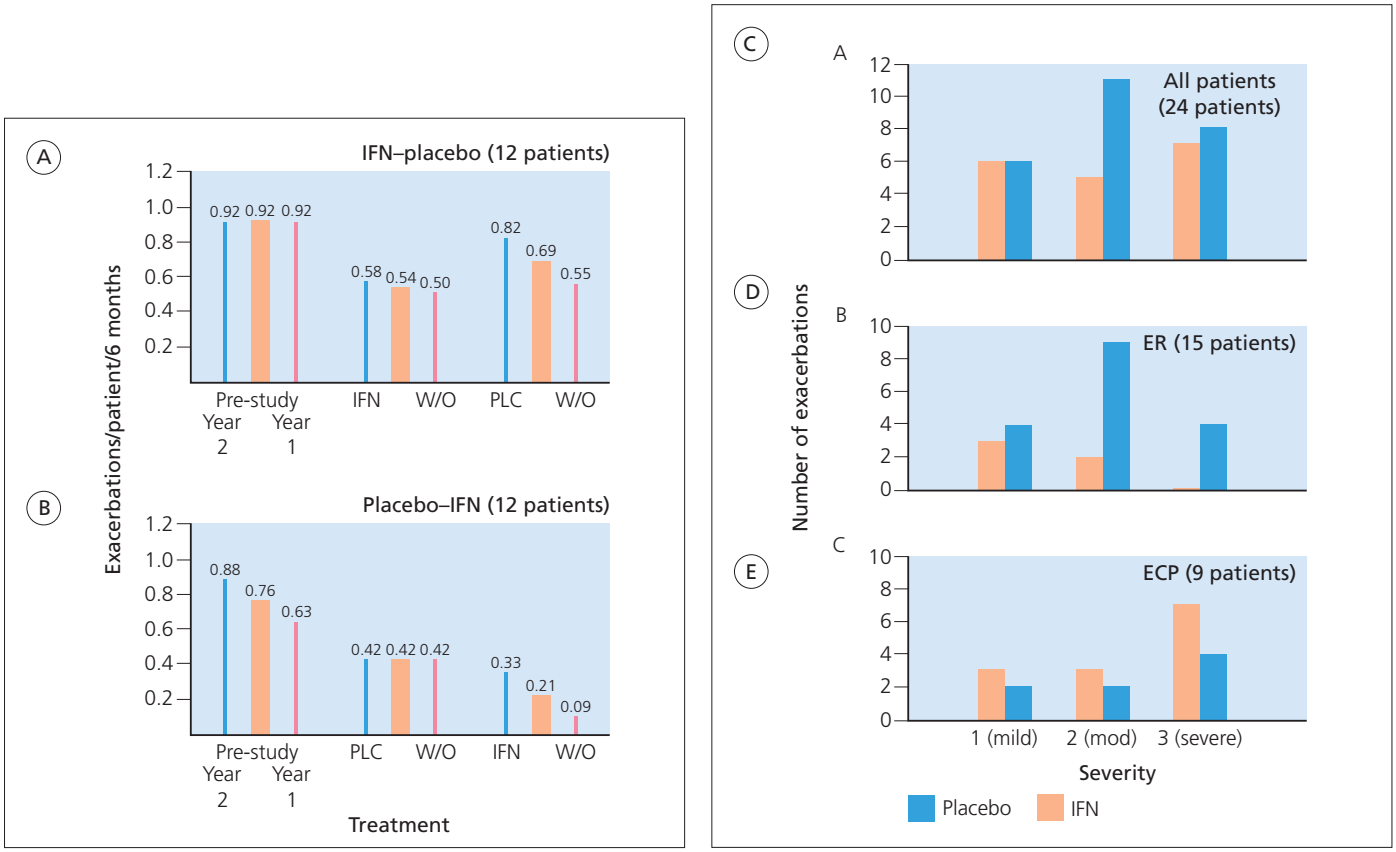



**Figure 18.3** Treatment of multiple sclerosis with IFN-α. (A and B) Relationship between treatment sequence and response. The effect of interferon (IFN), placebo (PLC) and respective washout (W/O) periods on mean number of exacerbations/patient/6 month period are indicated by red and blue solid lines. The orange bars are average values for the flanking red and blue lines. Exacerbations occurring during prestudy year 2 or year 1 are also expressed per 6 month period. There is a greater reduction in exacerbation frequency associated with the PLC–IFN sequence than the IFN–PLC, which may reflect carryover effects of the crossover design or composition of the two groups. (C–E) Relationship between subgroup of multiple sclerosis patients, treatment and exacerbation severity. The latter was graded as mild (MLD), moderate (MOD) or severe, dependent on change in the Scripps (SNRS) score and duration of the exacerbation in days, during IFN and placebo treatment and respective washout periods. (C) IFN did not appreciably alter exacerbation severity when all 24 patients were compared. (D) However, the 15 exacerbating–remitting (ER) patients had no severe and fewer moderate exacerbations ($p = 0.10$) on IFN compared with placebo. (E) In contrast, the nine exacerbating chronic progressive (ECP) patients had more exacerbations of each grade during IFN treatment than during placebo treatment. Adapted from Knobler *et al* (1984). © 1984, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

disease. However, more treated than placebo cases moved from the relapsing to the progressive phase of the disease and, unlike those on placebo preparations, treated cases experienced an increase in disability after discontinuing treatment (Camenga *et al* 1986).

It is perhaps surprising that, in the face of these results, Durelli *et al* (1994) repeated the study of IFN-α given by intramuscular injection on alternate days to patients with relapsing–remitting multiple sclerosis. Individuals on IFN-α showed a lower exacerbation rate (Figure 18.4), longer time to first relapse, and milder episodes less often requiring supplementary treatment with corticosteroids compared to the placebo group. However, disability was unaffected. Fatigue and other systemic adverse effects associated with the use of interferon were the main complications of treatment. There was an effect on disease activity measured by MRI. One of 12 patients on active treatment had a single enlarging lesion (which corresponded to a new clinical episode) whereas six of the eight controls had both new and enlarging lesions (27 of either type, equivalent to five for each active scan). The treated group also showed some suppression in the systemic production of IFN-γ.

In a follow-up study, Durelli *et al* (1996) examined the resumption of clinical, MRI and immunological activity in patients who had to discontinue IFN-α (after 6 months of treatment) for administrative and financial reasons. In the four 6 month epochs preceding treatment, the numbers of patients remaining relapse free in the 12 patient cohort later randomized to IFN-α were two, one, four and three. The numbers without episodes in the group of eight patients randomized to placebo were two, zero, three and one, respectively. Against the background of these baseline estimates, two further relapses occurred during treatment with IFN-α compared with eight in the placebo group. In the 6 months after completion of the active treatment phase, there were three relapses in individuals who had received IFN-α compared with four in the placebo group. The numbers of patients remaining relapse free during and after the period of treatment with IFN-α were ten and nine, compared with two and four of the eight patients in the placebo

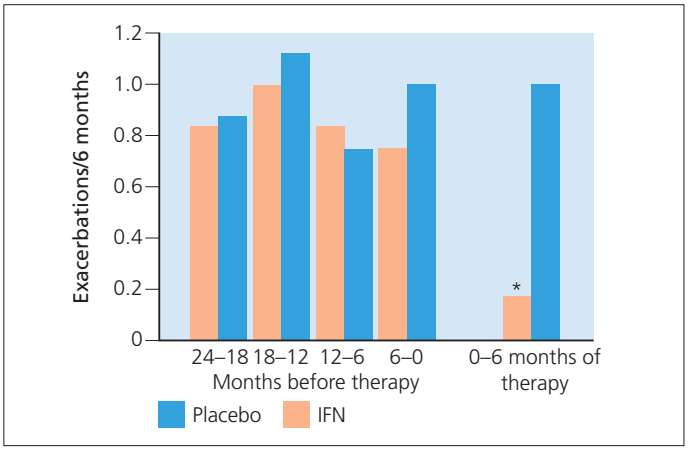



**Figure 18.4** Exacerbation rate (calculated on a 6 month basis) in the 2 years before and during treatment for patients receiving high-dose systemic recombinant IFN-α2a (IFNA) or placebo. Asterisk indicates significantly different from prestudy ($p \leq 0.03$) and from placebo ($p \leq 0.03$) groups. Adapted from Durelli *et al* (1994). 

group. Taken together, these observations suggest a transient increase in the number of relapse-free patients during treatment with IFN-α.

The MRI results also suggested a transient reduction in disease activity which reversed on discontinuing treatment with IFN-α. There was one active lesion in the IFN-α patients during treatment and 14 after treatment, compared with 27 and 17 in the placebo group, repectively. Corresponding results for the number of active scans were one (during) and six (after) of the 12 IFN-α-treated patients, compared with six and six for the placebo group. There was no obvious effect on disability during treatment or apparent acceleration after discontinuing IFN-α. Durelli *et al* (1996) concluded that two of the 12 patients receiving IFN-α and seven of the eight placebo-treated patients had active disease during treatment, compared with six (IFN-α-treated) and six (placebo-treated) after completion of the active treatment phase. Immunological assessments showed that reduced IFN-γ and TNF-α levels, associated with the use of IFN-α for 6 months, also returned to baseline values on discontinuing treatment. Adverse effects attributed to the use of IFN-α were reversed within 1 or 2 months of treatment. This study adds to the evidence that clinical, radiological and immunological observations can directly be attributed to IFN-α, but are rapidly washed out on discontinuing treatment.

Myhr *et al* (1999b) randomized 97 patients with relapsing–remitting multiple sclerosis to receive either 4.5 or 9 million international units (MIU) of IFN-α2a or placebo, by subcutaneous injection three times weekly for 6 months. Relapses were not reduced although monthly MRI measures suggested a possible benefit during the period of treatment. The authors reported that neutralizing antibodies developed early in the group given low-dose IFN-α, and they speculated that this may have reduced the treatment effect. However, as discussed below, in most of the large-scale recent IFN-β trials, changes in clinical and MRI measures of disease activity correlating with antibody formation are generally difficult to detect unless a large number of patients are followed up for a protracted period. Brod *et al* (2001) reported that oral IFN-α2a (10 000 or 30 000 units administered on alternate days for 9 months) was no better than placebo in suppressing MRI evidence of disease activity in a study of 30 patients with relapsing–remitting multiple sclerosis. However, despite some favourable results, we understand that IFN-α is not to be developed further for use in patients with multiple sclerosis.

## Transfer factor

Although the biological properties of IFN-α were already characterized, patients with multiple sclerosis were also treated in the 1980s with transfer factor – a dialysable leucocyte extract thought to restore cell-mediated immunity and to have antiviral actions similar to IFN-α and IFN-β. The AUSTIMS Research Group (1989) compared these two biological reagents [IFN-α ($3 \times 10^6$ units); transfer factor (0.5 units) made from the leucocytes of cohabitees to maximize the prospect of achieving specificity against whatever agent might be causing multiple sclerosis] with placebo preparation(s) in 182 patients. There was no stratification for relapsing versus progressive disease. Clinical outcome was assessed using the EDSS. There was no difference in progression of disability between groups and no apparent effect of treatment on laboratory indices. In fact, the only clear result was that transfer factor was poorly tolerated and many individuals withdrew from the treated group. Soon after, van Haver *et al* (1986) treated 105 patients with multiple sclerosis (a mixed group with relapsing–remitting and secondary progressive disease) using transfer factor prepared from the leucocytes of random donors or family members. They also failed to demonstrate an effect on disability, activities of daily living or laboratory indices of demyelination. Treatment did not affect IFN-γ production.

## Aciclovir

Although not strictly an immune modulator, we include discussion of the antiviral treatment, aciclovir, because (as with IFN-γ) it has been used on the basis that tissue injury in multiple sclerosis might result from persistent viral infection. Aciclovir (2.4 g orally for 2 years) has been evaluated in 60 patients with frequent relapses but very few persistent disabilities (C. Lycke *et al* 1996). There was a reduction in relapse frequency (from 1.7 to 1.0 in the aciclovir group and from 1.7 to 1.6 in placebo-treated patients; $p = 0.08$). Aciclovir did not affect the time to first and second exacerbations over the 2 years of the study. Despite the reduction in relapse rate, patients accumulated clinical deficits at an equivalent rate in both groups and there was no difference in disability on completion of the study. This dose of aciclovir achieved some reduction in herpes simplex virus-2 but not varicella zoster, Epstein–Barr virus or cytomegalovirus antibody titres. As expected, aciclovir was well tolerated with few adverse effects.

A second phase two, randomized, double-blinded, placebo-controlled study of anti-herpes therapy was reported by Bech *et al* (2002). They compared valaciclovir (1 g orally three times daily for 24 weeks) with placebo in 70 patients with relapsing–remitting multiple sclerosis. To be eligible, patients needed to have a history of two or more relapses in the previous 2 years yet still be ambulatory (EDSS 0–5.5). The primary outcome

(number of new active MRI lesions over the 24 week course of the trial) was negative (valaciclovir: 11.9 ± 17.6 SD; placebo 14.5 ± 21.4 SD) and there were no differences in any of the clinical end points. A planned exploratory analysis detected that the valacilovir-treated patients who had at least one active MRI lesion during the pretreatment phase of the trial (4 weeks plus baseline MRI) had fewer new MRI lesions and were more likely to remain free of new MRI evidence for disease activity during the treatment period. An accompanying editorial encouraged further well-designed trials with antiviral agents while acknowledging that valaciclovir at conventional doses has no apparent role in the treatment of multiple sclerosis (Goodman and Miller 2002). Friedman *et al* (2005) reported that a placebo-controlled, randomized trial of valaciclovir (3000 mg/d) involving 58 patients with multiple sclerosis failed to demonstrate convincing clinical or MRI evidence for benefit although there were statistical trends in favour of some outcomes in the most severely affected patients.

Against this background, the further use of drugs that are known to stimulate one aspect or another of the immune response seems inappropriate and unlikely to satisfy scrutiny by ethical committees. Rather, the focus of therapeutic attention has turned to a range of strategies that have in common suppression of the immune response. It would take a very churlish observer to conclude that nothing has been learned and no patients helped from this approach (but such therapeutic nihilists exist). Equally, no informed critic could reasonably argue that the achievements to date are anything other than modest and represent no more than an indicator of the way forward. Perhaps, the crucial limitation has been the timing of treatment and the exposure of patients to drugs that are not fully appropriate for the stage reached in the illness by that particular patient. Now, we review in detail the various drugs that suppress one aspect or another of the immune response through a variety of mechanisms – some identified, others mysterious.

## DRUGS THAT NONSPECIFICALLY SUPPRESS THE IMMUNE RESPONSE

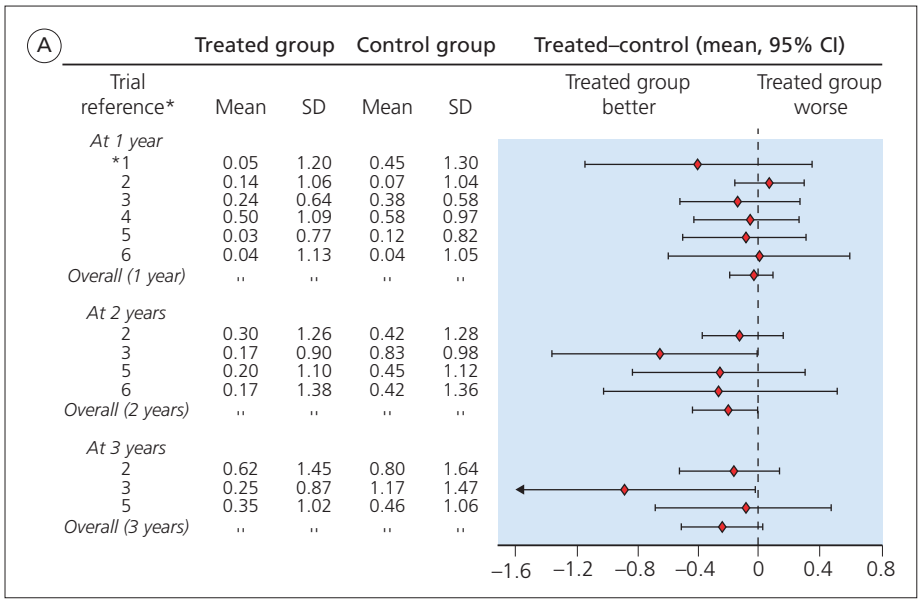
Advances in understanding the nature of tissue injury in multiple sclerosis, and the lessons from attempts to stimulate the immune response and so purge the nervous system of persistent viral infection, prompted the use of drugs that suppress the immune response. This seemed logical even though most inflict prolonged punishment on the whole immune system for the misdemeanours of a small proportion of its constituent cells.

### Azathioprine

Azathioprine, used for many years to treat individual patients with multiple sclerosis, was evaluated in clinical trials during the 1970s and 1980s (Mertin *et al* 1982; U. Patzold *et al* 1982; Rosen 1979; Swinburn and Liversedge 1973). The possibility that this reasonably well-tolerated nitroimidazole substituted form of 6-mercaptopurine might reduce progression of the disease in patients with moderately severe forms of multiple sclerosis prompted the (United Kingdom) Medical Research Council to sponsor a double-blind, placebo-controlled trial involving 354 unselected patients, on the advice of its working party on clinical trials (British and Dutch Multiple Sclerosis Azathioprine Trial Group 1988b). There was slower deterioration and fewer relapses in patients treated with azathioprine but these differences were not statistically significant or considered clinically useful for the individual patient. Other work in progress at that time was subsequently reported including a trial in which small numbers of patients were treated with azathioprine, methylprednisolone or placebo preparations. The treatment groups each contained fewer than 30 patients (Ellison *et al* 1989). No significant differences emerged, although subgroup analysis showed that patients tolerating the combination of active treatments deteriorated less rapidly. The authors recommended that, because of the poor risk to benefit ratio, azathioprine should not be given alone or with corticosteroids to patients with progressive multiple sclerosis. After publishing a preliminary account, and including their data in the meta-analysis of azathioprine (see below), Milanese *et al* (1993) subsequently provided a final report on their study of 40 patients with relapsing or chronic progressive multiple sclerosis receiving 2 mg/kg/day for 3 years. There was a very high drop-out rate but the authors concluded, on an intention to treat analysis, that a treatment effect was demonstrated on relapse rate (90% remained relapse free on azathioprine vs. 60% of the placebo group) and the proportion of patients remaining clinically stable (62% vs. 18%).

Kappos *et al* (1990) reported on 37 matched pairs selected retrospectively from amongst 277 with clinically definite multiple sclerosis who had all been fully ambulant when treatment with azathioprine was started >10 years previously. Six treated patients were bedridden and four had died compared with 13 and eight, respectively, amongst untreated historical controls. The mean EDSS at 10 years was less in the azathioprine-treated group (4.9 vs. 6.0). There were similar numbers of patients in both groups who remained nearly normal (EDSS 0–2.5), reflecting again the important observation that a subgroup of untreated patients with multiple sclerosis remain with limited disability for prolonged periods. Goodkin *et al* (1991) also showed a lower relapse rate in 43 of 59 patients recruited to a study of azathioprine (3 mg/kg/day) compared with placebo in relapsing multiple sclerosis. Annual pretreatment, year 1 and year 2 rates in the azathioprine and control groups were 1.6, 0.7 and 0.3 and 1.5, 1.2 and 0.8, respectively. The numbers having a relapse in years one and two, for each group, were 16 and 7, and 17 and 11, respectively. The proportions showing progression in the EDSS and ambulation index in the treated group were 19% and 22% compared with 32% and 40%, respectively, in the placebo group. Not surprisingly, azathioprine does not prevent the onset of multiple sclerosis. Constantinescu *et al* (2000) described two patients developing multiple sclerosis after treatment for inflammatory bowel disease with azathioprine after 3.5 and 10 years, respectively.

Against this background of small studies suggestive of a treatment effect, Yudkin *et al* (1991) performed a meta-analysis of published trials. Ten were considered, of which seven were included. In five, the design was double-blind and placebo-controlled but not all had been analysed on an intention to treat basis. Of the 793 participants, 719 (91%) were followed for at least 1 year, 563 for 2 years and 459 for 3 years (with information available on 94% and 90%, respectively). Patients with relapsing–remitting and both primary and secondary progressive multiple sclerosis were included but evenly distributed between



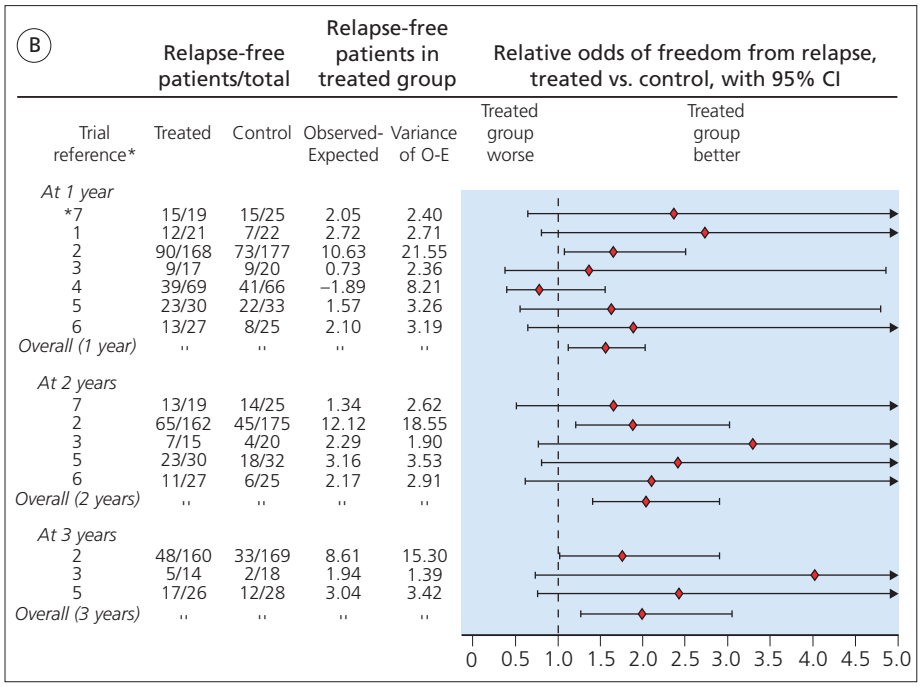




**Figure 18.5** Meta-analysis of treatment trials using azathioprine in multiple sclerosis. (A) Changes in [E]DSS. (B) Probability of freedom from relapse. Adapted from Yudkin *et al* (1991). References: 1 = Mertin *et al* (1982); 2 = British and Dutch Multiple Sclerosis Azathioprine Trial Group (1988); 3 = Milanese *et al* (1988); 4 = Ghezzi et al (1989); 5 = Ellison *et al* (1989); 6 = Goodkin *et al* (1991); 7 = Swinburn and Liversedge (1973). © 1991, with permission from Elsevier.

active and placebo treatment groups. The odds ratio for a treatment effect achieving a reduction in the EDSS attributable to azathioprine was –0.03 (95% CI –0.19, +0.12) but this had increased after 2 and 3 years to –0.22 (95% CI –0.43, +0.003; $p \leq 0.06$) and –0.24 (95% CI –0.51, +0.03; $p < 0.09$: Figure 18.5A). The probability of remaining free from relapse, attributable to azathioprine, at 1, 2 and 3 years was 1.5 (95% CI 1.1–2.0; $p < 0.01$), 2.0 (95% CI 1.4–2.9; $p < 0.001$) and 2.0 (95% CI 1.3–3.0; $p < 0.01$), respectively (Figure 18.5B).

Although the mode of action of azathioprine is well established, little is known concerning its effects on those aspects of immunity considered most relevant to multiple sclerosis. Salmaggi *et al* (1997) compared a range of immunological markers in individuals receiving up to 3 mg/kg azathioprine daily and untreated patients with multiple sclerosis. Therapy was characterized by pan-neutropenia which disguised selective increases attributable to azathioprine in the proportion of lymphocytes coexpressing the CD3/4, CD3/56, CD3/16 and CD4/45Ra markers, with a corresponding reduction in natural killer cells (but not natural killer cell activity) and TNF-α production. There was no effect on immunoglobulin production despite the increase in CD4/45Ra cells. These findings do not obviously enhance our understanding of the immunopathogenesis of multiple sclerosis or provide an independent logic for reintroducing azathioprine as a disease-modifying treatment in multiple sclerosis.

Reduction in relapse rate with a delayed and modest effect on disability anticipates results subsequently obtained using the currently licensed therapies but the tone of discussion around these earlier treatments could not have been more different. The meta-analysis of azathioprine is a model of caution and

understatement, emphasizing that the effects are modest, probably explained by interobserver variation, of doubtful value to the individual patient, quite possibly attributable to unblinding, and potentially posing serious long-term risks. Nevertheless, until the advent of IFN-β, many clinicians used azathioprine in patients with multiple sclerosis despite general concern over the long-term risks (Kinlen 1985). Reassuringly, Amato *et al* (1993) provided evidence against an increased rate of malignancy in patients with multiple sclerosis receiving azathioprine. Five of 207 patients taking 2 mg/kg daily for a mean of 4.2 years developed a malignancy compared with seven of 247 controls, giving prevalence rates of $3.6/10^3$ patients (95% CI 1.2–8.4) and $4.2/10^3$ patients (95% CI 1.7–8.7) and a relative risk (RR) of 0.8 (age adjusted) for cancer in the treated patients with multiple sclerosis. In a more detailed assessment, Confavreux *et al* (1996) showed in a case–control study that 14 of 23 patients with multiple sclerosis who developed one form or another of cancer had been treated with azathioprine for at least 1 month (RR = 1.7; 95% CI 0.6–4.6). There was a direct relationship between risk and duration of exposure (<5 years, RR = 1.3, 95% CI 0.4–4.0; 5–10 years, RR = 2.0, 95% CI 0.4–9.1; >10 years: RR = 4.4; 95% CI 0.9–20.9). Nevertheless, adverse effects appear to influence decisions over the use of azathioprine.

Most clinicians concluded, when these studies were published, that the clinical benefits of azathioprine fall short of satisfactory treatment for the individual patient, and as new immunosuppressants became available, they were evaluated in the hope that the new medicines would prove more effective. Nevertheless, azathioprine has not disappeared from the list of drugs used in multiple sclerosis. Some consider that prolonged oral azathioprine is no less effective than IFN-β and glatiramer acetate – since efficacy was not evaluated using MRI outcomes at the time opinions were being formed. Later, Massacesi *et al* (2000) reported that MRI measures of disease activity were reduced by treatment with azathioprine in 14 patients followed for 2 years. Meanwhile, Palace and Rothwell (1997) reviewed published data for the 2 year probabilities of freedom from relapse with each of the approved but partially effective agents including azathioprine and compared these projections with the observed outcomes of placebo-treated patients from these studies. The overall odds ratios for an effect on relapse rate demonstrated that oral azathioprine may indeed be comparable to the now more widely used parenteral agents (glatiramer acetate, 1.37; IFN-β1a, 1.68; IFN-β1b, 2.38; intravenous immunoglobulin, 2.01; and azathioprine 2.04) – and at a fraction of the cost (Clegg and Bryant 2001).

The recent trend has been to use azathioprine in combination with other therapies. Intravenous immunoglobulin was given in divided doses (total 2 g/kg) over 72 hours followed by monthly infusions of 0.2 g/kg for 3 years to 38 patients with relapsing–remitting multiple sclerosis who also received oral azathioprine (3 mg/kg/day: Kalanie and Tabatabai 1998). Combination therapy was well tolerated by the 34 patients completing this trial. After 3 years of monthly evaluations by an assessor blinded to details of the protocol, no patients developed clinical evidence of worsening (relapse rate or disease progression). These results are rather remarkable, and more favourable than expected from experience with natural history and clinical trial data sets. However, the study was uncontrolled and, to date, has not been replicated. Moreau *et al* (2001) reported that the combination of azathioprine and IFN-β1a appears safe and well tolerated, at least for the 6 months of follow-up available at the time of abstract submission – but, to date, the study has not generated a full research publication. Recently, Lus *et al* (2004) reported their small prospective study of 23 patients treated with a combination of azathioprine and IFN-β1a (Rebif) followed for 2 years. For the purpose of data analysis, patients were considered in three groups: previously untreated individuals (n = 8) and patients previously treated with either azathioprine (n = 8), or IFN-β1a (n = 7). Combination therapy was safe and generally well tolerated. Relapse rates and MRI evidence of disease activity ($T_2$ lesions, contrast enhancements and $T_1$ hypodense lesions) were reduced in the prospective phase of the study compared with historical data. In a small study (n = 6), Markovic-Plese *et al* (2002) reported that the combination of azathioprine and IFN-β1b (Betaseron) provided synergistic effects on stabilization of the blood–brain barrier as determined by MRI studies.

Whilst alert to the changing landscape of treatment trends in multiple sclerosis, at present we do not routinely use azathioprine, pending evidence of superior efficacy and adequate safety from contemporary controlled trials but it remains an acceptable approach in patients who are unable to contemplate injected therapies. That said, Craner and Zajicek (2001) consider that, unlike those with myasthenia gravis or rheumatoid arthritis, the majority of patients with multiple sclerosis (55%) are unable to tolerate azathioprine. It has been recommended that levels of thiopurine methyltransferase should be measured in advance of a prescription, so as to avoid serious bone marrow toxicities (F.J. Thomas *et al* 2001; Weinshilboum and Sladek 1980).

## Ciclosporin

Although not now routinely used in clinical practice or featuring in new trial protocols, we retain our earlier account of ciclosporin (formerly cyclosporine) for the lessons it provides in the evolution of ideas concerning the basis for treatment in multiple sclerosis. In a modest way, ciclosporin influences progression of multiple sclerosis, relapse rate and severity but only at doses that produce unacceptable adverse effects. Rudge *et al* (1989) showed no difference in the number of patients remaining relapse free between ciclosporin-treated and placebo-treated groups during a 2 year clinical trial. However, episodes were more frequent in the placebo group, and these were judged to be more severe and to have occurred earlier. More ciclosporin-treated patients than controls remained stable, in terms of the EDSS, over the first 6 months of the trial but this effect was not maintained thereafter. One difficulty that arose was the need to stratify the analysis to account for a centre effect. Selection of patients on the basis of clinical course and the dose of ciclosporin that was tolerated differed between the two participating centres. Critics therefore assume that, for many participants, the study was unblinded. They worry about the dependence on subgroup analysis and conclude that there is no clinical role for ciclosporin. We know of very few patients with multiple sclerosis in whom this immunosuppressant is still used. This trial taught the useful lesson that the course of multiple sclerosis is more likely to be altered by immunological treatments used at doses producing significant adverse effects that outweigh the modest clinical advantages. In a comparison with

azathioprine, low-dose ciclosporin is shown to be less well tolerated and no more beneficial in terms of disease stabilization (Kappos *et al* 1988). Although the participants experienced very little deterioration during the trial, this study was not designed to show that either drug influenced the natural history of the disease.

Subsequently, in a placebo-controlled study of ciclosporin involving 547 patients with moderate to severe progressive multiple sclerosis (EDSS between 3 and 7 with a change in the year before entry of between 1 and 3 points) treated with a range of doses, some aspects of disability were significantly influenced. However, a substantial number of patients withdrew from the active treatment group because of adverse effects, notably nephrotoxicity and hypertension (Multiple Sclerosis Study Group 1990). Reduction in the mean increase in EDSS in treated patients compared with controls (0.39 ± 1.07 vs. 0.65 ± 1.08; mean ± SD) was associated with delay in time to use of a wheelchair but not to sustained progression, and there was no effect on activities of daily living. Ruutianen *et al* (1991) compared ciclosporin (7.5 mg/kg) with oral prednisolone (tapering from 0.8 mg/kg). Despite no immediate difference in outcome, greater improvement was reported in patients on corticosteroids at 3 months. There was no difference in the frequency of adverse effects.

Taken together, clinicians are not persuaded that ciclosporin represents a significant advance over the modest effects associated with the use of azathioprine. Long-term oral therapy with azathioprine appears better tolerated but not sufficiently useful (see above), whereas ciclosporin is considered more effective but unacceptably complicated in patients with multiple sclerosis.

## Cyclophosphamide

The same problems have characterized the evaluation of treatment with cyclophosphamide. This immunosuppressant has been used on an open uncontrolled basis for many years, especially in continental Europe. Attention was drawn to its use with the publication of a study reporting that high-dose intravenous cylcophosphamide stabilizes the clinical course in patients with progressive multiple sclerosis when given with corticotropin by comparison with patients receiving corticotropin alone, or plasma exchange with corticotropin and low-dose oral cyclophosphamide (S.L. Hauser *et al* 1983). By present standards, this study was of short duration and underpowered, only involving between 18 and 20 patients in each arm. Summarizing the quantitative observations in an overall qualitative assessment, four of the 20 patients receiving corticotropin stabilized or improved at 1 year, compared with 16 of the 20 patients in the cyclophosphamide/corticotropin group and nine of 18 patients in the plasma exchange. As a result of this trial, many patients received high-dose intravenous cyclophosphamide for several years, tolerating a variety of unpleasant short-term adverse effects in the hope of disease stabilization. Subsequent experience with dose ranging studies in which maintenance therapy was adjusted against indices of immune suppression (circulating CD4 counts) merely confirmed the potential toxicity of cyclophosphamide and led some to conclude that the drug is too toxic for routine use (L.W. Myers *et al* 1987). Nevertheless, an approach using repeated pulses of well-tolerated doses, given at monthly or longer intervals, was later evaluated in 14 patients using a partial crossover design. Those treated with cyclophosphamide were considered to have less frequent and shorter episodes than the placebo group and the trial sustained the belief that the beneficial effects of cyclophosphamide could be maximized and the adverse effects could be reduced using pulsed therapy (Killian *et al* 1988).

The Kaiser study (Likosky *et al* 1991) examined the efficacy of pulsed intensive immunosuppression with intravenous cyclophosphamide (c.500 mg/day until the leucocyte count reached $<4000/mm^3$) given in an outpatient setting under randomized single-blind conditions with folic acid as the comparator. At 1 year, 14 of 22 (64%) immunosuppressed patients were unchanged or stable compared to 14 of 20 (70%) taking folic acid. At 2 years, the figures were nine of 19 (47%) and nine of 17 (53%), respectively. There was no change in the rate of disability at 1 year between groups and each had worsened by approximately 0.5 EDSS points. However, at 2 years, patients on folic acid were accumulating disability at a faster rate than immunosuppressed patients (+0.4, 95% CI 0.4–1.2: the corresponding figure for the ambulation index was +0.8, 95% CI 0.5–2.2). Throughout, the authors nicely understate these results showing wide confidence intervals, in marked contrast to some other enthusiasts for the use of cyclophosphamide.

The definitive clinical trial of cyclophosphamide involved 168 patients (Canadian Co-operative Multiple Sclerosis Study Group 1991). Participants had progressive multiple sclerosis which had deteriorated by >1 EDSS point in the previous year. The proportions showing sustained deterioration of a further point (or more) were 35%, 32% and 29% in three groups – given intravenous cyclophosphamide with oral prednisolone, daily oral cyclophosphamide with alternate day prednisolone and weekly plasma exchange, or placebo preparations of all these treatments, respectively. There were no differences between groups in the proportions who improved, stabilized or worsened, nor in the final EDSS scores (Figure 18.6). Despite the necessarily complicated trial design, failure to demonstrate a difference in the overall outcome or interim assessments between groups was conclusive with respect to cyclophosphamide, not least because the study involved nearly three-fold more patients than earlier evaluations. However, perhaps the conclusion that 'immunosuppressive treatments do not stabilize or improve the clinical course in patients with multiple sclerosis' was overstated. Our position is that physician blinding prevented an erroneous conclusion being reached about the efficacy of intravenous cyclophosphamide in the Canadian study since Noseworthy *et al* (1994) point out that a treatment effect would have been reported (for the 6, 12 and 24 month epochs) had the analysis been based on the scores of neurologists who were unblinded during the trial and not (as was the case) the masked investigator. This analysis demonstrates, as well as any in the literature, the importance of evaluator blinding in the assessment of a putative treatment effect.

Although the Canadian study offered cyclophosphamide little future prospect as a treatment for multiple sclerosis, new studies have continued to appear. Weiner *et al* (1993a) extended their previous assessment of intravenous cyclophosphamide, modifying the induction regimen and adding so-called 'boosters' to maintain the effects. This required a comparison of four treatment groups but there was no difference in outcome between the two methods of induction. A higher proportion of patients who received further treatments with intravenous cyclophosphamide

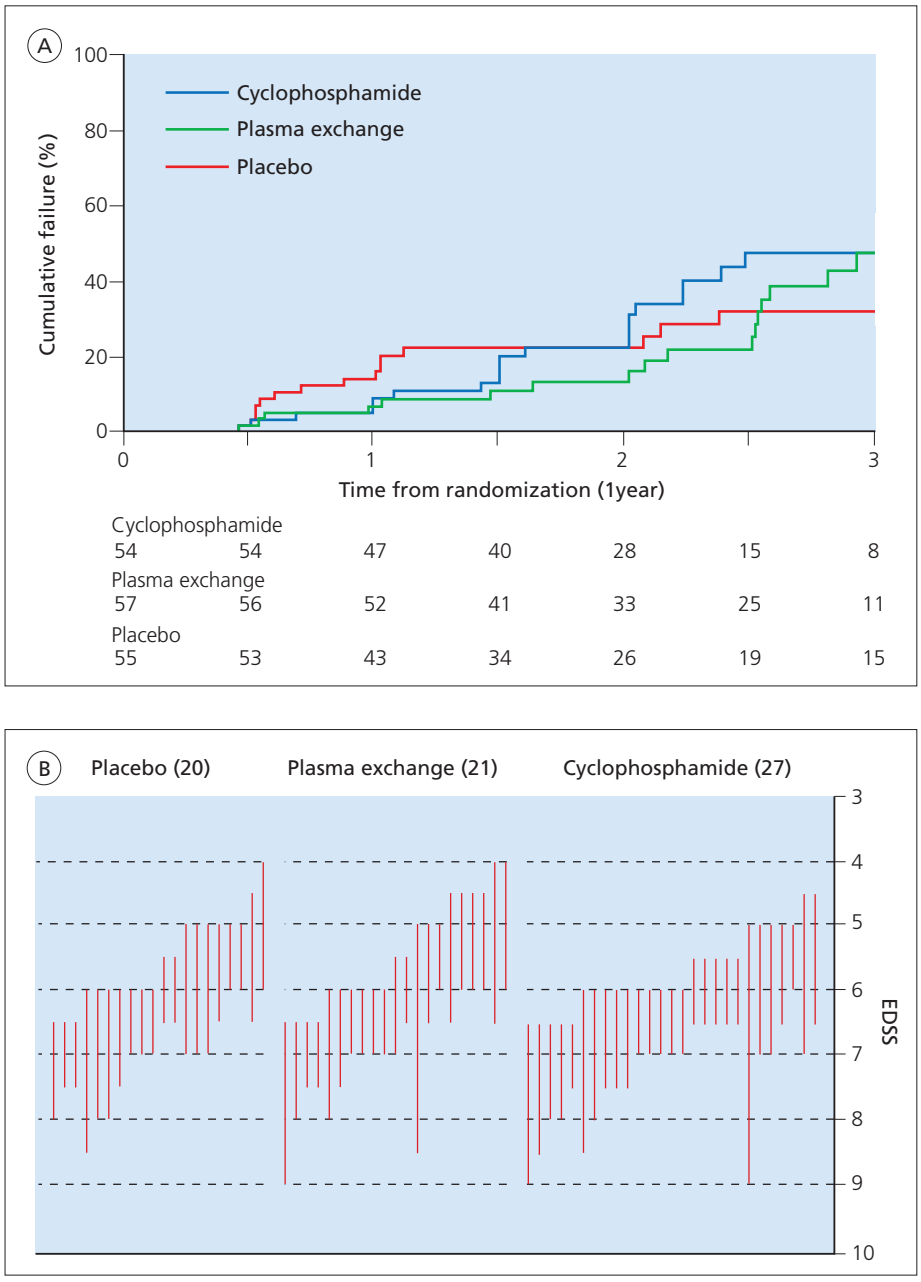



**Figure 18.6** Canadian cyclophosphamide trial. (A) Time to treatment failure. (B) Extent of deterioration in EDSS. Every patient whose EDSS increased by >1 point (evaluating neurologist's assessment) at any one time during the trial is represented by a line connecting the EDSS at entry with the worst EDSS recorded during the trial. Numbers in parentheses are the numbers in each group who showed an increase of at least 1 EDSS point. Adapted from the Canadian Co-operative Multiple Sclerosis Study Group (1991). © 1991, with permission from Elsevier.

every 2 months for 2 years was clinically stable or improved at 24 and 30 (but not 6, 12 and 18) months and the time to treatment failure was prolonged in these two groups. Thirty-eight per cent responded clinically at 24 months in the two groups receiving boosters compared with 24% in the induction-only groups. Comparable figures at 30 months were 27% and 17%, respectively (Figure 18.7).

Weiner *et al* (1993a) emphasize that these clinical effects (which we consider to be modest and achieved at some price in terms of risk and potential adverse effects) are more likely to occur in young patients (aged <40 years) and not in individuals with primary progressive multiple sclerosis. In another report from this group, Gauthier *et al* (2003) reported a retrospective analysis of their experience using cyclophosphamide in 47 relapsing–remitting patients with multiple sclerosis considered unresponsive to glatiramer acetate and the various forms of IFN-β. The combination of pulsed intravenous methylprednisolone and cyclophosphamide appeared to stabilize MRI and clinical measures of progression in up to 75% of cases.

There have been no recent, randomized, controlled trials using cyclophosphamide but several investigators have reported apparently positive clinical experience. Based on an open label series of 17 patients with advanced disability (EDSS 6.0–8.5), who had deteriorated by at least 1.5 EDSS points despite recent treatment with corticosteroids, Weinstock-Guttman *et al* (1997) consider that high-dose intravenous cyclophosphamide and methylprednisolone followed by IFN-β therapy may stabilize rapidly worsening multiple sclerosis. They administered intravenous cyclophosphamide 500 mg/m$^2$ and 1.0 g intravenous methylprednisolone daily for 5 days along with abundant intravenous fluids to reduce the risk of haemorrhagic cystitis. Patients were then given a tapering course of oral prednisone for 12 days.

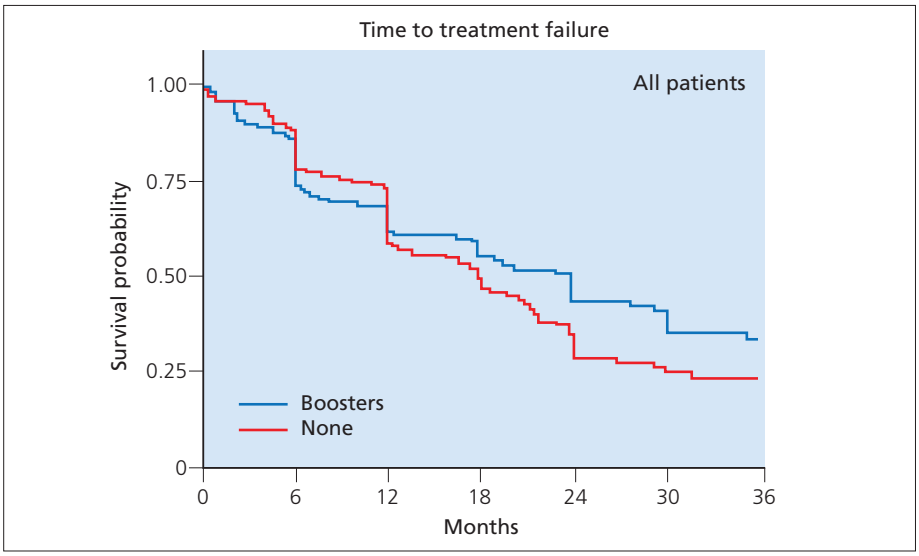



**Figure 18.7** Kaplan–Meier survival curves comparing time to treatment failure in patients receiving and not receiving bimonthly cyclophosphamide booster therapy. Percentages of individuals who were not treatment failures are plotted against time. No significant difference was found ($p = 0.18$) over the entire course of follow-up, but in examining booster effects starting at 1 year, a significant benefit ($p = 0.03$) was detected. Adapted from Weiner *et al* (1993a). © 1993, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

Thereafter, 'maintenance immunotherapy' was continued at the discretion of the prescribing physician. This varied from repeated bimonthly treatments with intravenous cyclophosphamide and methylprednisolone, to weekly methotrexate or bimonthly intravenous methylprednisolone, and IFN-β1b. They reported that this complex immunological regimen was well tolerated (one patient had fever and two developed severe nausea and vomiting). Thirteen of 17 were either stable or improved at 1 year, and nine of 13 at 2 years. Although encouraging, collective experience has shown that nonrandomized, uncontrolled studies are often not validated by prospective studies using rigorous trial designs. In addition, the extreme variability of the 'maintenance immunotherapy' given to these patients leaves open too many freedoms in concluding what has and has not contributed to the complex equation of efficacy and clinical cost. Hohol *et al* (1999) reported their consecutive series of 95 patients with progressive forms of relapsing–remitting, secondary progressive and primary progressive multiple sclerosis. Each patient received 5 days of 1 g intravenous methylprednisolone followed on day 4 or 5 by a single course of intravenous cyclophosphamide (800 mg/m$^2$). Thereafter, patients received repeated single courses of 1 g intravenous methylprednisolone and cyclophosphamide (monthly dose increasing as needed to induce a mid-month leukopenia of 1500–2000 cells/mm$^3$). Patients were treated monthly for 1 year, every 6 weeks in year 2, and then every 8 weeks in year 3. This approach appeared most beneficial for patients with relatively recent onset secondary progressive multiple sclerosis (mean 2.1 years) whereas those with primary progressive disease responded less well. The authors reported that, at 2 years, 76% of the chronic progressive patients were stable or had improved using EDSS criteria. However, when using a combined outcome of either EDSS change or the examining physician's global impression of worsening, 54% of the patients with chronic progressive disease were judged to have deteriorated at 2 years.This experience is again unblinded and uncontrolled. Perhaps of equal importance, 70 of 95 patients discontinued the planned protocol prior to analysis, with approximately an equal number dropping out during each of the 3 years of follow-up. The authors conclude, as have many others, that the yield from treating secondary progressive multiple sclerosis using intensive immunosuppression diminishes with time. Gobbini *et al* (1999) administered high-dose pulse intravenous cyclophosphamide monthly for 6 months in a hospital setting to five patients with relapsing–remitting disease judged to have failed licensed therapies. Patients were adequately hydrated and underwent a 24 hour bladder irrigation protocol to reduce the likelihood of haemorrhagic cystitis. Cyclophosphamide was administered as 1 g/m$^2$ monthly with dose adjustments as needed to achieve a peripheral white blood cell count nadir of 1500–2000 cells/mm$^3$ at 10 days. Ondansetron hydrochloride 10 mg by intravenous injection was used to reduce nausea and vomiting. Monthly MRI studies demonstrated that all patients had a reduced number of gadolinium enhancing lesions by month five and two patients demonstrated a reduced $T_2$ lesion load. Two others could not be evaluated because of inadequate MRI. One patient continued to demonstrate an increase in $T_2$ lesion load despite stabilization of contrast enhancing lesions. One patient developed alopecia, another developed herpes zoster and, in two patients, a seizure disorder was observed but attributed to advanced multiple sclerosis. The authors conclude that this approach may be useful in patients failing approved therapies.

Monthly pulses of intravenous cyclophosphamide were used by S. Khan *et al* (2001a) in 14 patients with 'rapidly deteriorating' relapsing–remitting multiple sclerosis. Each had worsened by at least 3.0 EDSS points in the preceding year despite at least 6 months of an approved immune-modulating parenteral therapy and at least two courses of intravenous methylprednisolone. They administered 1 g/m$^2$ cyclophosphamide by monthly intravenous infusion, adjusting the dose based on a target peripheral white blood cell nadir of 2000–2200 cells/mm$^3$ at 14 days. Most patients were treated for 6 months and then started on one of the approved therapies. Dexamethasone (20 mg) and ondansetron (32 mg, each by intravenous injection) were administered, along with intravenous fluids to prevent haemorrhagic cystitis. All patients were thought to have stabilized or improved by 6 months and this apparent clinical benefit persisted for an additional year (assessed at 18 months, postinduction). Mild or moderate nausea and transient alopecia were reported but no participant experienced haemorrhagic cystitis or clinical relapses. Self-evidently, cyclophosphamide is a complicated drug to administer and the

net contribution to the welfare of people with multiple sclerosis is hard to evaluate. For example, in a comparative study of patients receiving monthly infusions of methylprednisolone (n = 15), bimonthly intravenous cyclophosphamide with methylprednisolone (n = 32), methotrexate (n = 5) or IFN-β (n = 15), there was early and sustained selective increase in eosinophilia and raised levels of stimulated CD4 T-cell-secreted IL-4 and IL-10 with a reduction in production of IFN-γ in the cyclophosphamide group – representing both inhibition and enhancement of potentially immunopathogenic processes – not seen with the other putative therapeutic agents (D.R. Smith *et al* 1997). A recent Cochrane systematic review concluded that cyclophosphamide does not prevent worsening of the EDSS but appears favourably to influence the rate of EDSS change at 12–18 months (La Mantia *et al* 2002). Astonishingly, only four randomized trials from a total of 326 published reports were judged suitable for review because of limitations in trial design and conduct. These authors cautioned against the use of this agent because of the frequency of sepsis and amenorrhoea in treated patients.

We rarely, if ever, use cyclophosphamide in our clinical practice. It may be that this powerful immunosuppressive agent has a role in stabilizing patients with very active disease but our reading of the published reports suggests extreme caution. As in many trials where the first reported effect has not been confirmed, the treated group fared no better than patients receiving placebo but nonetheless participating in trials of chronic progressive multiple sclerosis. This calls to mind the remark of the late Dale McFarlin:

> *when I get multiple sclerosis, put me in a trial and make sure I get the placebo.*

## Plasma exchange

Plasma exchange has been used in patients with multiple sclerosis in the hope of matching the uncomplicated benefits achieved in other inflammatory disorders. It has been evaluated both as a disease-modifying agent and in the management of refractory acute episodes (see Chapter 16). Although the mode of action in disorders where details of the immunopathogenesis remain to be fully characterized is obscure, plasma exchange presumably removes or indirectly restores to balance soluble mediators of immunity. The same general principle is thought to underlie the use of immune globulin (see below).

Khatri *et al* (1991) reviewed their experience of plasma exchange in 200 patients with progressive multiple sclerosis (based on a recent retrospective review of case records) also receiving cyclophosphamide, prednisolone and symptomatic treatments. Pooled human globulin was used to replace fluid after exchanges given weekly for 3 months with a subsequent weaning period, the duration of which depended on initial response. The results showed a reduction in EDSS at 1, 2 and 3 years by comparison with scores at entry, and the authors considered that >80% of patients had improved or stabilized by 3 years. Four potentially active treatments were used in the study. Patients were selected on the basis of ability to pay for therapy through insurance. There were no controls. It is therefore difficult to reach any conclusions from this evidence on whether plasma exchange has an independent effect, complements immunosuppressants or makes no contribution to the management of disease progression. Whereas the Canadian Cooperative Multiple Sclerosis Study Group (1991) concluded on the basis of their study that immunosuppressants (then available) were generally ineffective in multiple sclerosis, Khatri *et al* (1991) reached diametrically opposite conclusions using a comparable regimen of combined therapies.

Most reported studies use plasma exchange as an adjunct to other forms of immunological treatment. Thus, the clinical course has been shown to stabilize in patients with progressive disease treated with corticosteroids and cyclophosphamide, whether or not plasma exchange is also used (Khatri *et al* 1985). An earlier trial comparing plasma exchange in patients also receiving azathioprine showed that both groups deteriorated at a comparable rate (Tindall *et al* 1982). Confirming that the short-term consequences of relapse are reversed more rapidly in patients receiving plasma exchange in addition to intramuscular corticotropin and cyclophosphamide, Weiner *et al* (1989) were unable to demonstrate any long-term effects. The contribution made by plasma exchange in patients also receiving azathioprine was assessed in a crossover design by P.S. Sorensen *et al* (1996). Fourteen exchanges were given over 20 weeks in the active period. Plasmapheresis had no effect on disease activity as assessed by gadolinium enhanced MRI, although the total lesion load and central motor conduction times were reduced during the exchange period. A specific role for plasma exchange in the treatment of fulminant demyelination was reported by M. Rodriguez *et al* (1993a). This observation is substantiated by both a randomized, double-blinded trial (Weinshenker *et al* 1999b) and an uncontrolled, prospective series (Keegan *et al* 2002) of patients who failed to improve following a course of steroid treatment in the setting of acute inflammatory demyelination because of established multiple sclerosis, neuromyelitis optica or a first episode of demyelinating disease. Bringing together empirical observations treating fulminating episodes of demyelination with plasma exchange and histological observations made in the highly selected group of cases studied by brain biopsy, Keegan *et al* (2005) subsequently correlated the presence of antibody and complement deposition (type 2: see Chapter 12) with moderate to substantial functional improvement – responses that were not seen in patients with other histological features. It remains unclear at what point in the natural history of an episode with poor recovery, plasma exchange might be considered as one option for limiting the extent of persistent or long-term disability, thereby constituting a disease-modifying treatment (see Chapter 16).

## Intravenous immunoglobulin

We refer elsewhere (see below, and Chapters 10 and 19) to the potential for remyelination from the use of intravenous immunoglobulin in experimental demyelination and the clinical setting. Intravenous immunoglobulins are widely used in the management of peripheral and central nervous system disorders (Wiles *et al* 2002). Intravenous immunoglobulin has been assessed in detail for a variety of indications in multiple sclerosis (Stangel and Hartung 2002), including attempts to alter the natural history of relapsing–remitting and secondary progressive disease, and to reverse established deficits by enhancing remyelination (Asakura 1996; Rodriguez and Lennon 1990; M. Rodriguez *et al*

1996). Immunoglobulins may stimulate remyelination in the Theiler's murine encephalomyelitis virus animal model. Other possible mechanisms of action include an effect on anti-idiotypes (Tenser *et al* 1993), interference with complement (M.M. Frank *et al* 1992) or Fc-receptor-mediated interactions between microglia and their opsonized targets (Jungi *et al* 1990), or a reduction in cytokine production (U.G. Anderson *et al* 1993). Whatever the mode of action, intravenous immunoglobulin appears to be safe and generally well tolerated.

Schuller and Govaerts (1983) first used immune globulin in multiple sclerosis, reporting that 11 of 31 patients with chronic progressive disease showed improvement. Nine were unchanged and the remaining 11 deteriorated. These results are rather reminiscent of the rule of thirds in multiple sclerosis treatment trials (one-third each better, same and worse). Achiron *et al* (1992b) later reported an open controlled trial using 0.4 g/kg intravenous immunoglobulin given for 5 days and then every 2 months for 1 year in ten patients and ten controls. Treatment was well tolerated. Relapse rate changed in the treated group from 3.7 (± 1.2)/year to 1.0 (± 0.7)/year, and from 3.3 (± 1.4)/year to 3.0 (± 1.6)/year in controls (which is rather high for unselected patients). At 12 months, the EDSS had changed from 4.5 to 4.2 in treated patients and from 3.5 to 3.7 in controls. Cook *et al* (1992) combined intravenous immunoglobulin (0.5–2 g/kg) with methylprednisolone given monthly to 14 patients with progressive multiple sclerosis. These were unusual in that 11 of the patients were considered to be corticosteroid dependent. During follow-up (mean duration 7.8 months) 11 patients experienced 17 relapses, many of which occurred within 1 month of treatment or coincided with attempts to taper the dose of corticosteroids. Tenser *et al* (1993) treated six patients with relapsing progressive multiple sclerosis for 2 days with 0.8 g/kg of intravenous immunoglobulin. Whilst we question the value of learning that two of them felt better, the main purpose of this study was to demonstrate immunological effects on immune function. van Engelen *et al* (1992) treated five patients with stable visual deficits, in the context of multiple sclerosis which had not previously responded to intravenous methylprednisolone, with 0.4 g/kg intravenous immunoglobulin for 5 days followed by a single dose twice monthly for 3 months. Vision started to improve within 12 months of treatment and was maintained for >1 year, but this did not correlate closely with psychophysical tests or imaging appearances.

Fazekas *et al* (1997) randomized a larger group (150 patients with relapsing multiple sclerosis having clinical evidence for moderate but neither trivial nor severe disability and without chronic progression) to a single monthly infusion of intravenous immunoglobulin (0.15–0.2 g/kg). This is a low dose. Exposure to other forms of immunosuppression up to 3 months (2 weeks for corticosteroids) previously was permitted, as was methylprednisolone in pulses of up to 10 g during intercurrent relapses. This design limits the confidence with which the otherwise impressive and statistically significant effects on disability (the primary outcome measure) and relapse activity can be assessed. In an intention to treat analysis, the proportions improving, worsening or unchanged in the treated group were 31%, 16% and 53% compared with 14%, 23% and 63% in placebo patients, respectively. However, the magnitude of change was small, being –0.2 EDSS points in treated patients and +0.1 in the placebo group (a difference of 0.3; $p = 0.008$). The effect on relapse frequency shows the now familiar pattern. Treated patients had a reduction in baseline rate from 1.3 to 0.5 relapses during the first year (a reduction of 0.8 per year), which stabilized at 0.4 per annum in the second year compared with baseline, 1 year and 2 year rates of 1.4, 1.3 and 0.8 (reductions of 0.1 and 0.5, respectively) in the placebo group. Thus, the impact was all in the first year. Adverse effects were few and probably unrelated to medication. On closer inspection, however, a couple of additional points should be mentioned. Surprisingly, less reduction in relapse rate was seen in the placebo group than is usual in comparable trials. We wonder whether blinding was adequate. Failure of regression to the mean in the control group may have inflated the apparent treatment benefit. Investigators did not require a second confirmatory examination to determine that the apparent delay in EDSS progression was sustained at further examinations separated by 3, 6 or 12 months. The effect of intravenous immunoglobulin on MRI behaviour was not assessed in this study. However, in a small study, G.S. Francis *et al* (1997) demonstrated that intravenous immunoglobulin had no apparent effect on MRI behaviour in nine patients given induction and monthly booster doses. They continued to relapse, progress and accumulate $T_2$-weighted MRI lesions.

Achiron *et al* (1998) randomized 40 patients to induction and maintenance treatment with intravenous immunoglobulin (0.4 g/kg for 5 days with a single treatment every 2 months for 2 years) or placebo. Primary outcome measures related to relapse frequency, interval, time to next episode, and severity. These were patients with high pretreatment relapse rates and, unusually, the placebo cases showed fluctuations in relapse rate (1.5, 1.8 and 1.4 per year before and during each of the 3 years of the study, respectively), whereas treated patients showed a reduction (1.8, 0.7 and 0.4 per year, respectively; $p = 0.0006$, overall). Annual change in relapse rate across the 3 years of observation was –1.1 and –0.3 in patients receiving intravenous immunoglobulin compared with +0.2 and –0.4 in the placebo group. Thus, the effect on relapse rate depended entirely on the first year effect during which treated patients improved and the placebo group deteriorated (a difference in activity of 1.4 relapses/year). A greater proportion of treated patients (six of 20) than controls (none of 20) remained exacerbation free during the entire period of the study, and the time to first relapse was longer (233 compared with 82 days). There was no difference in mean EDSS scores between groups but a favourable distribution in the proportion within each group who worsened, improved or remained stable (14%, 24% and 63% in those receiving immunoglobulin compared with 17%, 11% and 72% in the placebo group, respectively) was observed. The protocol for MRI does not allow useful conclusions to be drawn. Twenty-six patients were treated by P.S. Sorensen *et al* (1998) in a crossover design with intravenous immunoglobulin 2 g/kg or placebo monthly each for 6 months. There were fewer new enhancing lesions on MRI (the primary end point; however, no benefit was seen in the number of new $T_2$ lesions) and a greater proportion of patients was relapse free (the secondary outcome) during periods of active therapy. Although promising, these smaller studies all failed to reproduce the original claim of Fazekas *et al* (1997). Consequently, intravenous immunoglobulin is not widely used as maintenance therapy to reduce relapse frequency in relapsing–remitting multiple sclerosis but, rather, is considered a second-line therapy (Rieckmann and Toyka 1999).

In a preliminary study involving 108 pregnancies, Achiron *et al* (2004b) investigated the specific issue of reducing the possibility of disease activity – manifesting as new relapses – in the puerperium by prophylactic use of intravenous immunoglobulin. Two treatment groups (intravenous immunoglobulin 0.4 g/kg/day for 5 consecutive days in week one after delivery with the same regimen at weeks six and twelve after delivery; or 0.4 g/kg/day for 5 consecutive days within 8 weeks of conception, and once every 6 weeks until 12 weeks postpartum) were compared with untreated mothers. No confounding factors were identified and there were no serious adverse events. The group treated during pregnancy showed fewer relapses during pregnancy (0.43, 0.15 and 0.0 annualized rates for each trimester compared with 0.72, 0.61 and 0.41 in controls); both treated groups had fewer episodes in the puerperium (0.28 and 0.58 annualized rates, respectively) compared with controls (1.33). This initial study suggests that further controlled trials of intravenous immunoglobulin in this clinical setting are needed.

A recently completed phase three study of intravenous immunoglobulin in secondary progressive multiple sclerosis involved 318 patients randomized to receive monthly infusions of either intravenous immunoglobulin 10% at a dose of 1 g/kg body weight (to a maximum of 80 g; eight vials) or the same volume of placebo with 0.1 g albumin per vial. Although there was a treatment advantage over the first year of the trial, this benefit was soon lost since treatment did not influence the proportion of patients classified as treatment failures (confirmed progression of EDSS of 1.0, or 0.5 for baseline EDSS of ≥ 6.0), or reduce MRI evidence of $T_2$ lesion accumulation. The trial was stopped after 27 months based on this interim analysis demonstrating futility (Hommes *et al* 2004). Of interest, however, was a reported beneficial effect on the development of brain atrophy (Lin *et al* 2002).

Following one clinical report that intravenous immunoglobulin might benefit patients with longstanding visual loss due to multiple sclerosis (van Engelen *et al* 1992), Noseworthy *et al* (2000b; 2001) conducted two randomized, double-blinded, placebo-controlled phase two trials to determine if intravenous immunoglobulin might restore function in the setting of persistent (visual) clinical deficits. In the first study, 67 patients with either relapsing–remitting (n = 19) or secondary progressive multiple sclerosis (n = 48), known to have a moderately severe fixed motor deficit (confirmed by isometric biomechanical muscle strength testing), were randomized to receive either 0.4 g/kg intravenous immunoglobulin daily for 5 days then every 2 weeks for 3 months (representing a total of 11 infusions) or placebo. Treatment failed to demonstrate an improvement in strength of the targeted muscle groups or benefits in any secondary outcome measures. In the second study, 55 patients with persistent visual loss from inflammatory optic neuritis were randomized to receive either 0.4 g/kg intravenous immunoglobulin daily for 5 days then monthly for 3 months (a total of eight infusions) or placebo. Treatment did not improve the primary visual outcomes (visual log acuity scores at 6 months) and the trial was again stopped on the futility principle. Stangel *et al* (2000a) were also unable to demonstrate that treatment with either placebo or intravenous immunoglobulin (0.4 g/kg/day for 5 days) separated by 6 weeks improved central conduction motor conduction velocity in ten patients with multiple sclerosis.

In summary, there is only limited evidence to support a role for intravenous immunoglobulin in patients with demyelinating disease of the central nervous system (other than those who have failed to respond to high-dose steroids or plasma exchange in the setting of a catastrophic relapse; see above and Chapter 16). Future randomized studies may change this recommendation.

## Methotrexate

Despite being available for many years, methotrexate has only recently been evaluated in multiple sclerosis. The first study (J.W. Neumann and Ziegler 1972) alternated treatment with methotrexate (2.5 mg/day) and 6-mercaptopurine (75 mg/day) in 3-monthly cycles. There was no clinical effect but the study design was not ideal. Subsequently, Currier *et al* (1993) reported a reduction in relapse rate for patients in the relapsing–remitting phase treated with methotrexate but there was no effect on disability in patients with progressive multiple sclerosis. The role of methotrexate in this clinical situation was specifically assessed by D.E. Goodkin *et al* (1995). Sixty patients with secondary or primary progressive disease were randomized to treatment with a weekly oral dose of 7.5 mg methotrexate or placebo. Methotrexate was well tolerated and the relative absence of adverse effects allowed blinding to be maintained throughout the study. Overall, patients and independent observers were unimpressed by the results. Objective assessments, using a complex composite scale which independently assessed the EDSS, ambulation index, box and block and nine-hole peg tests (upper limb function), and new or enlarging MRI lesions, showed a statistically significant effect of methotrexate on function in the peg test but not the box and block method for assessing upper limb function or mobility.

Subsequently, D.E. Goodkin *et al* (1996) reported on changes in active MRI lesions and $T_2$-weighted total lesion load but, by comparison with other claims for an effect on surrogate markers of disease activity, methotrexate was relatively unimpressive. In correspondence, Olek *et al* (1996) indicated that weekly subcutaneous injections of a higher dose (20 mg) of methotrexate were generally well tolerated by 38 patients although one developed an injection site abscess and transient liver enzyme elevation was occasionally seen. The full report of this study appears not to have been published.

In a preliminary trial of 15 patients, Calabresi *et al* (2002b) showed that, when added to weekly IFN-β1a, methotrexate 20 mg orally, also in a single dose each week, seemed to reduce gadolinium enhancements and may have provided an additional protection against relapses. In a very small study, Rowe *et al* (2003) reported preliminary findings from adding high-dose intravenous methotrexate (2 g/m$^2$) every 2 months for 1 year in 15 patients with relapsing–remitting multiple sclerosis who had demonstrated neurological worsening during the preceding period on IFN-β1a weekly by intramuscular injection. Patients continued on weekly IFN-β1a tolerated combination therapy with evidence for stabilization of the clinical course as judged by the MSFC (see above), and with immunological markers suggesting an influence on disease mechanisms. We understand that a four-arm trial designed to determine whether methotrexate (20 mg orally per week) alone or in combination with methylprednisolone (1000 mg by intravenous infusion for 3 days every 2 months) provides a treatment advantage over weekly IFN-β1a in 900 patients with relapsing–remitting multiple sclerosis who have failed interferon alone is in progress. However, despite

these ongoing studies, at present methotrexate joins cyclophosphamide and azathioprine as medications rarely, if ever, prescribed in our clinical practice.

## Mitoxantrone

Mitoxantrone is an anthracenedione antineoplastic agent that intercalates with DNA and inhibits both DNA and RNA synthesis, suppressing T-cell and B-cell immunity. Mauch *et al* (1992) first treated 12 patients perceived to have rapid progression of disability with mitoxantrone (12 mg/m$^2$). All reported clinical stabilization and eight of them were considered to have improved at 1 year. The patients had 169 gadolinium-DTPA enhancing lesions at entry but only 10 were visible on completion of the study. Adverse effects were minimal. Mitoxantrone was next assessed in a small open study involving 13 patients with progressive multiple sclerosis (Noseworthy *et al* 1993). Participants received seven intravenous infusions over 3 weeks. Nine of the 13 patients had been observed over the previous 18 months and, in the remainder, historical evidence for rate of progression was available from case records. Initially, the clinical course appeared to stabilize and no changes in EDSS were seen for up to 12 months, but progression was apparent 6 months later. Although the authors considered progression to have occurred at a slower rate than expected from pretreatment observations in this cohort of patients, the changes were consistent with the natural history of multiple sclerosis previously seen in their placebo-controlled study of cyclophosphamide (see above). In eight of the 12 patients, there was evidence for continuing MRI activity during treatment with mitoxantrone.

In a subsequent study (Edan *et al* 1997), 42 patients with aggressive active clinical and radiological disease all receiving monthly injections of methylprednisolone were randomized to 6 months of treatment with intravenous mitoxantrone (20 mg/month) or no additional therapy. The baseline relapse rate was three per year in those who met the radiological guidelines for inclusion (there had to be gadolinium enhancing lesions) compared with 0.7 per year in patients who reported attacks in advance of selection but did not meet the radiological criteria for inclusion. Mitoxantrone was associated with a significantly higher frequency of conversion to disease inactivity as judged by gadolinium enhanced MRI activity. The mean number of enhancing lesions was reduced by about 90%, similar to that seen with other aggressive immunosuppressive regimens. Although both the number of participants and duration of follow-up prevented detailed assessment, there was an apparent beneficial effect of treatment on relapse rate and disability. The profile of adverse effects inhibited blinding, but no serious consequences of treatment were observed. In a 1 year study aimed at demonstrating whether mitoxantrone is cardiotoxic, De Castro *et al* (1995) showed a reduction in relapse rate in treated patients. There were no electrocardiographic or echocardiographic abnormalities. Millefiorini *et al* (1997) treated 27 patients monthly for 1 year with intravenous mitoxantrone (8 mg/m$^2$) or placebo. The differences in rate of accumulation of disability and number of relapses favoured a treatment effect. Nine of 24 placebo-treated patients deteriorated by up to 1 point on the EDSS compared with two of 27 patients given mitoxantrone. Five of 24 from the placebo group were free from exacerbations during the trial compared with 17 of the 27 patients given mitoxantrone. This was reasonably well tolerated and, again, with no cardiac toxicity. However, MRI did not show a significant reduction in disease activity and, in this respect, the results provide less persuasive evidence for the therapeutic role of mitoxantrone than those reported by Edan *et al* (1997).

After a 4 year interval between the initial declaration of results in abstract form and full publication, Hartung *et al* (2002) reported on MIMS (Mitoxantrone in MS Study Group). In this double-blind, placebo-controlled, multicentre study (17 centres in four European countries: Germany, Belgium, Hungary and Poland), MIMS randomized 194 patients with either worsening relapsing–remitting (progressive relapsing) or secondary progressive multiple sclerosis to treatment either with placebo (3 mg methylene blue) or mitoxantrone (5 or 12 mg/m$^2$ intravenously every 12 weeks for 24 months). Inclusion criteria required that patients had deteriorated by up to 1.0 EDSS point in the 18 months prior to enrolment with a baseline EDSS of 3.0–6.0. Annual MRI scans were performed on a subset of 110 patients. The primary outcome measure was a composite score comprised of five clinical measures: change in EDSS at 2 years; change in ambulation index at 2 years; change in the baseline standardized neurological status at 2 years; number of relapses requiring corticosteroid treatment; and time to first relapse. Seventy-seven per cent completed 24 months of follow-up (71% completed 36 months in the study). Those who discontinued treatment were slightly more common in the control group. At 24 months, benefit was reported in all five components of the composite measure for both active treatment arms, with the overall greatest benefit noted between placebo and the group receiving mitoxantrone at a dose of 12 mg/m$^2$ ($p < 0.0001$: Figure 18.8). That said, the magnitude of the effect on EDSS was rather modest [essentially mild benefit vs. mild deterioration; mean EDSS change for high-dose mitoxantrone, –0.13 (SD 0.90) vs. +0.23 (SD 1.01) in the placebo group] as expected in a trial of relatively brief duration. Preliminary MRI analysis also indicated a treatment effect with fewer $T_2$-weighted lesions and fewer patients experiencing enhancing lesions at 2 years in the high-dose group (see below). Post hoc analysis was performed

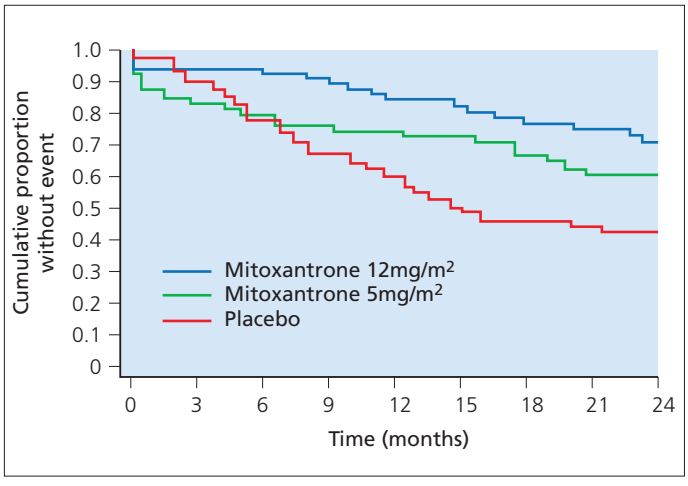



**Figure 18.8** Treatment of progressive multiple sclerosis with mitoxantrone. Time to first relapse. Both doses of mitoxantrone delayed time to first recorded relapse by the treating physician. This individual was aware of the treatment assignment. Adapted from Hartung *et al* (2002). © 2002, with permission from Elsevier.

based on the 18-month pre-enrolment relapse history, to determine whether mitoxantrone was equally effective in patients with ongoing relapses and those progressing with superimposed relapses. This subgroup analysis was underpowered but showed a similar benefit in both groups of patients. However, there was a trend for EDSS progression in all relapse-free patients irrespective of treatment assignment, albeit to a lesser degree in those who received mitoxantrone. Indeed, the mean EDSS worsening at 2 years in previously relapse-free mitoxantrone recipients was virtually the same as that seen in the placebo-treated relapsing patients.

A few points merit additional comment. This study generated widespread use of mitoxantrone in patients failing to respond to the interferons and glatiramer acetate (K.K. Jain 2000). It contributed to the Food and Drug Administration (FDA; United States) approval of mitoxantrone for use in progressive multiple sclerosis even though a peer-reviewed manuscript was not published for a further 2 years. This delay remains unexplained. Additionally, the detailed MRI analysis is still not available. With respect to design and conduct of the study, an unblinded physician was used to determine relapse status. Success of the blinding procedure was not assessed. Nausea and mild alopecia were reported but tolerated. Secondary amenorrhoea lasting at least 1 year developed in 25% of women receiving high-dose mitoxantrone. No patients developed significant cardiomyopathy. Goodin *et al* (2003) recently highlighted an important concern that re-analysis by the sponsor (Immunex) with selective censoring of the treatment arms contributed to the reported treatment and its magnitude. Goodin *et al* (2003) point out that, at 3 years, the benefit in standardized neurological status persisted but the EDSS and ambulation index results did not. They question whether methylene blue may have been neurotoxic and thereby contributed to the clinical and MRI decline in control patients. They also emphasize that high-dose mitoxantrone did not affect the mean number of gadolinium enhancing lesions ($p = 0.1$). The apparent effect of low-dose mitoxantrone was not subjected to statistical analysis. High-dose mitoxantrone reduced $T_2$ number ($p = 0.03$) and the number of new contrast enhancing lesions ($p = 0.02$) but there was no apparent effect on $T_2$ lesion load.

Taken together, the limited evidence to date supports the conclusion that mitoxantrone reduces relapse frequency and MRI evidence for blood–brain barrier disruption in patients with very active multiple sclerosis. The benefit for patients with relapse-independent progression is less certain. The recently published report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (Goodin *et al* 2003) recommends caution in the use of this drug, and calls for confirmatory studies. We recommend this report as a balanced and comprehensive review of the evidence for efficacy and the range of toxicity associated with the use of mitoxantrone in multiple sclerosis. The magnitude of the expected treatment effect is perhaps best stated using the 'numbers needed to treat (NNT)' approach (Sackett *et al* 2000). From the MIMS results, one would need to treat 11 patients with secondary progressive multiple sclerosis for 2 years to prevent one person from worsening by 1.0 EDSS point.

Mitoxantrone is a toxic agent that must be administered with care to reduce the likelihood of marrow suppression, opportunistic infection and cardiomyopathy. Amenorrhoea is an important concern for many young women. The risk of cardiomyopathy is generally dose dependent and may be as great as 6% in cancer patients receiving up to 140 mg/m$^2$ (Dukart 1984; Mather 1987). In most trials involving patients with multiple sclerosis, and in our clinical practice, regular pretreatment echocardiograms can be used to screen for reduced left ventricular function. The MIMS investigators recommend measuring cardiac output at baseline and thereafter, once patients have received a total of 100 mg/m$^2$. In practice, we measure cardiac output before each infusion and discontinue mitoxantrone if there is evidence for a reduction. Irreversible cardiomyopathy requiring transplantation has been reported in patients with multiple sclerosis exposed to excessive doses of this agent. Pathological findings in such cases include noninflammatory myofilament rarefaction and degeneration, sarcoplasmic dilatation, and interstitial fibrosis (Gbadamosi 2003b). Goffette *et al* (2005) reported three cases of delayed cardiomyopathy (heart failure) beginning 24–80 months after the last dose of mitoxantrone (total cumulative dose 144 mg/m$^2$) with no adequate explanation other than prior treatment with cyclophosphamide (two patients). This report reminds us of the need to use caution in the decision to use this agent and to be rigorous in maintaining close follow-up thereafter. Mitoxantrone is a topoisomerase II inhibitor and therefore may predispose to treatment-related leukaemia. There are now several reports possibly linking mitoxantrone to the development of acute leukaemia (Brassat 2002; Cattaneo 2003; Mogenet *et al* 2003; A.M. Vicari 1998). In a review of the literature, Ghalie *et al* (2002) estimated the risk of therapy-related acute leukaemia in patients with multiple sclerosis receiving mitoxantrone at 0.05–0.1%. This perceived rate may be on the low side; by 2004, there were currently five examples of acute leukaemia amongst a register of 2336 patients with multiple sclerosis receiving mitoxantrone, representing a cumulative incidence of 0.21% (Voltz *et al* 2004).

In the United States, Novantrone (mitoxantrone) is licensed by the FDA for

> *reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e. patients whose neurologic status is significantly abnormal between relapses). Novantrone is not indicated in treatment of patients with primary progressive multiple sclerosis.*

In Europe, although unlicensed, mitoxantrone is not infrequently used to treat patients who are deteriorating along the lines described in the FDA licence. We use the drug sparingly, reserving mitoxantrone for patients who continue to suffer clinical and MRI evidence of active disease (frequent significant relapses and multiple contrast enhancements) despite treatment with interferons (or glatiramer acetate). In one of our centres (D.H.M.), it is required that there has been a deterioration of at least 2 EDSS points within 12 months, accompanied by evidence for active inflammatory disease based either on the occurrence of clinical relapses or the presence of gadolinium enhancing MRI lesions. We generally administer 12 mg/m$^2$ by intravenous infusion every 3 months for not more than eight cycles but hope for a stronger evidence base from ongoing trials resolving the issue of whether higher cumulative doses offer

increased efficacy but without increasing the risk. We sometimes use the protocol of Edan *et al* (1997), namely mitoxantrone 20 mg monthly by intravenous injection for 6 months, in the small group of patients with particularly aggressive fulminant disease, in whom rapidly increasing disability has accumulated on the basis of frequent, severe relapses and many active inflammatory lesions on gadolinium enhanced MRI.

## Cladribine

Cladribine specifically induces apoptotic death in resting and dividing lymphocytes but is otherwise relatively nontoxic. After assessing safety and obtaining a preliminary impression of efficacy, Sipe *et al* (1994) compared monthly pulses of cladribine given by an indwelling intravenous line with placebo in 51 patients with progresssive multiple sclerosis. The analysis was confined to 48 participants randomized initially to receive cladribine or placebo, completing the assessment at 1 year. Of the three remaining patients, one died from acute hepatic failure, one withdrew after suffering a hip fracture and one was lost to follow-up. Three other treated patients had significant episodes of infection and there was evidence for bone marrow suppression in another, but these all continued in the study. This was terminated on the basis of results at 1 year without embarking on the planned crossover phase. Placebo-treated patients deteriorated by approximately 1 EDSS point and by a comparable amount on a locally designed neurological rating scale (the Scripps scale), whereas those receiving cladribine remained stable or showed modest clinical improvement in preexisting disabilities. The numbers of patients showing deterioration (by >1 EDSS point), improvement or stabilization were seven, one and 15 of the 23 patients in the placebo group compared with one, four and 19 of the 24 patients randomized to cladribine, respectively. Within pairs, a greater number showed no disease activity in serial MRI characteristics in the cladribine group compared with their placebo-treated partners (Figure 18.9A and B). There was some evidence for a difference in concentration, but not in the number, of oligoclonal bands in cladribine-treated patients compared with the placebo group. Since cladribine can now be given subcutaneously, the authors recommend its use at a lower dose than was evaluated in their trial of chronic progressive multiple sclerosis on the basis of efficacy and acceptable risks. Critics have argued that the original trial design was not strictly followed, and that the result was largely achieved through the atypical and severe course of the placebo group. However, in a preliminary communication, others have since endorsed the difference in natural history of progressive multiple sclerosis between patients receiving pulsed treatment with cladribine and placebo (Grieb *et al* 1994).

In a subsequent publication, Beutler *et al* (1996) extended the period of observation for the original study. Maintaining the blinded design, they crossed over the two randomized groups of patients, administering placebo to the original cladribine group and gave a reduced dose of cladribine to the patients who had first received placebo. A treatment effect was still claimed. The magnitude was reduced but toxicity was also less marked with the lower dose. The authors noted that cladribine can be given safely and with apparent equal efficacy by the subcutaneous route. Our position is that bone marrow toxicity (especially thrombocytopenia), herpetic infection in six patients and reported protocol violations undermine the likelihood that the trial was sufficiently blinded to be convincing.

There are several more recent reports exploring the potential use of cladribine in multiple sclerosis. Romine *et al* (1999) claimed clinical benefit, measured as a reduction in the combined outcome of relapse severity and frequency, in a short (18 month) double-blind, placebo-controlled trial of cladribine (0.07 mg/kg subcutaneously daily for 5 days and repeated monthly for 6 months; total 2.1 mg/kg) given to 52 patients with relapsing–remitting disease. Relapse rate fell dramatically during the first 6 months of the trial, especially in the placebo group but, thereafter, treated patients continued to show fewer episodes. Cladribine-treated patients also had fewer gadolinium enhancing MRI lesions. In a phase three trial involving patients with progressive multiple sclerosis, Rice *et al* (2000) demonstrated that each of two doses of cladribine (0.07 mg/kg subcutaneously daily for 5 days each month repeated for either 2 or 6 months) reduced MRI evidence of disease activity in the subset of patients with secondary progressive disease. Unfortunately, this trial was limited to 1 year of follow-up and no clinical benefit was apparent in the primary outcome measures (EDSS and Scripps Neurologic Rating Scale). Both doses reduced the number and volumes of contrast enhancing lesions. The higher dose also reduced $T_2$ lesion load. Significantly, there was no effect on the progression of cerebral atrophy (Filippi *et al* 2000a; 2000b). We remain to be convinced that cladribine is useful, and do not recommend its use in the management of patients with multiple sclerosis.

## Sulfasalazine

Noseworthy *et al* (1998) conducted a phase three trial designed to determine whether prolonged administration of sulfasalazine might reduce disease activity in patients with active multiple sclerosis. The trial was started before completion of the first definitive trial of IFN-β and at a time when there were no approved therapies for multiple sclerosis. Sulfasalazine is a well-tolerated oral agent for which a number of relatively mild immunosuppressive activities had previously been claimed together with moderate efficacy in other chronic immune-mediated disorders including rheumatoid arthritis and inflammatory bowel disease. Interim analysis suggested that treatment had been mildly effective early in the trial. Wisely, the data monitoring committee recommended that the study be continued to completion – and the early benefits disappeared so that, in the final analysis, there was no overall benefit (Figure 18.10). The decision to continue this trial without informing the investigators or sponsors of the early apparent benefit, and the subsequent recognition that early effects are often transient, provides an important lesson for the design and conduct of treatment trials in multiple sclerosis that has subsequently been well learned. Thus, sulfasalazine joins the list of agents that do not have a role in the treatment of multiple sclerosis.

## Corticosteroids

Despite the unambiguous evidence that corticosteroids hasten clinical recovery in the setting of acute relapse (see Chapter 16), it has previously been held as axiomatic that they have no effect on the natural history of multiple sclerosis. But until recently,

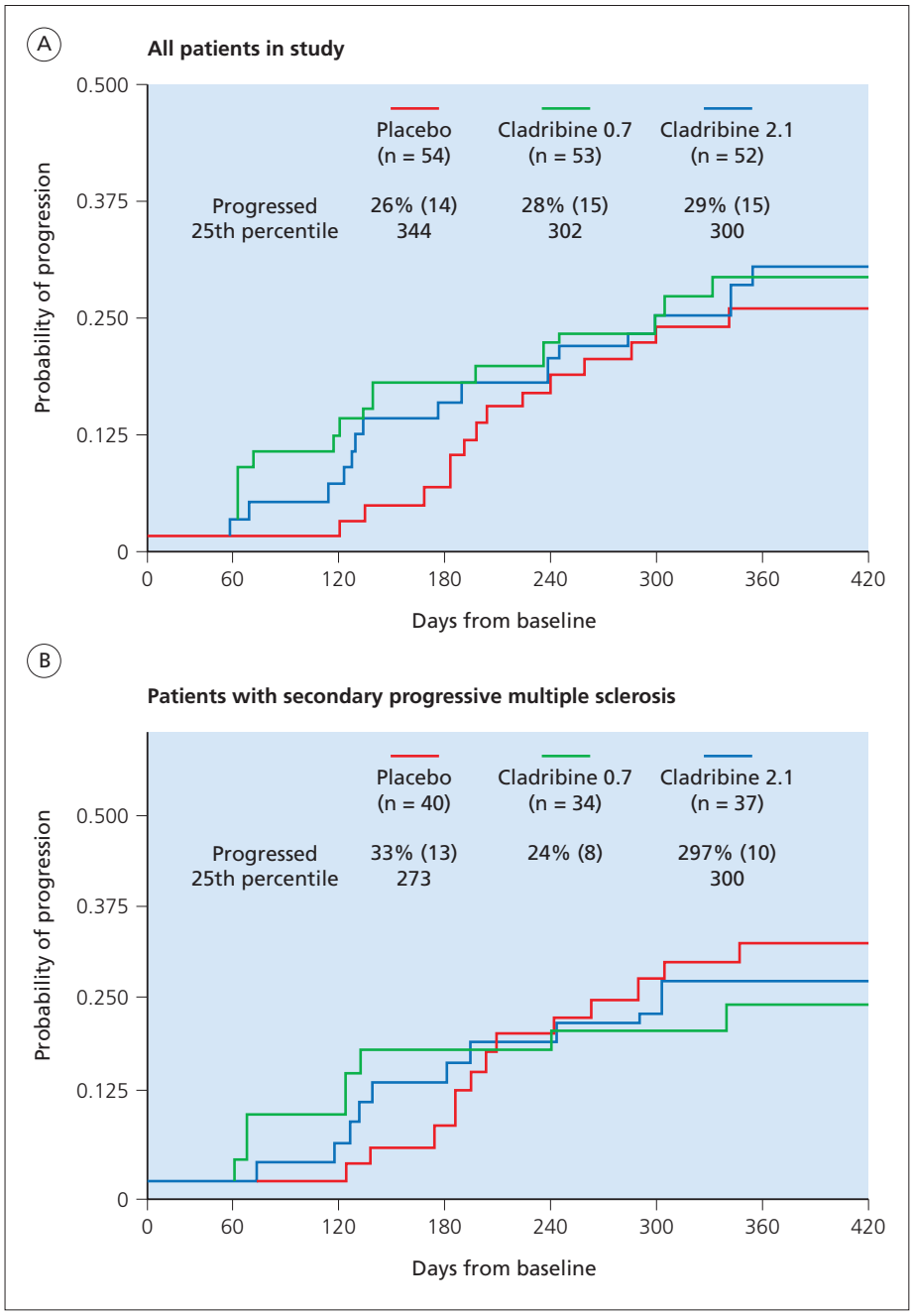



**Figure 18.9** Treatment of multiple sclerosis with cladribine. Probability of disease progression (A) All patients; (B) Secondary progressive multiple sclerosis. This study was underpowered and of insufficient duration to determine whether cladribine would benefit patients with secondary progressive multiple sclerosis. Adapted from Rice *et al* (2000). © 2000, reproduced with permission of Lippincott Williams & Wilkins.

there had not been an adequate, long-range, properly controlled study to establish the validity of this axiom.

In a recent report, Zivadinov *et al* (2001a) randomized 88 ambulatory (baseline EDSS ≤ 5.5) patients with relapsing–remitting multiple sclerosis to receive either corticosteroids as needed to treat acute relapses, or on a predetermined schedule (every 4 months for 3 years and then every 6 months for 2 years). The regimen used methylprednisolone 1000 mg by intravenous infusion for 5 days followed by 4 days of oral prednisone (2 days each of 50 and 25 mg). To be eligible, patients needed to be at least 3 months removed from prior corticosteroid treatment and on no immune-modulating agents. Only the radiologist was blinded to study assignment. The results of this study were impressive. Only seven patients were lost to follow-up. The primary (MRI) and secondary (disease progression as measured by EDSS) outcomes favoured the scheduled regimen. Patients randomized to regular courses of corticosteroids showed a benefit in terms of $T_1$ lesion volume and brain parenchymal volume. Although no significant differences were seen in $T_2$ volume, surprisingly there was a trend suggesting that $T_2$ volume increased more in the group receiving scheduled corticosteroids. Clinical measures also favoured the scheduled regimen. These included confirmed EDSS change (≥ 1.0 worsening for baseline EDSS ≤ 5.0; ≥ 0.5 points for EDSS ≥ 5.5 at baseline; and changes confirmed for at least 8 months in the first 2 years and at least 12 months in years four and five), proportion with EDSS worsening, proportion converting to secondary progressive multiple sclerosis, and mean EDSS change. There were no

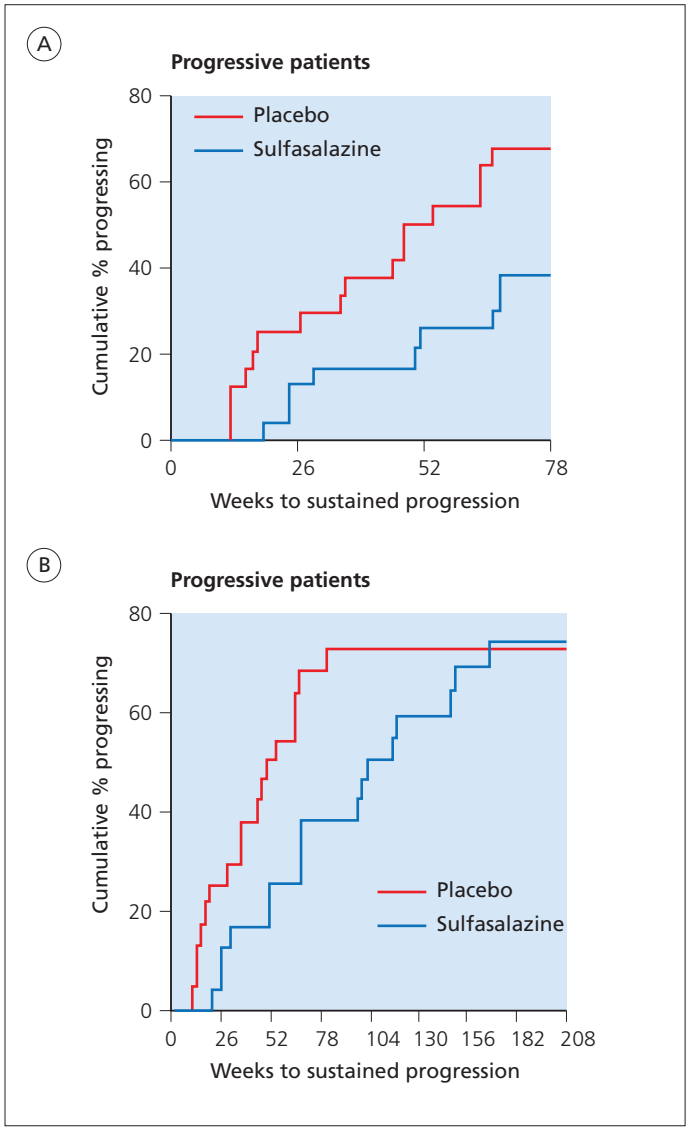



**Figure 18.10** Treatment of active multiple sclerosis with sulfasalazine. (A) At the time of the interim analysis, there appeared to be an early treatment advantage for patients with progressive MS. (B) This later disappeared with prolonged follow-up. The data monitoring committee wisely did not terminate the trial early 'for apparent efficacy'. Adapted from Noseworthy *et al* (1998). © 1998, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

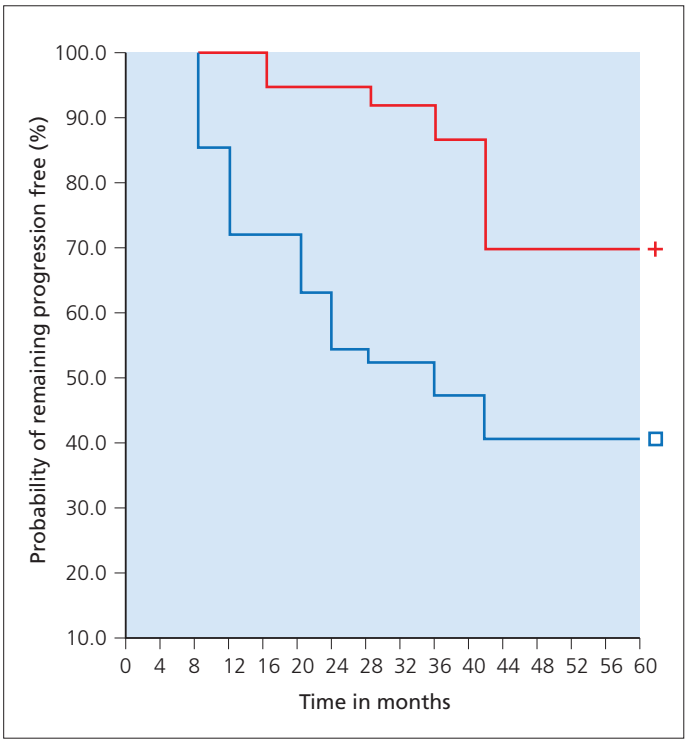



**Figure 18.11** Treatment of relapsing–remitting multiple sclerosis with scheduled pulses of methylprednisolone (MP). Time survival curve to the onset of sustained EDSS score worsening. Log rank test $p < 0.001$. + = pulse MP; □ = control group. Adapted from Zivadinov *et al* (2001a). © 2001, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

differences in relapse rates, number, or time to relapse (Figure 18.11). Are these findings definitive? Regrettably not. Although certainly they are of great interest in that this is the longest trial to date (5 years) and corticosteroids are inexpensive and generally well tolerated; the putative effects on cerebral atrophy reported are, to date, unmatched so that the study needs to be repeated. The decision not to blind the evaluator was a major design flaw. This omission may have significantly biased the clinical assessments, lending a spurious credence to the reported result (Noseworthy *et al* 1994). That said, the MRI evaluations were blinded and seem robust, although cerebral atrophy measures have not been validated as definitive outcomes. Cerebral volumetric measures are clearly influenced in the short term by the use of corticosteroids, and artefacts arising from suppression of inflammation. If independently confirmed, the findings would suggest that regularly administered corticosteroids delay or prevent irreversible tissue injury. In turn, such a result would support the hypothesis that corticosteroids act to inhibit nitric oxide and excitotoxic mechanisms of neuronal and axon injury (see Chapter 10). We are not aware that a confirmatory trial is under way.

As we discuss in Chapter 4, new episodes cluster in women with relapsing–remitting multiple sclerosis during the puerperium. For this reason, De Séze *et al* (2004) treated 20 women who had recently completed a pregnancy prophylactically with methylprednisolone (1 g monthly for 6 months) and noted a lower relapse rate (0.8 ± 0.41) compared with 22 females observed expectantly a few years earlier (2 ± 0.66).

## THE BETA INTERFERONS

The 1990s were dominated by the publication of large clinical trials evaluating the three brands of IFN-β and glatiramer acetate as disease-modifying drugs in multiple sclerosis, and the consequent managed introduction of these products into clinical practice. Interferons were first used in multiple sclerosis because of their antiviral activities. At first, no emphasis was placed on the type of interferon and each was assessed after administration by the systemic or intrathecal route. A series of pilot studies, mostly uncontrolled and involving small numbers of patients, was performed in the 1980s. These involved IFN-α (Camenga *et al* 1986; Knobler *et al* 1984), IFN-β given systemically

(Baumhefner *et al* 1987; M. Huber *et al* 1988; K.P. Johnson *et al* 1990; Ververken *et al* 1979) or by the intrathecal route (Confavreux *et al* 1986; Jacobs *et al* 1981; 1982; Milanese *et al* 1990), and IFN-β (Panitch *et al* 1987a; 1987b). The role of IFN-α and IFN-γ is discussed above. In general, many details of these inaugural studies are now more of historical interest than providing evidence for the clinician wishing to assess the role of IFN-β in the management of multiple sclerosis, since they have been updated and superseded by the pivotal clinical trials discussed below. However, the pioneering work of Larry Jacobs (1938–2001) should be mentioned.

Initially, Jacobs carried out an unblinded trial of intrathecal natural IFN-β in 20 patients (Jacobs *et al* 1981). There was an effect on relapse rate and this work was extended to a single-blind (sham lumbar puncture) study in which 69 patients also showed a reduction in annual relapse rate (0.8 in treated patients compared to 1.5 in controls; $p < 0.001$: Jacobs *et al* 1986b; 1987). There were practical problems associated with the use of intrathecal interferon and difficulties in obtaining natural IFN-β. Together with results suggesting an increase in disease activity in patients receiving natural interferon (Milanese *et al* 1990), no further progress was made until recombinant IFN-β was shown to be effective after parenteral administration. It was subsequently recognized that the immunological effects and physiological situations that characterize release of the naturally occurring interferons differ for IFN-α and IFN-β from IFN-γ. The results of clinical trials led to the conclusion that IFN-γ is contraindicated in multiple sclerosis and that IFN-α is not obviously effective, although its use has not altogether been abandoned (see above). However, IFN-β survived this filtration process, attracting increasing attention because of the accumulation of evidence for its partial efficacy together with vigorous marketing on a scale to which neurologists looking after people with multiple sclerosis had not previously been exposed. By comparison with azathioprine, for example, the processing of comparative clinical results attributable to IFN-β (see below) has been demonstrably less restrained.

In summary, the IFNB Multiple Sclerosis Study Group trial showed that patients receiving IFN-β1b (Betaseron 8 MIU by self-administered subcutaneous injection on alternate days) had a reduced relapse rate, although the effects on disability and disease progression did not reach conventional levels of statistical significance. Much was made of the reduction in MRI activity seen in the IFN-β1b (Betaseron) study and the extent to which this provided evidence for a disease-modifying effect. Subsequently, IFN-β1a (Avonex; 6 MIU intramuscularly on a weekly basis) was shown to reduce relapse rate and slow the rate of disability and the time to progression. The report on IFN-β1b (Betaseron) appeared in 1993, with an update in 1995. The study of IFN-β1a (Avonex) received much advance publicity but did not appear until January 1996. Sandwiched between these primary publications was a deluge of commentaries, vigorous marketing efforts by the pharmaceutical companies who stood to gain from the introduction of these products, and the jottings of several seriously ill-informed journalists. The immediate consequence was that, initially, neurologists were asked to prescribe IFN-β before it was licensed or widely available and often in settings where governments restricted its use. This complex situation subsequently evolved. Interferons became widely available for use in relapsing–remitting multiple sclerosis and, in some countries, for secondary progressive disease. Governmental efforts to ration their use still vary widely. Many countries and groups of opinion leaders have developed guidelines for prescribing these agents. Despite these efforts, however, there remains no evidence-based definition of 'responder' status or 'treatment failure'. Consequently, practitioners and patients struggle daily with decisions of when to start, change or stop the use of these agents.

## The mechanisms of action

Most cells express receptors for type 1 interferons. IFN-α and IFN-β share and compete for the same site, transducing signals through protein tyrosine kinases, phosphorylation of signal transducers and activation of transcription factors (STAT1 and STAT2), formation of the IFN-stimulated gene factor 3 from the association of STAT1 and STAT2 with the p48 protein, and binding of this gene factor to promoter elements resulting in gene transcription (Karpusas 1998). IFN-γ uses a different receptor but stimulates some of the same intracellular signalling molecules. Collectively, the interferons show a variety of antiviral, antimicrobial, antitumour and immunological effects (for review, see Goodkin 1994; Weinstock-Guttman *et al* 1995; Yong 2002). If IFN-β has a role in modifying the long-term course of multiple sclerosis, it is almost certainly not through any effect on the response to viral infection, as originally suggested, and the recent logic for continued use in clinical practice rests on the results of laboratory studies that shift the emphasis on mode of action to immunological properties. T-cell-derived IFN-γ has mainly proinflammatory effects and this explains why it increases disease activity in multiple sclerosis.

The logic for using IFN-β is now based not only on the argument that IFN-β inhibits the actions of IFN-γ, but also from a wide variety of additional presumed mechanisms of action including inhibition of T-cell activation, modulation of cytokine production and reduction in T-cell migration. In this respect, IFN-β can be considered as an anti-inflammatory cytokine but it also enhances some components of the immune response. This literature is abundant and often conflicting. Research remains active and, as expected given the plethora of potential sites of activity, the story is self-evidently incomplete and not without its share of ambiguities on the specific immunological effects and their relevance for treated patients. Inevitably, individual commentators tend to focus on the mechanisms that address their preferred concepts for the pathogenesis of multiple sclerosis. We are not exempt from these accusations of parochialism. Table 18.2 provides contemporary references for recent work on the potential mechanisms of action of IFN-β, a subject comprehensively reviewed by J. Zhang *et al* (2002). Exposure of microglia to IFN-γ *in vitro* increases the expression of cell surface class II MHC antigen (Woodroofe *et al* 1989) and the constitutively expressed T helper type 1 (Th1) costimulatory molecule B7 (K.E. Williams *et al* 1994). This upregulation is inhibited by IFN-β in a dose-dependent manner. The effect is most pronounced when IFN-β is introduced *in vitro* prior to IFN-γ exposure but is still evident when IFN-β is added after exposure of microglia to IFN-γ. Since this inhibition is not associated with a decrease in class II mRNA within cells, the mechanism is considered to be post-transcriptional and, given that class II heavy chain accumulates within cells, presumably post-translational. Revel *et al* (1995) have shown that the molecular interactions of IFN-β and IFN-γ involve the STAT1 transcription

**Table 18.2 Presumed mechanisms of action of the beta interferons**

**Inhibits T-cell costimulation and/or activiation processes**

- Inhibits IFN-γ-induced expression of MHC class II molecules and other molecules required for T-cell activation (Arnason *et al* 1996)
- Modulates costimulatory molecules on dendritic and other cell types (Y.M. Huang *et al* 2001a; 2001b; 2001c; 2001d; Z. Liu *et al* 2001)
- Reduces precursor frequency of myelin-reactive T cells (Kozovska *et al* 1999; Zang *et al* 2000b)
- Treatment-induced reduction in costimulatory molecules (Shapiro *et al* 2003)
- Treatment-induced reduction in the number of antigen-presenting dendritic cells (Bergh *et al* 2004)

**Modulates anti-inflammatory and proinflammatory cytokines**

- Increases IL-10 and IL-4 production/expression at protein and mRNA levels (Ozenci *et al* 2000; Rep *et al* 1996; Rudick *et al* 1996b; 1998b; Tuohy *et al* 2000)
- Decreases IL-12 production (Karp *et al* 2001; McRae *et al* 1998; Tuohy *et al* 2000)
- Decreases TNF-α and IFN-γ production (Kozovska *et al* 1999; Rep *et al* 1996; Zang *et al* 2000b)
- Suppresses Th1 cells and upregulates IL-10 production (Zang *et al* 2003)

**Decreases aberrant T-cell migration**

- Enhanced shedding of VCAM-1 from endothelium into soluble form (Calabresi *et al* 1997c)
- Decreases T-cell migration (Prat *et al* 1999)
- Reduced integrin gene expression (Muraro *et al* 2004)
- Inhibits expression of mRNA for MIP-1α, RANTES, and CCR5 (Zang *et al* 2000a; 2001)
- Reduces migration of T cells toward the chemokines RANTES and MIP-1 (Zang *et al* 2001)
- Decreases IL-2-stimulated secretion of MMP (Leppert *et al* 1996; Lou *et al* 1999)
- Treatment-induced reduced MMP-9 levels in PPMS (Yushchenko *et al* 2003)
- Treatment-induced enhanced TIMP-1 levels in RRMS (Karabudak *et al* 2004)
- Reduces secretion of TNF-α and IL-1 (Lou *et al* 1999)

*MHC = major histocompatibility complex; IL = interleukin; mRNA = messenger ribonucleic acid; TNF = tumour necrosis factor; VCAM = vascular cell adhesion molecules; MIP = macrophage inflammatory proteins; RANTES = regulated on activation, normal T-cell expressed and secreted; CCR = chemokine receptor; MMP = matrix metalloproteinases; TIMP-1 = natural tissue inhibitors of MMPs. Adapted from Zhang* et al *(2002) with permission.*

factor and they propose a model involving antagonistic and synergistic actions on different genes whose products relate to cell activation. The increased class II antigen expression on microglia enables these to function as antigen-presenting cells and the proliferation of primed T cells exposed to antigen and IFN-γ activated microglia is inhibited by IFN-β (G. Hall *et al* 1997a). It is well recognized that IFN-β has an antiproliferative effect on T (and other non-immune) cells, inhibiting markers of activation such as IL-2 receptor, transferrin receptor and CD2 (A. Noronha *et al* 1993). Others have shown that the release *in vitro* of IFN-γ by mononuclear cells is reduced in patients treated with IFN-β (Petereit *et al* 1997).

Antigen-specific and IL-2-stimulated proliferation of Th1 cells are inhibited by IFN-β but without reducing their secretion of IFN-γ, TNF-α or macrophage inflammatory protein-1α. In fact, IFN-γ secretion is slightly increased, further demonstrating that the effects of IFN-β are complex and cannot simply be seen as suppression of IFN-γ-stimulated proinflammatory events (M. Pette *et al* 1997). In a comprehensive assessment, H. Jiang *et al* (1995) showed that IFN-β inhibits the ability of human antigen-presenting cells and B lymphocytes to induce T-cell proliferation. These inhibitions are associated with reduced expression of class II MHC antigens and adhesion molecules.

Taken together, these *in vitro* results suggest that IFN-β prevents the arrival of T cells and limits antigen presentation within the central nervous system, disengaging the amplification of local immune responses involving microglia and (antigen-specific) infiltrating T cells. IFN-γ also promotes the cytotoxic and phagocytic activities of microglia by increasing their respiratory burst and inducing the release of many mediators, but the interaction of IFN-γ and IFN-β on these properties is less straightforward. Rodent microglia exposed to IFN-γ increase the expression of Fc receptors and this effect is enhanced by IFN-β (G.C. Hall *et al* 1997b). IFN-β also directly stimulates the production of potentially harmful cytokines including TNF-α by microglia, further promoting their cytotoxic and phagocytic properties. TNF-α has a complementary effect on the ability of IFN-γ to increase class II antigen expression, demonstrating that intricate networks exist between pro- and anti-inflammatory cytokines. In samples obtained from patients before and during treatment, Brod *et al* (1996) showed that mitogen-induced production of cytokines (IFN-γ, IL-2, IL-6 and IL-10 but not IL-4 or TNF-α) is increased by IFN-β. Porrini *et al* (1995) took a slightly different position claiming that, *in vitro*, IFN-β induces the production of IL-10 and cytokines characterizing Th2 cells – a response not reproduced by IFN-γ. IL-10 released in response to IFN-β inhibits the production of TNF-α and IL-6 induced by IFN-γ and other macrophage activators. Others have since confirmed the antiproliferative effect of IFN-γ on human T cells *in vitro*, adding the observation that cooperation between T and B cells is also inhibited and emphasizing the anti-inflammatory consequences of the associated enhanced IL-10 production (Rep *et al* 1996; Rudick *et al* 1996b; see Chapter 11). IL-1 and IL-10 and transforming growth factor-β (TGF-β) tend to reduce class I antigen expression, providing evidence for a cascade of anti-inflammatory effects on antigen presentation in the central nervous system (Cowan *et al* 1991b; Racke *et al* 1991). IFN-β also inhibits antigen presentation of peripheral blood mononuclear cells through an effect on class II antigen expression (H. Jiang *et al* 1995). IFN-β inhibits IL-1-induced and IFN-α-induced production of nitric oxide (L.L. Hua *et al* 1998) and protects neurons from nitric oxide-mediated damage to mitochondrial complexes II/III and IV (Stewart *et al* 1998).

IFN-β and IFN-γ may therefore independently enhance the cytotoxic and phagocytic properties of microglia. At the very least, there does not appear to be complete reciprocal inhibition. Conversely, the antigen-presenting effects of IFN-γ-stimulated microglia are inhibited by IFN-β (G. Hall *et al* 1997a; 1997b). Given the part inhibitory and part complementary effects, it would be too simple to designate IFN-γ and IFN-β as entirely proinflammatory and anti-inflammatory cytokines, respectively.

The fact that IFN-β also inhibits class II expression on endothelial cells [in this situation, probably through a transcriptional mechanism (A. Miller *et al* 1996)] provides an additional potential mechanism of action through effects on cell migration across the blood–brain barrier (Huynh *et al* 1995). Further evidence is

provided by the demonstration that the IL-2-induced secretion of metalloproteinases by T cells, which normally enhances their ability to adhere and migrate through endothelial barriers, is reduced by preincubation *in vitro* with IFN-β, probably by a direct effect on IL-2 receptors (Leppert *et al* 1996). Others have assessed changes in the endothelium and conclude that IFN-β, by reducing the secretion of matrix metalloproteinases, inhibits cell migration and limits the ability of T cells and natural killer cells to cleave fibronectin on the basement membrane of endothelial cells (Stuve *et al* 1996). These studies specifically implicate matrix metalloproteinase-9. Corsini *et al* (1997) showed a reduction in adherence between mononuclear cells from patients treated for at least 6 months with IFN-β on cultured brain endothelia derived from a patient with multiple sclerosis. This was associated with reduced expression of HLA-DR on endothelial but not mononuclear cells, and with no effect on other adhesion molecules. Related work shows also that IFN-β affects the migratory activity of mononuclear cells by inhibiting their production of matrix metalloproteinase-9 (Stuve *et al* 1997). Recently, two groups have studied the effects of interferons on matrix metalloproteinase-9 and a tissue inhibitor of metalloproteinase (TIMP-1). Yushchenko *et al* (2003) showed that treatment with IFN-β1b produced reduced levels of serum matrix metalloproteinase-9 in all but one of 19 patients with primary progressive multiple sclerosis; there were no consistent changes in TIMP-1 levels. Karabudak *et al* (2004) reported that IFN-β1a treatment induced transient increases in TIMP-1 levels compared with baseline (at 3 and 6 months but not at 1 year) in a study of 16 patients with relapsing–remitting multiple sclerosis. However, no consistent changes were detected in matrix metalloproteinase-9 levels. Again, the relevance of these findings remains uncertain.

In a study of 35 patients with relapsing–remitting multiple sclerosis and 12 with secondary progressive disease, Shapiro *et al* (2003) demonstrated that treatment with IFN-β1a (Rebif) may induce changes in the ratio of costimulatory molecules (for example, suppression of CD80 and induction of CD86) detected within the first year of treatment that favour a Th2 predominance. They raise the theoretical concern that these patients could be at risk of humoral mediated autoimmunity or allergic phenomena.

An effect of IFN-β on lymphocyte migration, and hence inflammation, is also provided by the demonstration of reduced very late antigen-4 (VLA-4) expression on monocytes (Soilu-Hanninen *et al* 1995) and lymphocytes from a small group of treated patients, but this finding could not be reproduced *in vitro* (Calabresi *et al* 1997a; Muraro *et al* 2000). The interferons may increase shedding of vascular cell adhesion molecule (VCAM) and intracellular adhesion molecule-1 (ICAM-1) from endothelial cells thereby increasing circulating levels of these adhesion molecules (Calabresi *et al* 1997c). IFN-β treatment could thereby block migration of activated T cells by reducing the concentration of endothelial membrane-bound adhesion molecules. Alternatively, once shed from the cell surface, these soluble adhesion molecules may block their respective receptors on activated peripheral blood mononuclear cells [for example, soluble ICAM-1 binding to lymphocyte function associated antigen (LFA) and Mac-1; and soluble VCAM binding to VLA-1]. In a recent study of 50 patients with relapsing–remitting multiple sclerosis treated with IFN-β1a and IFN-β1b, Muraro *et al* (2004) reported that integrin gene expression of VLA-4 and LFA-1 is reduced in patients classified as 'IFN responders', raising the intriguing (but unconfirmed) suggestion that transcription of integrin genes may correlate with the treatment effect.

In summary, IFN-β probably exerts its effects through a variety of mechanisms. These include actions that reduce T-cell and monocyte activation and lymphocyte proliferation, decrease the proinflammatory cytokine bias that is thought to underlie some of the steps in tissue injury, reduce the IFN-γ upregulation of class II expression, diminish antigen presentation, and reduce T-cell migration through the blood–brain barrier. As discussed later, the putative mechanisms of action of glatiramer acetate differ from those for the interferons but with some interesting overlap and redundancy. These major differences raise a possible role for combination therapy.

## The pivotal trials

The evidence that informed prescribing patterns, and led to product licences for the three brands of IFN-β, was derived from a series of pivotal studies incorporating randomized, double-blind and placebo-controlled designs carried out in the 1990s. IFN-β1b is produced by recombinant DNA technology using *Escherichia coli*. It differs from natural human and recombinant IFN-β1a (made in Chinese hamster ovary cells) in having 165 amino acids (lacking the methionine at position 1), a serine residue substituted for cysteine at position 17 to prevent incorrect disulphide bond formation, and no glycosylation of the asparagine residue at position 80. In the pivotal trials IFN-β1a (Avonex) was administered by weekly intramuscular injection (6 MIU), and IFN-β1a (Rebif; 22 or 44 μg thrice weekly) and IFN-β1b (Betaferon; 8 MIU), and as alternate day subcutaneous injections. These regimens were justified by the demonstration that serum levels of IFN-β1b peak between 8 and 24 hours and return to baseline by 48 hours (O.A. Khan *et al* 1996). There are no obvious differences between IFN-β1b and IFN-β1a in their biological activity or *in vivo* pharmacokinetics. Each is associated with the development of neutralizing antibodies. Here, we review the efficacies and adverse effects of these therapies, and the position that has emerged on the timing of treatment with respect to disease course. In turn, these inform the evidence base for the role of IFN-β in the management of multiple sclerosis at several stages of the illness. The sponsors of trials n multiple sclerosis have used an inconsistent and unhelpful format for designating doses of the interferons. To avoid controversy with regard to bio-equivalence, we refer to these studies using the doses as published. For reference, subcutaneous IFN-β1b has been tested in doses of 1.6 and 8 MIU (Betaseron) and 22 and 44 μg (Rebif). Intramuscular IFN-β1a (Avonex) has been tested predominately at 30 μg. On a mass basis, 6 MIU equates to 22 μg and 8 MIU to 44 μg.

### *IFN-β1b (Betaferon)*

The pilot study of IFN-β1b was used to determine primary outcome measures for the definitive trial (K.P. Johnson *et al* 1990). Compared with seven controls, treatment in 24 patients using different doses of IFN-β1b showed a modest effect on relapse frequency. During treatment, patients receiving IFN-β1b had a

relapse rate of 0.7 per year compared with 0.9 per year in the placebo group; and the probability of remaining relapse free at 3 years was 83% compared with an estimated pretreatment rate of 63%. There was no effect on disability. In fact, the treated group did marginally worse.

The phase three trial was conducted simultaneously in Canada and the United States (IFNB Multiple Sclerosis Study Group 1993). It involved 372 patients, each having two relapses in the previous 2 years and with pre-entry EDSS scores <5.5 (the mean was about 3.0; Table 18.3). Treated cases were younger and had slightly longer disease duration. Corticosteroids were used during the trial period by 35% and 50% of treated and placebo cases, respectively. Those who did not complete the study (19%) were considered to have remained stable from the point at which they dropped out. The study was not therefore analysed strictly on an intention to treat basis. The results were broadly similar in the Canadian and United States groups. Most commentators consider this to have been a single trial, although attempts were made to represent these as independent and hence confirmatory studies, respectively.

In patients receiving 8 MIU of IFN-β1b, both primary outcome measures – relapse rate and number of relapse-free patients – achieved statistically significant results ($p = 0.0001$ and $p = 0.007$, respectively). Of the secondary end points, reduction in relapse rate in those who continued to relapse ($p = 0.001$), increase in time to first relapse ($p = 0.015$) and second relapse ($p = 0.007$), and reduction in the proportion of relapses judged to be moderate or severe (placebo vs. 8 MIU, $p = 0.002$) were also achieved.

The subsequent experience of these participants was later reported. The overall tone of the second publication (IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group 1995) was notably more sober than the initial paper. Participants had remained in the study for a median time of just under 4 years. Taking this entire period, the reduction in relapse rate associated with the use of IFN-β1b reported in 1993 was maintained at follow-up (8 MIU: 0.78 per year compared with 1.12 for the placebo group; $p = 0.0006$). The main effect of treatment was achieved in the first year. Although there was a reduction in relapse rate, both in treated patients and the placebo group, in each subsequent year, the cumulative reduction beyond year 1 was in fact greater as part of the untreated natural history (–0.63 between years 2 and 5 in placebo-treated patients compared with –0.39 in the treated group; Table 18.3 and Figure 18.12). However, this observation may be somewhat disingenuous since the baseline was lower at the start of year 1 in the treated group, therefore providing less room for manoeuvre in terms of further reduction in relapse rate by comparison with controls. Understandably, the authors emphasized these results as showing a continuing difference in exacerbation rates between treated and placebo groups, year on year, borrowing the substantial reduction in the first year for the subsequent cumulative reduction in

**Table 18.3** **IFN-β1b: updated report of pivotal trials**

| | Placebo | 1.5 MIU | 8 MIU |
|---|---|---|---|
| **Exacerbation rates** | | | |
| Enrolled | 123 | 125 | 124 |
| Number entering year 5 | 56 | 52 | 58 |
| Overall exacerbation rate (baseline-year 5) | 1.12[a] (1.02–1.23) | 0.96 (0.87–1.06) | 0.78[a] (0.70–0.88) |
| **Year-on-year exacerbation rates** | | | |
| Year 1 | 1.44 | 1.22 | 0.96 |
| Year 2 | 1.18 | 1.04 | 0.85 |
| Year 3 | 0.92 | 0.80 | 0.66 |
| Year 4 | 0.88 | 0.68 | 0.67 |
| Year 5 | 0.81 | 0.66 | 0.57 |
| **Reduction in exacerbation rate** | | | |
| Baseline-year 1 | –0.36 | –0.48 | –0.74 |
| Year 2–5 | –0.63 | –0.56 | –0.39 |
| **Disability** | | | |
| Enrolled | 123 | 125 | 124 |
| Number entering year 5 | 56 | 52 | 58 |
| No. with EDSS >1 point | 56/122 (46%) | 59/125 (47%) | 43/122 (35%)[b] |
| Baseline EDSS <3 | 26/58 (45%) | 30/59 (51%) | 20/55 (36%) |
| Baseline EDSS >3 | 30/64 (47%) | 29/66 (44%) | 23/67 (34%) |
| Median time to progression (years) | 4.18 | 3.49 | 4.79[c] |
| **MRI: lesion load** | | | |
| Enrolled | 73 | 66 | 78 |
| Number entering year 5 | 72 | 61 | 75 |
| Baseline MRI (median) | 1503 | 1086 | 1525 |
| Completing year 1 | +6.7 | +5.7 | –4.9 |
| Completing year 4 | +30.2[d] | +10.6 | +3.6[d] |
| Increase: year 2–5 | +23.5 | +4.9 | +8.7 |

*a $p = 0.0001$; b $p = 0.096$; c $p = 0.087$; d $p = 0.04$.*

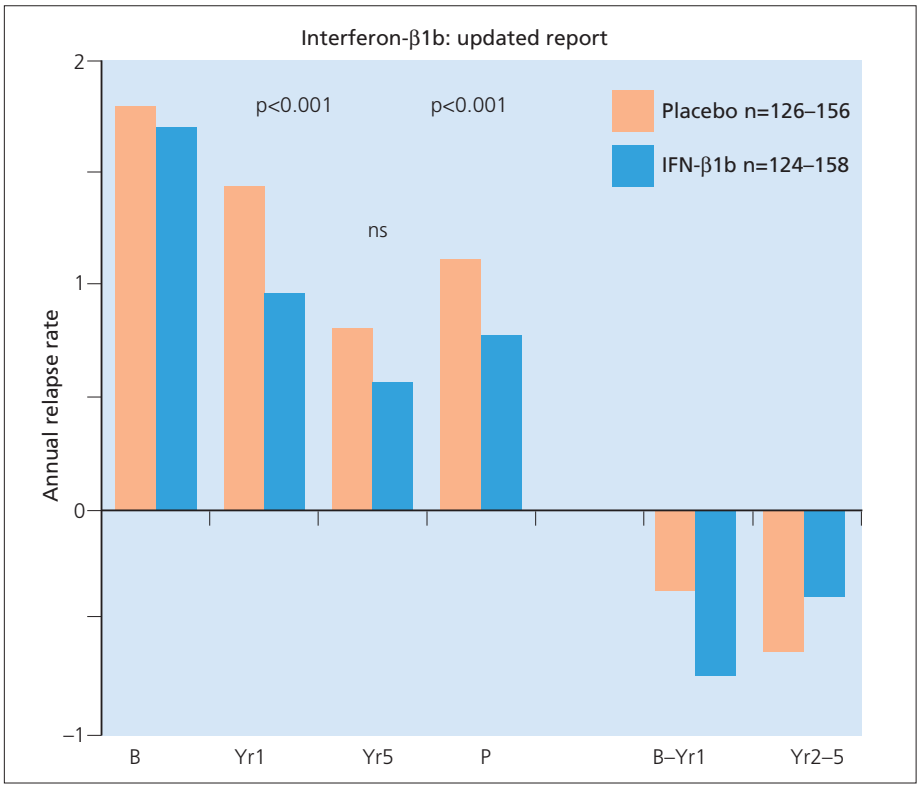



**Figure 18.12** Annual relapse rates at baseline (B), baseline to year 1 (Yr1) and baseline to year 5 (Yr5) and in placebo-treated patients (P) in a trial of IFN-β1b; the rate of reduction is shown from baseline to end of year 1 (B-Yr1) and end of year 1 to end of year 5 (Yr2-5). Adapted from the IFNB Multiple Sclerosis Study Group (1993; 1995). © 1993, 1995, reproduced with permission of Lippincott Williams & Wilkins (lww. com).

relapse rate over the entire period. In this second report, once again IFN-β1b at a dose of 8 MIU reduced the proportion of patients judged to have a moderate or severe relapse compared with placebo ($p = 0.012$) although the data are not shown.

It has since been much debated whether a modest effect on relapse rate is useful for the majority of patients with multiple sclerosis. Relapses are distressing but usually self limiting, although they cause disability if recovery is poor. IFN-β1b may reduce relapse severity but the magnitude of this putative protection is somewhat unclear. In the IFN-β1b trial reports, 'moderate and severe' relapses are grouped together. The numbers of patients with each type of relapse, including those of 'unknown' severity, are not given. That said, it may be that, in protecting individuals from about one relapse every 3 years, IFN-β1b may be more likely to reduce a severe attack than a mild one. Relapses affecting the pyramidal and cerebellar systems are often relatively disabling, at least in the short term, and there were fewer of these in the treated patients. The effect on relapse rate reduced the need for hospitalization, and presumably also the impact on aspects of daily living, although this could not directly be assessed. Critics pointed out that the relapses were self reported and not universally confirmed by the attending neurologist. We understand that analysis only of those relapses that were physician confirmed was still highly significant and so take a charitable view on this design fault, accepting that there was no bias in the distribution of pseudo- and non-relapses in treated patients compared with the placebo group.

In many natural history studies, relapse frequency has not emerged as a factor which predicts disability. In recent studies from the Mayo Clinic (with a small cohort of patients followed closely for several decades), it has been difficult to confirm a close link between relapses and disability. No single demographic or disease variable (including relapse number in the first year) closely predicted prognosis (Pittock *et al* 2004a). In this series, as reported previously (Confavreux *et al* 2000), relapses did not influence further progression after reaching EDSS 3.0 (Pittock *et al* 2004b). In the large Canadian series, however, the number of relapses in the first 2 years, and time to the first relapse after presentation, did each correlate with eventual disability (Weinshenker *et al* 1991a; see also Chapter 4). This has encouraged people with multiple sclerosis that the reduction in relapse rate may have a dividend for an altered natural history of disease. It remains completely unknown, however, whether a reduction in relapse rate attributable to treatment (if this was shown to be long lasting by appropriately designed trials) shares the same good prognosis enjoyed by untreated patients experiencing a relatively relapse-free existence as part of their natural history.

Much has been made of the extent to which the MRI results influenced the overall impact of the IFN-β1b study. The IFNB Multiple Sclerosis Study Group studied a cohort of cases with serial assessments of lesion load (an indicator of the volume of affected brain), supplemented by measures of new and active lesions (Paty *et al* 1993). Comparable at entry, IFN-β1b-treated cases showed a reduction in lesion load within the first year (–4.9%) compared with the placebo group (+6.7%). These differences were maintained into the year 5 but, here too, the early effect attributed to IFN-β1b slipped marginally with time (Figure 18.13). Thus, both for the effect on relapse frequency and MRI lesion load, the experience of the first year proved crucial in this pivotal trial (Table 18.3).

In a subsequent study involving patients not recruited for the IFN-β1b (Betaseron) trial, L.A. Stone *et al* (1995) compared the contrast enhancing new lesion rate in the 7 months before and 6 months after introduction of IFN-β1b. A minimum pre-treatment rate of 0.5 lesions/month was required for entry and

13 of the 14 participants showed a reduction in active lesions. This represented an average change from 3.1/month to 0.5/month ($p = 0.002$). The number was 230 before and 20 after starting treatment with IFN-β1b, a reduction of 90%. Many patients had been studied over a longer period (up to 50 months) and the new lesion rate changed from 2.7/month to 0.2/month. These patients had eight clinical episodes in the pre-treatment period and four during treatment – a surprisingly high number given the MRI results. As an extension of this work, L.A. Stone *et al* (1997) prospectively studied 29 patients having >0.5 lesions/month during a 7 month qualification period. Eighty-six per cent of scans were active before and 33% were active during treatment with IFN-β1b. The median number of new lesions per patient per month dropped from 2.5 to 0.17 ($p < 0.0001$). Inevitably, there was variation between patients, prompting the authors to define a group of nonresponders but these did not have identifiable clinical or natural history characteristics.

A different marker of biological efficacy, measurement of urinary myelin basic protein-like material, was used for some participants in the IFN-β1b study (Whitaker *et al* 1995b). In so far as levels of this breakdown product represent a marker of disease progression and both number of lesions and total MRI lesion load, this result provided further surrogate evidence for efficacy. However, randomization bias prevented detailed analysis of the effect of IFN-β on urinary myelin basic protein.

There was no statistically significant effect of IFN-β1b on disability in these mildly affected patients participating in the North American study and that situation did not change with extension to 5 years (Figure 18.14). Thus, 43 of 122 (35%) treated patients showed a sustained (>6 months) deterioration of ≥ 1 EDSS points compared with 59 of 122 (46%) of the placebo group ($p = 0.10$). These results were uninfluenced by stratification for disability (baseline EDSS <3 and ≥ 3 at entry). It has been argued that restriction of the trial to include only stable, ambulant, relapsing–remitting patients did not give the study adequate power to assess this outcome. Thus, the results can be read as providing evidence for no effect on disability, or no evidence for an effect on disability. This difference in outcome may relate to the relative ease with which new episodes can be defined and the low stringency conditions used to assign relapses in this study, together with the insensitivity of scales routinely used to define disability. We have made the point repeatedly that inflammation and degeneration make different contributions to the pathological processes underlying relapse and progression. Saida *et al* (2005) randomized 205 patients from Japan with relapsing–remitting multiple sclerosis either to receive high- [250 μg (8 MIU)] or low-dose [50 μg (1.6 MIU)] IFN-β1b (Betaseron) three times weekly. As reported previously in the original North American trial, high doses of IFN-β1b were superior to low doses in reducing relapse rates and other measures of

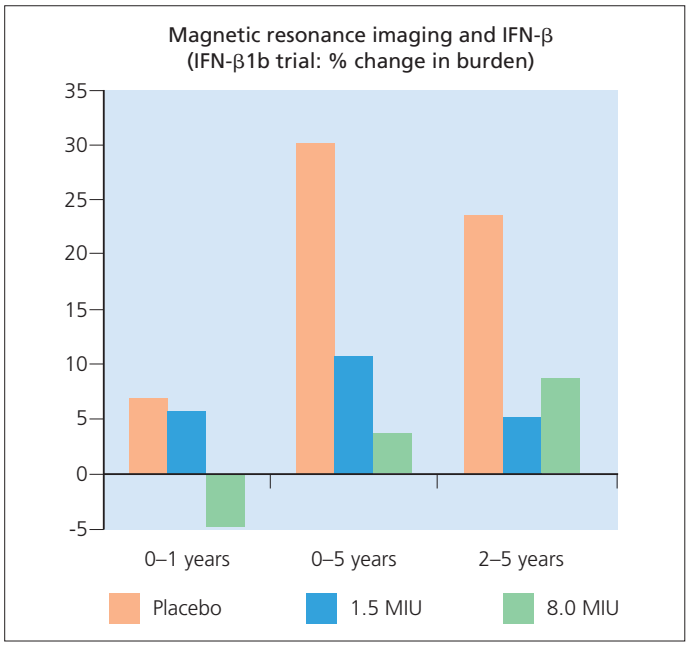



**Figure 18.13** Annual change in MRI disease burden at baseline, baseline to year 1 and baseline to year 5 in patients receiving IFN-β1b; the rate of reduction is shown from baseline to end of year 1 and end of year 1 to end of year 5. Adapted from Paty *et al* (1993) and the IFNB Multiple Sclerosis Study Group (1993; 1995). © 1993; 1995, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

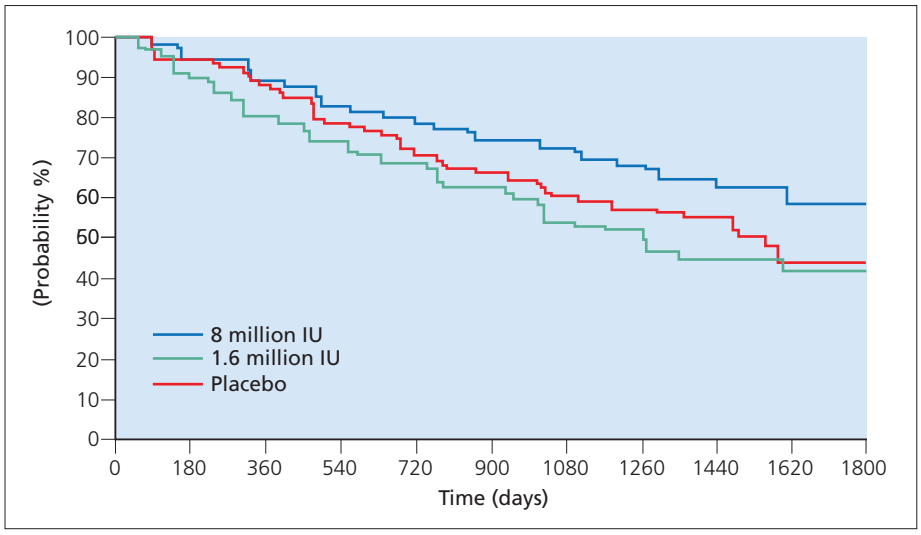



**Figure 18.14:** Kaplan–Meier curves showing, by treatment arm, the probability of avoiding progression of multiple sclerosis equal to at least 1 EDSS point. Adapted from the IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group (1995). © 1995, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

disease activity. This suggests that, despite some differences in phenotype, IFN-β may be no less effective in Japanese populations than elsewhere.

### *IFN-β1a (Avonex)*

The results of a study using IFN-β1a, with disability as the primary outcome measure, were first presented to a joint meeting of the American Neurological Association and Association of British Neurologists in October 1994 and immediately published in abstract form (Anon 1994). Despite widespread distribution of fly-sheets further advertising these results at scientific meetings and a description of the methodology (Jacobs *et al* 1995), no peer-reviewed publication of the results appeared until early 1996 (Jacobs *et al* 1996) by which time the procedure for granting a product licence in the United States and Europe was well advanced. In the trial, existing symptomatic treatments were not discontinued. Relapses were treated (at the discretion of physicians) with corticosteroids and immediate adverse effects of IFN-β1a were prophylactically managed with acetaminophen. Three hundred and one patients with clinically definite multiple sclerosis in the relapsing phase (some with persistent symptoms and signs), and with EDSS scores ranging from 1 to 3.5, were treated with placebo (n = 143 at entry; n = 87 for 2 years) or IFN-β1a (n = 158 and n = 85, respectively; Table 18.4). Each had two or more physician-documented relapses in the preceding 3 years but none in the previous 2 months, and the pretreatment exacerbation rate was >0.67 per year. Compliance with the trial protocol was good, with >99% of assessments completed. There were 23 early exits from the study but assessments continued in these patients. Sample size calculations allowed for 25% of patients to discontinue treatment but remain available for analysis on an intention to treat basis and with 10% lost to follow-up. The drop-out rate was <3%. The decision was taken to restrict recruitment to 288 patients (in fact, 301 had already been enrolled) and to stop the study a year earlier than planned. In retrospect, this was unwise because it has been assumed (wrongly according to the manufacturer) that premature termination of the study was taken with reference to interim efficacy analyses. Whatever the reason, this decision left the study significantly underpowered.

Treatment with IFN-β1a was shown to be associated with a slower rate of disability (defined in advance as deterioration by ≥ 1 point on the EDSS for ≥ 6 months; Table 18.4). The decision to stop the trial early left only 172 (IFN-β1a, n = 85; placebo, n = 87) participants observed for the intended duration of the study. Two years after the start, 22% of 158 patients who had received IFN-β1a were classified as treatment failures compared with 35% of the 143 placebo cases. At this point, two patients had not completed 6 months on the study; 14 (seven in each arm) had been involved for <1 year; 67 (IFN-β1a, n = 32; placebo, n = 35) had been studied for <18 months; and 134 (IFN-β1a, n = 56; placebo, n = 73) had been involved for <2 years (Figure 18.15). The numbers of treatment failures in those who completed 2 years were 18 of 85 (21%) in the IFN-β1a-treated group and 29 of 87 (33%) in the placebo group, respectively. Using the probability of sustained progression in the first year as an outcome also revealed the modest effect on disability (22% and 16% during year one, and 12% and 11% during year two, for placebo and treated patients, respectively; p = 0.02: Figure 18.16). These proportions did not differ between those who completed a second year in the study and those who did not.

**Table 18.4 IFN-β1a (Avonex): pivotal trial**

| | Placebo | IFN-β1a |
|---|---|---|
| Number enrolled | 143 | 158 |
| Number completing year 1 | 136 | 151 |
| Number completing year 2 | 87 | 85 |
| **Change in disability** | | |
| Sustained progression at year 1 | 22% | 13% |
| Sustained progression at year 2 (all patients)[1] | 35% | 22% |
| Sustained progression at year 1 | 22% | 13% |
| Sustained progression at year 2 (patients completing 2 years on study) | 33% | 21% |
| Change in EDSS at 2 years: –<1 point | 12% | 19% |
| Change in EDSS at 2 years: +<1 point | 37% | 24%[a] |
| **Change in relapse frequency** | | |
| Relapse frequency at 2 years: <2 | 56% | 68% |
| Relapse frequency at 2 years: >2 | 44% | 32% |
| Change in relapse rate: all cases | –0.38 | –0.53[b] |
| Change in relapse rate: at 2 years | –0.30 | –0.59[c] |
| **MRI** | | |
| Change in $T_2$ lesion volume: year 1 | –3% | –13%[a] |
| Change in $T_2$ lesion volume: year 2 | –7% | –13% |
| Number of Gd+ lesions: baseline | >174 | >196 |
| Mean number of Gd+ lesions: baseline | 2.32 | 3.17 |
| Number of Gd+ lesions: year 1 | >124 | >85 |
| Mean number of Gd+ lesions: year 1 | 1.59 | 1.04[a] |
| Number of Gd+ lesions: year 2 | >78 | >49 |
| Mean number of Gd+ lesions: year 2 | 1.65 | 0.80[d] |

*a p = 0.02; b p = 0.04; c p = 0.0002; d p = 0.05.*
*Gd = gadolinium.*

Relapse rate (each exacerbation had to last >48 hours and be confirmed by a neurologist) was a secondary outcome measure. Overall, the reduction amongst treated patients was 18%. Fewer treated patients in the cohort who completed 2 years (12 of 85, 14%) had three or more exacerbations during the study than controls (28 of 87, 32%; p = 0.03). In the group studied for 2 years, annual exacerbation rates reduced from 1.2 to 0.61 per year (–0.59) in patients receiving IFN-β1a compared with a reduction from 1.2 to 0.90 per year (–0.30) in the placebo group (a 31% difference; p = 0.002). The reduction in the annual exacerbation rate per patient per year suggested less benefit for all randomized patients (0.82 for placebo compared with 0.67 for treated patients; p = 0.04) than for the subset who completed 104 weeks of follow-up (0.90 for placebo compared with 0.61 for treated patients; p = 0.002; Figure 18.17). In marked contradistinction to the IFN-β1b study, the change in relapse rate was not apparent until the second year of the study. The proportions free from any relapse at 2 years in the IFN-β1a and placebo-treated groups were 38% and 26%, respectively (p = 0.03), and there was no significant difference in time to first relapse between the groups (36 and 47 weeks, respectively; p = 0.34; Table 18.4). Partly in response to critical comments on the IFN-β1a study, the investigators subsequently re-analysed their results using more stringent outcome measures (Rudick

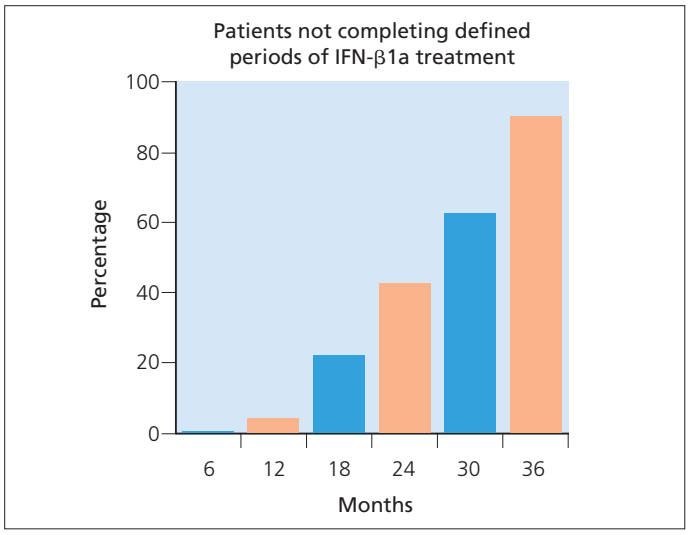



Figure 18.15 Percentage of patients not completing defined periods of treatment with IFN-β (Avonex). Data taken from Jacobs *et al* (1996). © 1996, reproduced with permission of John Wiley & Sons.

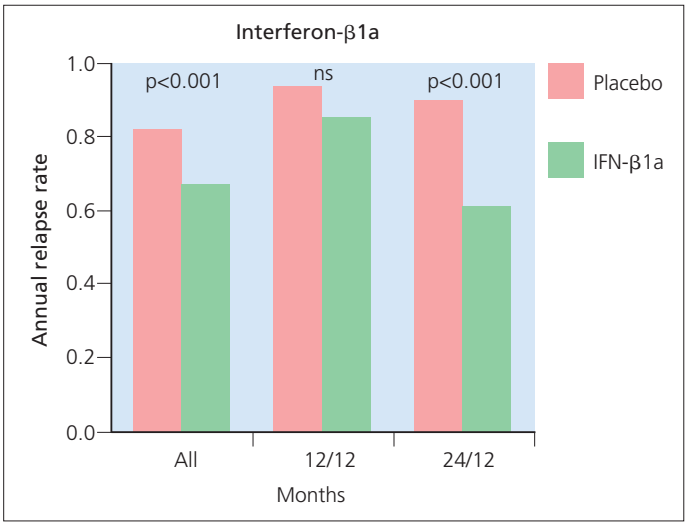



Figure 18.17 Annual relapse rates over the course of the study for all participants taking IFN-β1a (Avonex; All), and those completing year 1 (12/12) and year 2 (24/12). Adapted from Jacobs *et al* (1996). © 1996, reproduced with permission of John Wiley & Sons.

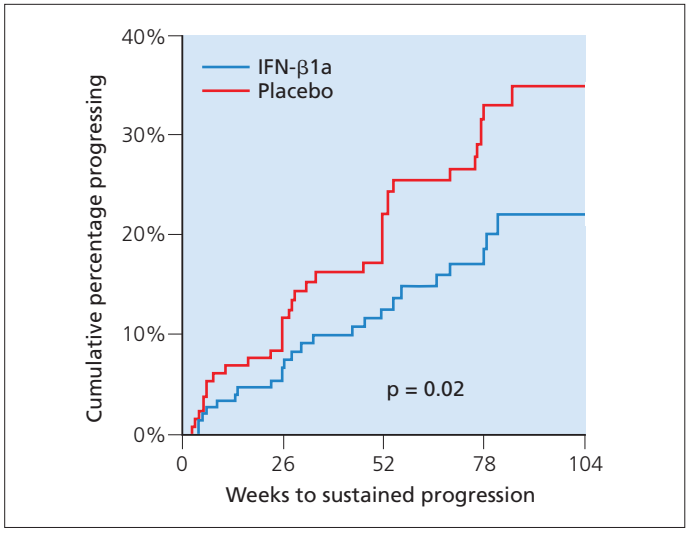



Figure 18.16 Kaplan–Meier failure time curve showing the cumulative percentage of patients taking IFN-β1a (Avonex) progressing according to number of weeks to beginning of sustained disability progression, compared with placebo-treated patients. Adapted from Jacobs *et al* (1996). © 1996, reproduced with permission of John Wiley & Sons.

*et al* 1997). Widening the gap between treated and placebo patients to >2 EDSS points or lengthening the duration of the >1 point difference to 1 year improved the benefits of IFN-β1a to 61% and 67% reductions, respectively, compared with the original estimate of 37% based on differences in the rates of accumulation of disability between groups. For those who did worsen, IFN-β1a failed to discriminate between functional systems. The authors concluded that IFN-β1a affects the magnitude but not the pattern of involvement in multiple sclerosis and that no factor other than randomization to the treatment arm could explain the outcome in this cohort of patients.

This trial also included surrogate markers of disease activity and lesion load. By year one, fewer IFN-β1a-treated patients had gadolinium enhancing lesions (30%) than in the placebo group (43%; p = 0.05) and there were also reductions in the number (p = 0.02) and volume (p = 0.02) of enhancing lesions. The assessment of $T_2$ lesion volumes, which featured strongly in the study of IFN-β1b, proved more difficult to resolve in the trial of IFN-β1a and the significant difference apparent at year one (–3% in IFN-β1a-treated patients compared with –13% in the placebo group; p = 0.02) was not maintained on completion of the second year (–7% and –13% respectively; p = 0.36; Table 18.4). The investigators subsequently updated these imaging results using a different method to measure $T_2$ lesion volume and reported a decrease in the number of new, enlarging, and new or enlarging $T_2$ lesions over 2 years. The increase in $T_2$ lesion volume was 628 $mm^2$ in patients receiving IFN-β1a compared with 1410 $mm^2$ in controls. In the subgroup with active lesions in advance of treatment, these differences were 1285 and 2980 $mm^2$, respectively, over the 2 years but with an increase in acquisition of new lesions in the treated group during the second year (J.H. Simon *et al* 1997). Pohl *et al* (2005) reported their experience treating 51 children and adolescents with relapsing–remitting multiple sclerosis using IFN-β1a once weekly. Although this was not a controlled trial, their report and the accompanying editorial (Banwell and Tremlett 2005) comparing pre- with post-treatment relapse rates suggested that children aged <16 years may benefit and tolerate IFN-β1a in this setting.

### *IFN-β1a (Rebif)*

The effects of IFN-β1a (Rebif) were first assessed in 68 patients using MRI measures as outcome (Pozilli *et al* 1996). The average number of gadolinium-DTPA enhancing lesions decreased from three (SD 4.3) per month during the 6 months prior to treatment with 3 or 9 MIU subcutaneously three times weekly, to 1.3 (SD 2.2) lesions per month during the 6 months on treatment. The

OWIMS study (Once Weekly Interferon for MS Study Group 1999) demonstrated that even small doses of IFN-β1a (22 or 44 μg) administered once weekly influenced MRI evidence of disease activity. In this study, 293 relapsing–remitting patients randomized either to placebo or two doses of IFN-β1a were followed for 1 year. MRI features, combined unique lesions (showing either proton density/ $T_2$ or $T_1$ gadolinium activity) and lesion load, favoured the active treatment groups over placebo although clinical effects were not apparent at either dose. Resolving these issues of dose and frequency of administration has been the subject of several studies carried out since IFN-β1a and IFN-β1b were licensed (see below).

In the pivotal study of IFN-β1a (PRISMS; Prevention of Relapses and disability by Interferon-β1a Subcutaneously in Multiple Sclerosis 1998), 560 patients with relapsing–remitting multiple sclerosis with two or more episodes in the 2 years before (but not within 2 months of) treatment, and an EDSS score of 0–5, received IFN-β1a by subcutaneous injection (6 or 12 MIU) or a placebo preparation three times each week for 2 years. The primary outcome of this 2-year study was the relapse count over the course of the trial. Both doses were associated with a significant reduction in relapse rate compared with controls (1.82, 1.73 and 2.56 over 2 years, respectively; $p < 0.0002$), achieving about a 33% reduction (12 MIU compared with placebo) across the study period. The proportion of patients free from relapse during the 2 years of the study was 32% (12 MIU), 27% (6 MIU) and 16% (placebo) in the two treated groups and controls ($p < 0.005$ and $p < 0.05$, respectively). Both doses achieved a reduction in the severity of those relapses that did occur. Time to confirmed progression of >1 EDSS point increased in each group but, much as in the trials of IFN-β1b and other IFN-β1a preparations, this was less marked than the effect on relapse rate ($p < 0.04$: Figure 18.18). A novel composite score of integrated disability (amounting to the 'area under the EDSS curve over time') showed a 77% reduction in accumulated burden of disability during the study period. MRI was performed twice during the study and a subgroup underwent more frequent analyses. There was a reduction, by around 70% but higher in the more frequently studied cohort, in median number of active lesions per patient on each MRI scan in both treated groups compared with controls. Burden of disease increased by 11% in the control patients and decreased by 1% and 4% in the low-dose and high-dose groups, respectively ($p < 0.0001$).

The authors did not evaluate the success of blinding. As with other contemporary interferon studies, it is likely that patients were able correctly to guess whether they were receiving placebo or active therapy. Whether blinding was maintained for the evaluating physician was not reported. For reasons that remain unclear, the number of patients available for assessing the rate of nonprogression was only 76% of the study population at 1 year, and 70% at 18 months. Follow-up at the time of primary analysis was only 2 years. The authors reported 'confirmed worsening' at 3 months but did not present the data on 6 month and 12 month confirmed worsening. The analysis did not address the degree to which EDSS worsening attributable to relapse contributed to the data on sustained worsening.

An extension trial was started upon the completion of PRISMS. Patients originally receiving placebo were randomized to either low- or high-dose IFN-β1a. Those already receiving interferon continued on their original regimen of active drug (PRISMS Study Group 2001). Ninety per cent of the original 560 patients participated in the extension trial and almost 88% of this cohort completed the 2 year extension study.

The primary outcome in the extension study was relapse count per patient over the 4 years of the entire study. As such, the clinical behaviour (relapse count) in the first 2 years of the original study contributed substantially to the 4 year analysis of the extension. Not surprisingly, the extension trial demonstrated that IFN-β1a provides some protection (in terms of reduction in relapse rate) for those originally treated with placebo, although the trial was no longer blinded since patients and evaluators knew that all were receiving interferon therapy (Figure 18.19). Relapse rates over the 4 years of the study were 0.72 and 0.80 for the 12 MIU and 6 MIU groups, respectively, compared with 1.02 for the placebo patients who were randomized to 12 MIU at the time of the extension phase ($p < 0.001$ for both 'always interferon' groups compared with the group that started on placebo). There was a trend suggesting a marginal benefit for the higher dose of IFN-β1a ($p = 0.07$). Secondary analyses also showed a possible delay in time to confirmed progression for the high-dose group. MRI analyses supported a greater effect on lesion load for the high-dose group ('always 44 μg', 6.2% reduction; all other groups showed an increase in lesion load). Once again, the proportion of patients with neutralizing antibodies was higher in the low-dose group (23.8% vs. 12.5%) and, for the first time, the PRISMS investigators acknowledged that the presence of neutralizing antibodies reduced the clinical benefit on relapse rate (44 μg antibody-negative group, 0.50; 44 μg antibody-positive group, 0.81). In the analysis of this study, the authors did not correct statistically for multiple comparisons. The largest proportion of drop-outs was seen in the high-dose (44 μg) group (23%) – a finding that somewhat undermines confidence in these data. Analysis of the MRI results (Li and Paty 1999) confirmed the previously reported benefit on lesion load at 2 years (placebo, increase of 10.9%; 22 μg, decrease of 1.2%; 44 μg, decrease of 3.8%). Fifty per cent of placebo patients showed >10% increase in lesion load. Similarly, treatment reduced the frequency of active lesions (22 μg, 67% reduction; 44 μg, 78% reduction) and the proportion of patients with inactive scans (placebo, 8%; 22 μg, 19%; 44 μg, 31%). A subset of patients studied with more frequent MRI provided evidence that the treatment benefit could be identified as early as 2 months after starting interferon therapy. MRI atrophy was not evaluated.

As noted, the decision to include the 'relapse counts per patient' in the first 2 years of the original trial seems to have served the sponsor well in the extension phase, as did the accompanying editorial reporting that 'the placebo group never caught up' with the patients originally receiving interferon (Schwid and Bever 2001). This is hardly surprising. To catch up, the original placebo patients would either have had to be more responsive to the effects of interferon than those who were first randomized to the active agents, or the trial would have needed to be sufficiently sensitive to a loss of treatment effect in the third and fourth years of exposure. It is unlikely that the study was powered to demonstrate this effect. Lack of blinding in the extension study limits the conclusions that can be drawn from this phase of the trial considering the subjective nature of the primary outcome. The authors did not report on use of corticosteroids in the patients who changed treatments. Regrettably,

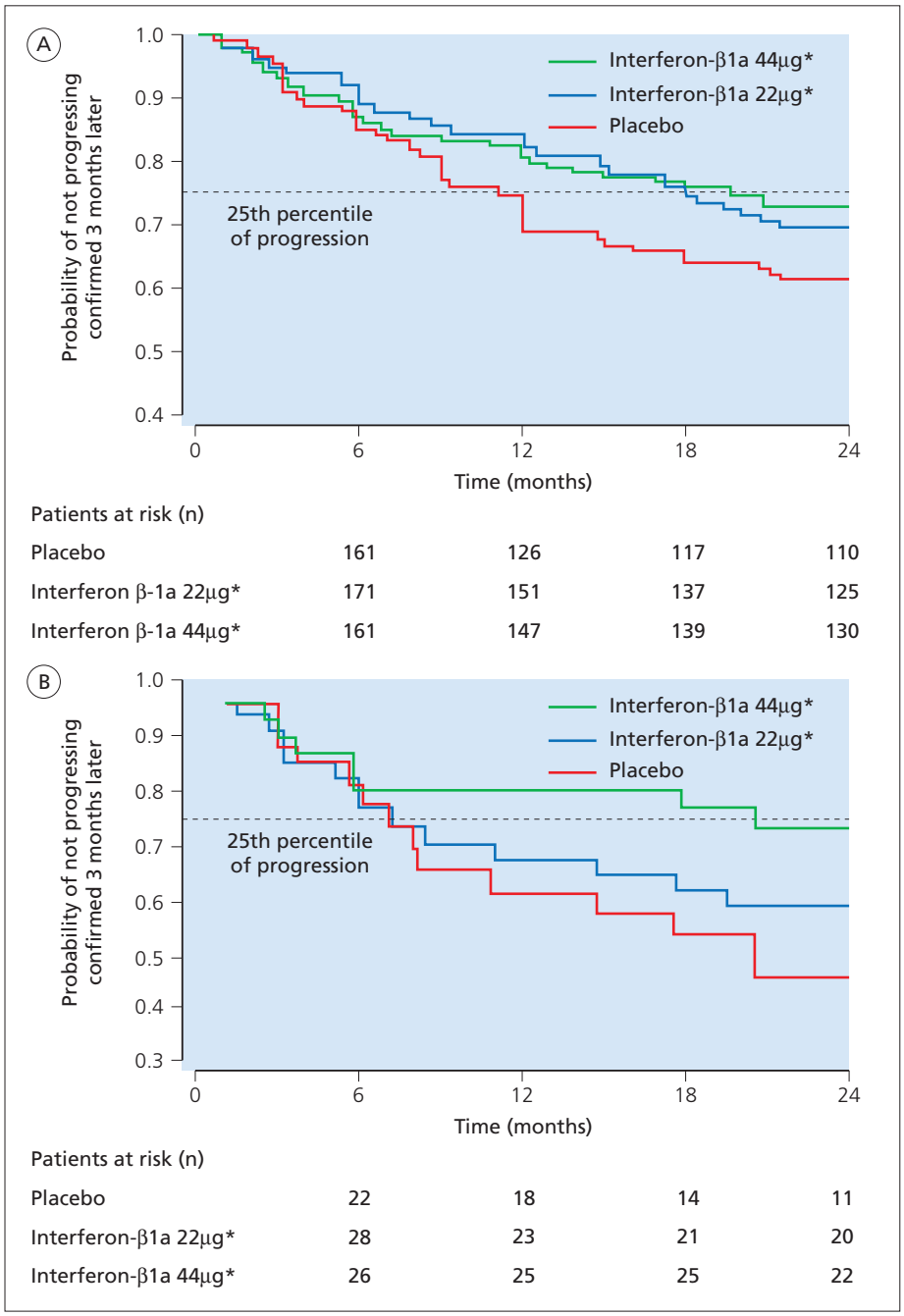



**Figure 18.18** Treatment of relapsing–remitting multiple sclerosis with subcutaneous IFN-β1a (Rebif; PRISMS study). (A) Time to confirmed progression in disability in whole study group. (B) Patients with baseline EDSS >3.5. *$p < 0.05$ compared with placebo. Adapted from PRISMS Study Group (1998). © 1998, with permission from Elsevier.

this study demonstrates once again that multiple sclerosis disease activity continues despite treatment with interferons even at high dose.

## Secondary progressive multiple sclerosis

Although there are many remaining questions surrounding the use of interferons in relapsing–remitting multiple sclerosis, there is at least a general belief that patients who choose to start therapy either with an interferon or glatiramer acetate (see below) can expect up to a 30% reduction in relapse rate over the initial 2 years on treatment. Treating physicians should indicate that there is no definite proof that treatment delays the development of persistent symptoms and signs. In secondary progressive multiple sclerosis, there is much less consensus on the short-term benefits of treatment. Although the interferons appear to reduce relapse frequency in the subset of individuals with secondary progressive disease who continue to experience attacks, it is hard to avoid the conclusion that clinical progression and MRI evidence of cerebral atrophy continue despite treatment. The published trials in secondary progressive multiple sclerosis are summarized in Table 18.5.

The European IFN-β1b study has been published in most detail (Kappos *et al* 1998; D.H. Miller *et al* 1999; Molyneux *et al* 2000). Thirty-two centres contributed 718 patients with secondary progressive multiple sclerosis (EDSS 3.0–6.5). Patients receiving active treatment demonstrated benefit for the primary outcome – time to worsening by 1.0 EDSS point confirmed at

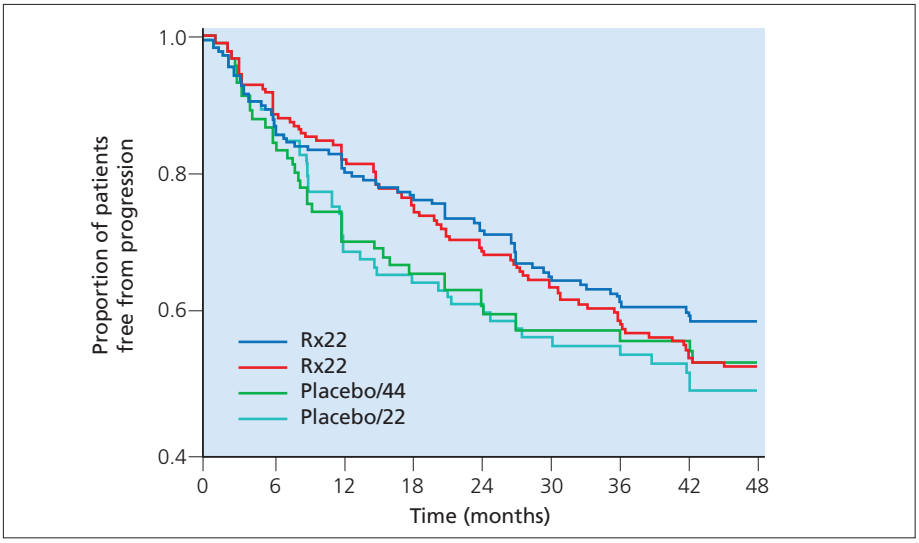



**Figure 18.19** Treatment of relapsing–remitting multiple sclerosis with subcutaneous IFN-β1a (Rebif; PRISMS-4 extension study). Kaplan–Meier curves for time to confirmed progression in disability for years 1 through 4 (all patients). Proportions of patients are those free from progression. Adapted from the PRISMS Study Group (2001). © 2001, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

**Table 18.5 Recent randomized trials in secondary progressive multiple sclerosis**

| Trial (number enrolled; follow-up) | Treatment | Primary outcome | Secondary outcome | Comments |
|---|---|---|---|---|
| European IFN-β1b (718; 3 years) | 8 MIU IFN-β1b by subcutaneous injection on alternate days vs. placebo | Time to EDSS worsening confirmed at 3 months (39% versus 50%; p = 0.0048). Probability of remaining progression-free noted by 1 year | Time to become wheelchair bound, hospitalizations, annual relapse rate, effect on MRI $T_2$ volume and activity. Time to 1.0 and 2.0 point EDSS change. Proportion with either relapses or progression | Year 3, increase of $T_2$ volumes in IFN-β-treated patients. Minor effect on preventing progressive cerebral atrophy |
| SPECTRIMS (618; 3 years) | 22 μg or 44 μg IFN-β1a s.c. on alternate days vs. placebo | No effect on time to 3 month confirmed EDSS worsening (p = 0.88) | Treatment reduced relapse rate. Delayed progression in women at both doses. MRI effect seen on number of active lesions per patient per scan, combined unique activity and $T_2$ volume | Male placebo patients did unusually well. Patients with neutralizing antibodies showed no MRI effect |
| IMPACT (436; 2 years) | IFN-β1a s.c. 60 μg i.m. 1×/week vs. placebo | Benefit on MSFC noted in year 2 | No effect on EDSS | MSFC not validated as disability measure |
| North American IFN-β1b (939; 3 years) | IFN-β-1b s.c. 8 MIU or 5 MIU/$m^2$ q2d vs. placebo | No effect on proportion with confirmed EDSS worsening | Positive effect on relapse rate, MRI activity and $T_2$ volume | No effect on EDSS |
| European mitoxantrone (188; 2 years) | 5 or 12 mg/$m^2$ mitoxantrone every twelfth week vs. placebo (methylene blue) | Benefit on composite measure (EDSS, AI, SNS, time to first attack needing steroids, time to attack) | Number of patients with EDSS progression. Fewer new $T_2$ and Gd+ lesions | Outcome measure not validated, potential cardiotoxicity |

*GA = glatiramer acetate; Gd+ = gadolinium enhancing MRI lesions; IFN = interferon; EDSS = Expanded Disability Status Scale; MIU = million international units; AI = Ambulation index; SNS = Scripps Neurologic Scale; s.c. = subcutaneous; i.m. = intramuscular. Adapted from Noseworthy and Hartung (2003) with permission.*

3 months (0.5 EDSS points, if baseline EDSS was 6.0 or greater; p = 0.0008). There was a 21.7% relative reduction in the proportion of patients reaching this outcome (placebo, 49.8%; IFN-β1b, 38.9%; p = 0.0048: Figure 18.20). This benefit was supported by an analysis of 6 month confirmed worsening, irrespective of whether patients lost to follow-up were counted as stable or worse (p = 0.0016). There was a difference in time to reach the primary end point between the two treatment arms of 9 months that first became apparent by survival analysis in the second year of treatment. A number of secondary outcomes also supported a treatment effect including time to unconfirmed wheelchair dependence (delayed by 9 months; and with a 32% reduction in the number of patients reaching this end point), progressive worsening without relapses, number of hospitalizations, annual

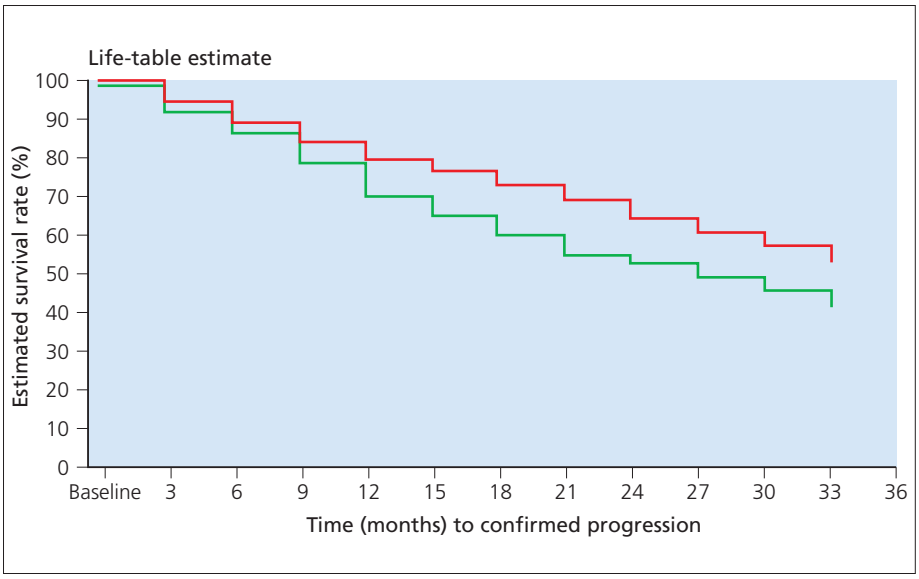



**Figure 18.20** Treatment of secondary progressive multiple sclerosis with IFN-β1b. Time to confirmed progression at study termination (p = 0.007): green line = placebo (n = 358); red line = IFN-β1b (n = 360). Adapted from Kappos *et al* (2001). © 2001, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

relapse rate, time to first relapse, proportion with moderate or severe relapses, and MRI $T_2$ volume (placebo, 8% increase; IFN-β1b, 5% reduction). An analysis of the 125 patients selected for frequent MRI studies (monthly scans between months 1 and 6 and 18 and 24) demonstrated fewer active scans early (65% reduction between months 1 and 6) and late in the study (78% reduction between months 18 and 24). The development of neutralizing antibodies in 27.8% of the IFN-β1b recipients reduced the benefit on relapse rate but not the disability findings (Polman *et al* 2003). Further analysis of the clinical findings reported a small number of patients lost to follow-up (48 of 358 placebo-treated patients; 40 of 360 patients given IFN-β1b). The proportion of patients with 3 month confirmed worsening of at least 2.0 EDSS points was reduced by 27% (p = 0.007). There was a 30% reduction in the proportion of patients either with fewer relapses or no progression (Kappos *et al* 2001). Subsequent analysis apparently confirmed that benefit from IFN-β1b was more likely in patients either with more than two pre-enrolment relapses or worsening of >1.0 EDSS points in the 24 months preceding randomization.

Two additional manuscripts detailed the MRI analysis of this large trial. It was reported by D.H. Miller *et al* (1999) that, at 3 years, there were persistent MRI lesion volume differences between the treatment arms (placebo, 16% increase; IFN-β1b, 2% decrease) although the MRI lesion volume increased for the first time in the IFN-β1b-treated cohort in the third year (p = 0.0001: Figures 18.21 and 18.22). Molyneux *et al* (2000), reporting on a subset of 95 patients in five centres that had MRI studies twice yearly during the 3 years of the study, found that atrophy continued in both treatment groups (placebo, 3.9%; IFN-β1b, 2.9% at 36 months). IFN-β1b treatment seemed to reduce the degree of atrophy developing in patients without evidence of contrast enhancing lesions at baseline (placebo, 5.1% loss of volume; IFN-β1b, 1.8%; p < 0.05: Figure 18.23). These atrophy studies, however, were underpowered because only 65 of 95 patients had the 3 year MRI scan.

The European study resulted in drug approval for the indication of secondary progressive multiple sclerosis in Europe although enthusiasm for its use varies widely amongst neurologists. The second large study of secondary progressive multiple sclerosis failed to confirm an effect on disability (SPECTRIMS; Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-β1a in MS: SPECTRIMS Study Group 2001). Failure of the other trials in secondary progressive multiple sclerosis to demonstrate a convincing benefit has influenced the degree to which this drug is used sparingly in clinical practice.

SPECTRIMS involved 22 centres in North America, Europe and Australia and included 618 patients with secondary progressive multiple sclerosis (baseline EDSS 3.0–6.5) randomized either to receive three subcutaneous doses of placebo each week or IFN-β1a (22 μg or 44 μg). The study failed to demonstrate a significant impact on the primary outcome measure (3 month confirmed EDSS worsening at 3 years; p = 0.146) although an early benefit was apparent at 1 year (Figures 18.24 and 18.25). Secondary analyses revealed the unexpected finding that the primary outcome was positive in female patients for both doses of IFN-β1a compared with placebo (22 μg, p = 0.036; 44 μg, p = 0.006). This may, in part, relate to the observation that men treated with placebo did unusually well (better than women treated with placebo). Interferon-treated patients with pre-enrolment relapses demonstrated a delay in time to progression. Treatment significantly reduced relapse rates (p < 0.001). Subsequent MRI analysis of SPECTRIMS (D.K. Li *et al* 2001) demonstrated a treatment effect on MRI parameters. Specifically, mean number of $T_2$ active lesions per patient per scan was reduced (placebo, 0.67; 22 μg: 0.20, 44 μg: 0.17, p < 0.001) as were monthly combined unique MRI activity ($T_1$ and $T_2$; p < 0.001) and accumulation of lesion load (baseline vs. 3 years; placebo, 10% increase; 22 μg, 0.5% decrease; 44 μg, 1.3% decrease; p < 0.0001). An effect of IFN-β1a was seen particularly in patients who reported relapses in the 2 years preceding randomization. The presence of neutralizing antibodies completely abrogated the evidence from MRI for a treatment effect in this trial.

The North American trial of IFN-β1b in secondary progressive multiple sclerosis is currently only published in abstract format (Goodkin 2000; see Table 18.5). Nine hundred and thirty-nine patients with secondary progressive multiple sclerosis were randomized either to receive placebo or one of two subcutaneous doses (8 MIU or 5 MIU per $m^2$) of IFN-β1b on

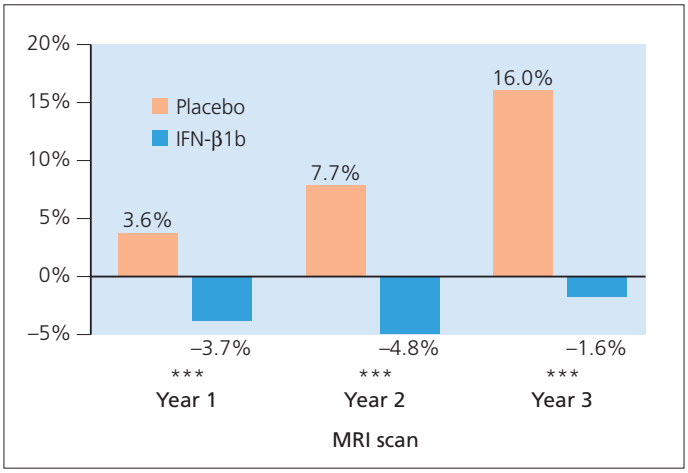



Figure 18.21 Treatment of secondary progressive multiple sclerosis with IFN-β1b. Annual MRI analysis. Percentage change in total lesion volume (TLV; mean) seen in the study cohort during years 1–3 compared with MRI scan at study entry. ***p < 0.0001 for difference between treatment groups. Adapted from D.H. Miller *et al* (1999). © 1999, reproduced with permission of John Wiley & Sons.

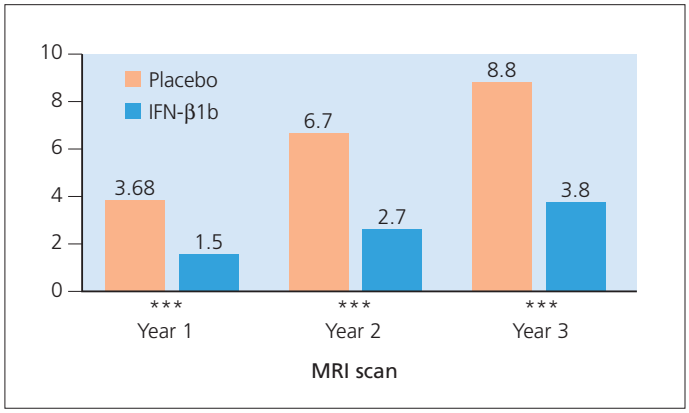



Figure 18.22 Treatment of secondary progressive multiple sclerosis with IFN-β1b. Annual MRI analysis. Cumulative number of active lesions (mean) seen in the study cohort during years 1–3 compared with MRI scan at study entry. ***p < 0.0001 for difference between treatment groups. Adapted from D.H. Miller *et al* (1999). © 1999, reproduced with permission of John Wiley & Sons.

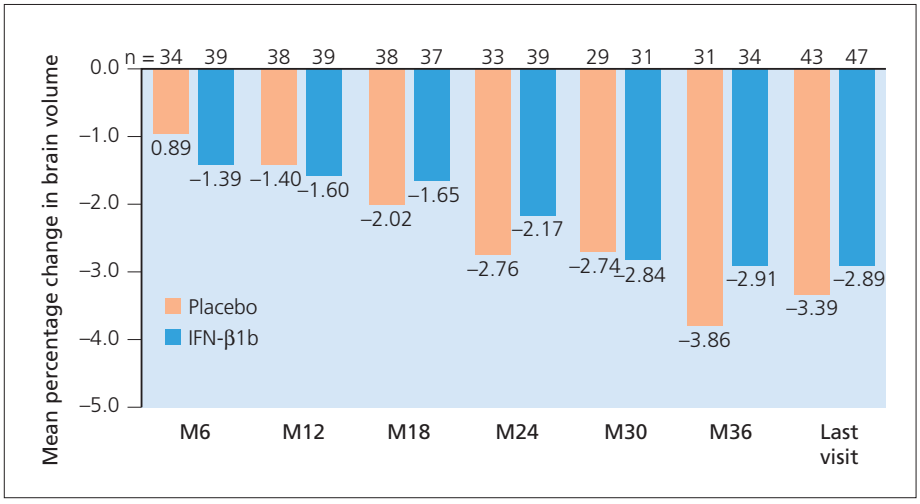



Figure 18.23 Treatment of secondary progressive multiple sclerosis with IFN-β1b. Percentage change in cerebral volume compared with baseline for all patients. M = month. Adapted from Molyneux *et al* (2000).

three occasions per week. The primary outcome (proportion of patients with confirmed EDSS progression at 3 years) was not reached although, as in SPECTRIMS, there were apparent treatment effects on relapse frequency and MRI measures (activity indices and $T_2$ lesion volume).

The final trial, of IFN-β1a in secondary progressive multiple sclerosis (IMPACT; International Multiple sclerosis secondary Progressive Avonex™ Controlled Trial; Cohen *et al* 2002) evaluated whether high dose (60 μg; compared with 30 μg used in relapsing–remitting multiple sclerosis) IFN-β1a given once weekly by intramuscular injection was more effective than placebo as measured by changes at 2 years in the MSFC. These investigators reported benefit using this 'more sensitive' but, as yet, incompletely validated outcome measure. Two components of the MSFC (the nine-hole peg test and the paced auditory serial addition task – PASAT) contributed to the positive findings in this trial (Figure 18.26). No benefit was seen in the timed gait or EDSS (secondary outcome). After reviewing these data, the FDA (United States) did not grant approval for once weekly IFN-β1a in secondary progressive multiple sclerosis.

Although much can be done to alleviate persisting symptoms (Chapter 17), the treatment of secondary progressive multiple sclerosis is largely unsolved. The classification of secondary progression is usually made retrospectively in a patient who, upon reflection, after a period of relapses with recovery appears to have worsened in recent months (years) either as a result of incomplete recovery from relapses or through a relapse-independent gradual decline in performance. In this context, the decision on whether or not to start (or continue) treatment is never easy and involves a careful discussion with the patient of expectations matched against the evidence available from published trials. The case for using IFN-β is perhaps most compelling for untreated patients who also report ongoing relapses. In this subset of patients, there is a good chance that treatment may reduce relapse frequency although the patient should be

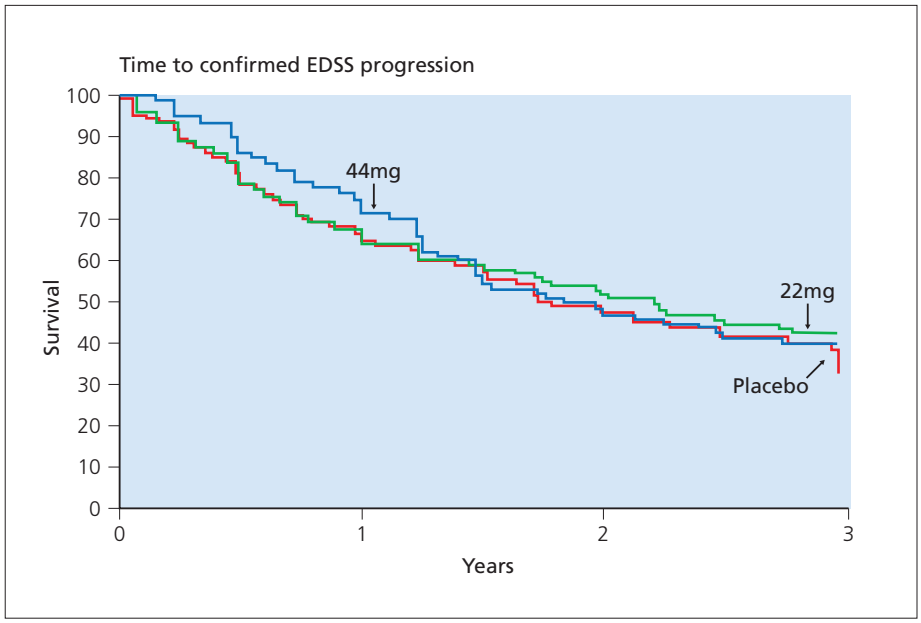



**Figure 18.24** Treatment of secondary progressive multiple sclerosis with IFN-β1a subcutaneously three times weekly. Kaplan–Meier curves for time to confirmed EDSS progression for all patients. Adapted from SPECTRIMS Study Group (2001).

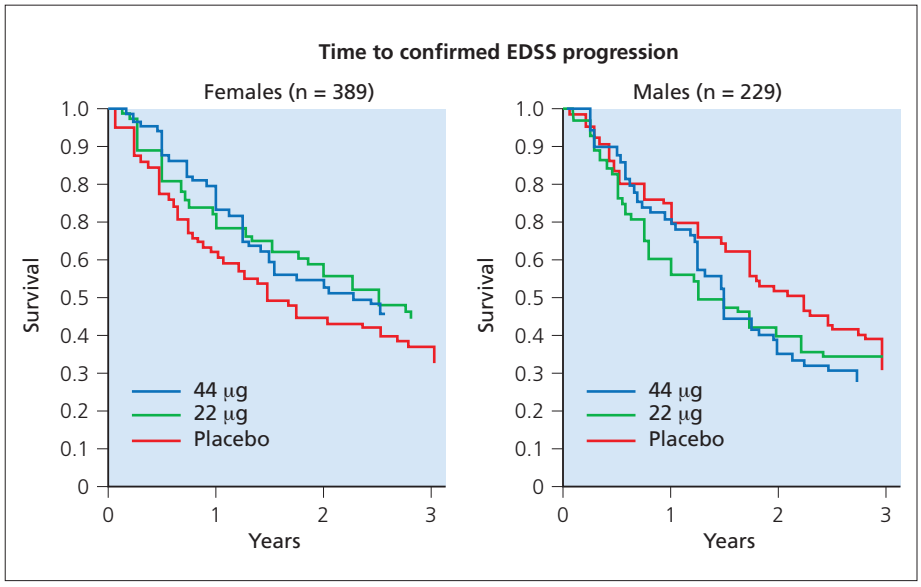



**Figure 18.25** Treatment of secondary progressive multiple sclerosis with IFN-β1a subcutaneously three times weekly. Kaplan–Meier curves for time to confirmed EDSS progression for male and female patients. Adapted from SPECTRIMS Study Group (2001). © 2001, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

advised that attack rate and progression do not necessarily correlate. The situation is no more promising for people with primary progressive multiple sclerosis.

## Primary progressive multiple sclerosis

Trials initiated before the mid1990s frequently failed to distinguish the various chronic progressive disease subtypes and primary progressive patients were lumped with those who once experienced or continued to suffer clinical relapses. In the absence of biomarkers to help determine that a therapeutic intervention is providing early benefit, treatment trials in primary progressive multiple sclerosis have relied upon changes in disability to determine efficacy (Neuhaus and Hartung 2001). Leary *et al* (2003) reported that IFN-β1a (30 μg and 60 μg weekly by intramuscular injection) was well tolerated at the lower dose but neither provided convincing evidence of benefit in a 2 year randomized, placebo-controlled, double-blinded trial of 50 patients with primary progressive disease. The lower dose may have marginally reduced $T_2$ lesion load accumulation but, paradoxically, measures of progressive brain atrophy appeared worse in those randomized to 60 μg weekly. Possibly this group had a greater lesion load at entry and, with a significant anti-inflammatory effect, the higher dose resulted in a more obvious reduction in brain volume.

Montalban (2004) has recently reported the preliminary analysis of a randomized, placebo-controlled phase two trial of IFN-β1b in 73 patients with either primary progressive or transitional multiple sclerosis. This preliminary report suggests that the IFN-β-treated patients demonstrated moderate benefits in the MSFC and MRI parameters ($T_1$ and $T_2$ lesion volume) at 2 years. The full report is awaited.

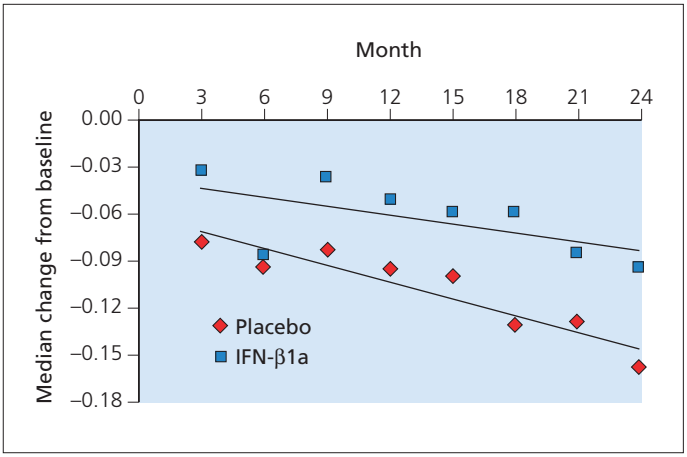



**Figure 18.26** Treatment of secondary progressive multiple sclerosis with IFN-β1a by intramuscular injection once weekly. Median MS Functional Composite change from baseline every 3 months. The trend lines were determined by linear regression. Adapted from J.A. Cohen *et al* (2002). © 2002, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

## Clinically isolated syndromes

Syndromes that may represent the inaugural episode in the natural history of multiple sclerosis have been the focus of subsequent attention with respect to disease-modifying treatments. Three reasons for this shift in attention can be suggested. First, the relative failure of IFN-β to influence features of multiple sclerosis, other than relapse rate, identifies the need to treat patients before the onset of disability and disease progression. Secondly, disease mechanisms that are predicted to be less responsive to cytokine therapy than inflammation are thought to increase with disease duration (see Chapter 10). Not only is there evidence from several sources that immune-mediated axonal injury is seen early in cases of relapsing–remitting multiple sclerosis but it also follows that early intervention with an anti-inflammatory agent might inhibit the cascade of events that leads to disease progression and thereby improve the long-term outlook. However, it should be pointed out that, whilst convincing for cases severe enough to warrant tissue examination, the same logic may not apply to more entrepreneurial examples of clinically isolated syndromes or relapsing–remitting multiple sclerosis. Thirdly, and to adopt a more entrepreneurial stance, early use of drug treatments makes good marketing sense, and each of these studies has been sponsored by pharmaceutical companies poised to benefit from prescribing drift.

Two recent randomized, double-blinded and placebo-controlled trials have addressed the issue of whether treatment with IFN-β1a at the time of presentation protects from recurrent clinical disease activity (Table 18.6). Fifty centres from the United States and Canada participated in the first of these two studies (CHAMPS; Controlled High risk subjects Avonex™ Multiple sclerosis Prevention Study; Jacobs *et al* 2000). Three hundred and eighty-three patients were randomized to receive either IFN-β1a at 30 μg weekly by intramuscular injection (n = 193) or a matched placebo (n = 190) for the duration of follow-up. Prior to starting active or placebo treatment, all patients were treated with methylprednisolone 1 g daily by intravenous injection for 3 days followed by 14 days of oral prednisone (1 mg/kg daily for 11 days then tapering in the final 4 days as follows – 20 mg on the first day, 10 mg on the second day, 0 mg on day three and 10 mg on the final day). Treatment commenced within 4 weeks from onset of the sentinel clinically isolated symptom. To be eligible, patients had to have two or more asymptomatic MR lesions on cranial imaging. Patients were assessed clinically at 4 weeks and every 6 months thereafter. The primary outcome measure was 'conversion to clinically definite multiple sclerosis (CDMS)' as defined by a further clinical relapse (Figure 18.27). When this occurred, patients were removed from the study and offered active treatment with IFN-β1a in an unblinded fashion. MRI studies were not performed at the time of putative conversion to multiple sclerosis. This high profile study was terminated early because of 'evidence for efficacy' in that fewer actively treated patients converted than controls ($p = 0.002$). At this point, 274 of the original 383 patients (71%) had completed 1 year of follow-up. We are struck by how quickly this study was brought to closure [of the 383 original subjects 210 (55%) were followed for 18 months; 131 (34%) were followed for 24 months; and only 61 (16%) were followed for 36 months]. Within months of publication, the United States FDA approved IFN-β1a for use in patients with clinically isolated syndromes deemed to be at high risk of developing multiple sclerosis.

The study bears further scrutiny. The trial was regrettably short, limiting the amount of available clinically relevant information. It is inconceivable that patients were blinded to the treatment received given the nearly universal occurrence of side effects from intramuscular administration of interferon. As such, patients receiving IFN-β1a would almost certainly have been aware that they were on active treatment, and vice versa. The possibility remains that incomplete blinding influenced the reporting of symptoms suggesting a first relapse. The primary outcome in this study was soft and merely required patients to identify symptoms suggesting a relapse. The conversion rate to clinically definite multiple sclerosis seems surprisingly rapid in CHAMPS (at 1 month: 18% in the placebo group vs. 9% of IFN-β1a-treated patients; and 26% compared with 12%, respectively, at 4 months). There have been many other examples where the placebo group did less well than expected thereby inflating the apparent treatment effect. The benefit of treatment in CHAMPS is less impressive if the patients who either converted or dropped out of the study and thereby could not benefit from treatment are considered together (44% of patients receiving IFN-β1a and 56% of the placebo group).

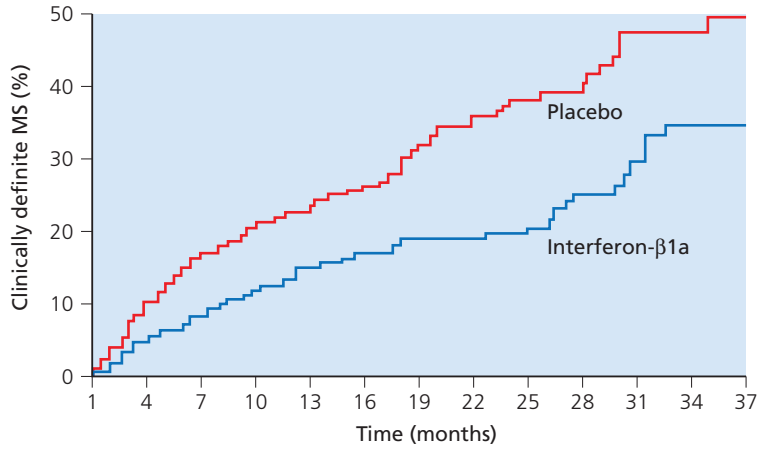
MRI data are presented as number of lesions rather than the proportion of patients showing MRI activity. The study design did not require MRI studies at the time of clinical conversion to multiple sclerosis. Furthermore, there are very few published clinical details and, as noted, no MRI data on two very important subsets of patients – the 46% of those enrolled who converted to clinically definite multiple sclerosis and the 15% who dropped out of the study. The absence of information beyond 18 months brings into question the durability of the effect on MRI features.

The relatively modest benefit of early treatment is perhaps seen more clearly in the observation from a subsequent paper that 50% of patients with clinically isolated syndromes treated with IFN-β1a demonstrated either clinical or MRI evidence of relapse while on treatment within the first 18 months of the study (R.W. Beck *et al* 2002: Figure 18.28). Additional analyses

**Table 18.6** Recent randomized trials in clinically isolated syndromes

| Trial (number enrolled; follow-up) | Treatment | Primary outcome | Comments |
|---|---|---|---|
| CHAMPS (383; 71% 1 year, 34% 2 year, 16% 3 year) | Corticosteroids, then: IFN-β1a 30 μg by intramuscular injection weekly vs. placebo | Delayed conversion to clinically definite multiple sclerosis (p = 0.002) | Patient unblinding likely. 'Soft' outcome measures. Limited follow-up. MRI only on 'stable' patients. No MRI studies beyond 18 months. Limited clinical data published |
| ETOMS (309; 2 year) | IFN-β1a 22 μg by subcutaneous injection once weekly vs. placebo | Delayed conversion to clinically definite multiple sclerosis (45% versus 34%) | Patient unblinding likely. 'Soft' outcome measures. Limited follow-up. MRI only on 'stable' patients. Not all MRI studies available for analysis of volume change |

*IFN = interferon. Adapted from Noseworthy and Hartung (2003) with permission.*




| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Interferon-β1a group | | | | | | | | | | | | |
| Number at risk | 193 | 177 | 164 | 151 | 143 | 139 | 112 | 112 | 73 | 69 | 41 | 36 |
| Clinically definite multiple sclerosis | 9 | 6 | 7 | 5 | 3 | 4 | 0 | 2 | 4 | 3 | 3 | 0 |
| Early withdrawal from study | 7 | 7 | 6 | 3 | 1 | 4 | 0 | 1 | 0 | 0 | 0 | 1 |
| Followed until end of study | | | | | | 19 | 0 | 36 | 0 | 25 | 2 | 1 |
| Placebo group | | | | | | | | | | | | |
| Number at risk | 190 | 165 | 145 | 139 | 131 | 124 | 98 | 90 | 58 | 54 | 26 | 25 |
| Clinically definite multiple sclerosis | 18 | 13 | 7 | 4 | 6 | 8 | 6 | 3 | 1 | 6 | 0 | 1 |
| Early withdrawal from study | 7 | 6 | 0 | 4 | 1 | 1 | 1 | 5 | 0 | 2 | 0 | 0 |
| Followed until end of study | | | | | | 17 | 1 | 24 | 3 | 20 | 1 | 0 |

**Figure 18.27** Treatment of patients with clinically isolated syndromes and abnormal cerebral MRI with once weekly intramuscular IFN-β1a (Avonex; CHAMPS Study). Kaplan–Meier estimates of the cumulative probability of the development of clinically definite multiple sclerosis according to treatment groups. Adapted from Jacobs *et al* (2000). © 2000, with permission of the Massachusetts Medical Society.

have reported that IFN-β1a provides only partial (and we would suggest limited) protection regardless of the specific syndrome (optic neuritis, brainstem/cerebellar or cerebral involvement) and that risk of conversion to clinically definite multiple sclerosis is slightly greater for individuals with optic neuritis (R.W. Beck *et al* 2002), for patients with two or more contrast enhancing MR lesions, and for those already fulfilling MRI criteria for multiple sclerosis in this clinical context (Barkhof *et al* 1997a; CHAMPS Study Group 2002).

In a trial of similar design, the ETOMS (Early Treatment Of Multiple Sclerosis; Comi *et al* 2001a) investigators from 57 centres in 14 European countries randomized 309 patients having

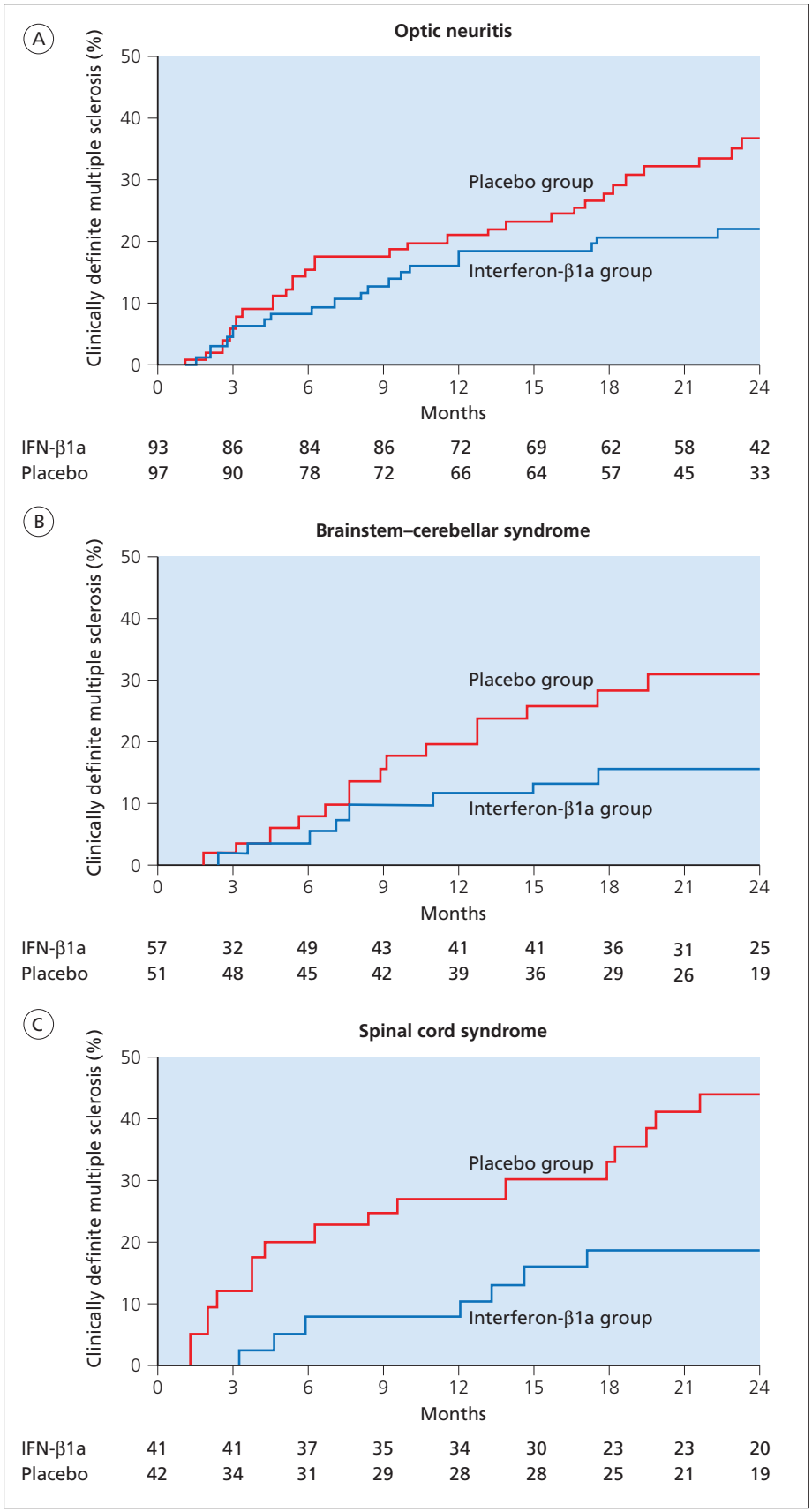



**Figure 18.28** Treatment of patients with clinically isolated syndromes and abnormal cerebral MRI with once weekly intramuscular IFN-β1a (Avonex; CHAMPS Study). Cumulative probability of the development of clinically definite multiple sclerosis by treatment groups according to type of presenting event. (A) Optic neuritis; (B) Brainstem–cerebellar syndrome; (C) spinal cord syndrome. Adapted from Beck *et al* (2002). © 2002, reproduced with permission of John Wiley & Sons.

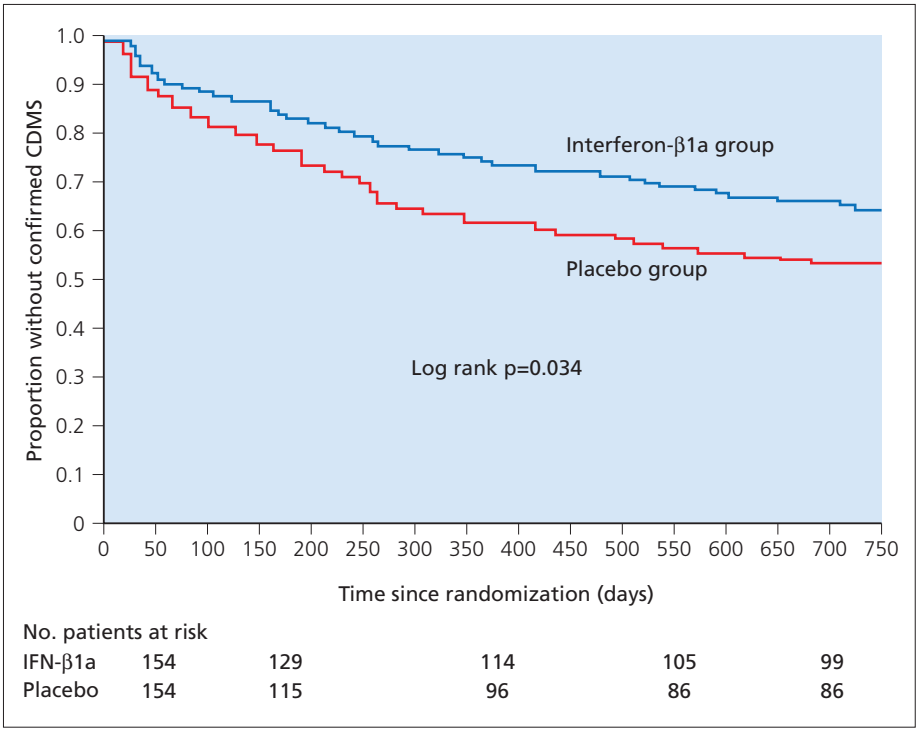



**Figure 18.29** Treatment of patients with clinically isolated syndromes within the last 3 months and abnormal cerebral MRI with once weekly subcutaneous IFN-β1a (Rebif; ETOMS Study). Kaplan–Meier survival curve of probability of no conversion to clinically definite multiple sclerosis over 2 years. Adapted from Comi *et al* (2001a). © 2001, with permission from Elsevier.

clinically isolated syndromes within the previous 3 months if they had four or more MRI lesions, to receive either once weekly low dose (22 μg) IFN-β1a subcutaneously or a matched placebo. Patients were assessed clinically at 1 month and then every 6 months for 2 years, with annual MRI scans. Ninety per cent completed follow-up. At 2 years, the authors claimed a treatment advantage with 45% of placebo-treated patients converting to multiple sclerosis compared with 34% of those receiving IFN-β1a (Figure 18.29). As with CHAMPS, no attempt was made to determine the success of blinding in this trial. In a subsequent manuscript, Filippi *et al* (2004b) reported an apparent benefit on the development of brain atrophy at 24 months in the treated group (30% reduction in the observed decrease in brain volume; –1.18% IFN-β1a vs. –1.68% for the placebo group; $p = 0.0031$). It remains to be determined whether this very small weekly dose of interferon offers an important and potentially long-term benefit. Indeed, the degree of atrophy is so small in the untreated patient (<2% of normalized brain parenchymal volume) that it stretches the imagination to accept that a 30% reduction in this metric will be biologically meaningful in this chronic disease. Accordingly, in an accompanying editorial, D.H. Miller (2004a) offers optimism for genuine protection from irrreversible brain injury but cautions that it remains to be confirmed that this effect on brain atrophy will translate into delayed or reduced disability.

The same concerns arise with respect to the subjective primary outcome measure as in CHAMPS. The frequency with which the MRI studies of asymptomatic patients showed evidence of recurrent disease activity (MRI conversion) has not been published but there are differences between the trials. The patients in ETOMS had a high frequency (39%) of multifocal symptoms at onset (compared with 0% in CHAMPS). The ETOMS patients, therefore, were at approximately a two-fold increased risk of converting to multiple sclerosis in a short time frame. Additionally, the longer interval between symptom onset and entry in the study (3 months vs. 1 month for CHAMPS) probably increased the conversion rate in ETOMS. Only 70% of participants in ETOMS received corticosteroids at the time of randomization compared with 100% in CHAMPS. Despite their limitations, these studies provide evidence that early treatment with IFN-β1a may have a partial, and at least short-term, benefit in delaying further episodes of demyelination either in patients at risk of multiple sclerosis or in those already established in the early stages of the illness. We emphasize again the obvious need to determine whether any of these therapies provides a treatment benefit that is sustained over a prolonged period and is clinically useful. In part, this reflects the lack of robust mechanisms for evaluating the long-term benefits of treatment but it is an enormously important question since there are theoretical benefits in strategies that arrest axonal injury before it has contributed to the progressive and presumably irreversible axonal degeneration that underlies the later stages of multiple sclerosis.

Using a whole brain ratio method, brain atrophy was assessed over 2 years in a placebo-controlled trial of IFN-β1a in relapsing–remitting disease (C.K. Jones *et al* 2001). Atrophy measures were available in 519 patients, 172 of whom were on placebo treatment. Significant brain atrophy was seen in the total cohort. Whole brain ratio at baseline correlated weakly with $T_2$ lesion load and decreased by 1.4% over 2 years but no difference in the rate of atrophy was seen between treatment arms. Cerebral atrophy has been evaluated in 52 relapsing–remitting patients for 6 months before and 24 months following treatment with IFN-β1a, and correlated with other MRI lesion and clinical parameters (Gasperini *et al* 2002). During the 2 years of

treatment, there was a significant reduction of brain volume (mean –2.2%) that correlated weakly with the mean number of enhancing lesions on 6 monthly pretreatment scans. Over the 2 years, 26 patients exhibited significant atrophy and 26 did not. Of the former, 13 experienced an increase in disability whereas only three of the latter became more disabled. This confirms other studies showing a link between increasing atrophy and disability (Losseff *et al* 1996b; Paolillo *et al* 1999). In a 2 year placebo-controlled trial of IFN-β1a in relapsing–remitting multiple sclerosis, atrophy was measured from yearly scans using brain parenchymal fraction. The mean decrease was similar in both arms in year one, but smaller in the IFN-β1a arm in year two (Rudick *et al* 1999). The changes in brain parenchymal fraction during this 2 year period showed little or no correlation with lesion measures. There was c.1% loss of central cerebral volume per year in both the treated and placebo arms. Prolonged 8 year follow-up of the placebo cohort from this trial assessed the long-term relationship between earlier brain parenchymal fraction change and later disability (E. Fisher *et al* 2002). Comparison of quartiles based on change over the first 2 years revealed a greater likelihood of developing severe disability (EDSS ≥ 6 at follow-up) in patients with most atrophy during the initial 2 years.

## Devic's disease (neuromyelitis optica)

As discussed in Chapter 16, the treatment of acute symptomatic neurological syndromes in patients with Devic's disease (neuromyelitis optica) is essentially the same as for multiple sclerosis in relapse. A significant proportion of these patients relapse and stepwise worsening may lead to severe and irreversible neurological disability, often with troublesome pain (Wingerchuk *et al* 1999; Wingerchuk and Weinshenker 2003). Some patients have a malignant course with early disability or shortened life expectancy.

There is limited published experience to guide treatment decisions. There are no proper, phase III randomized trials on which to make evidence-based decisions. Karussis *et al* (1998) have recommended that antiplatelet agents or anticoagulants be used to treat patients with Devic's disease if anti-phospholipid antibodies are present. Mandler *et al* (1998) published an uncontrolled series of seven patients, reporting that long-term oral prednisone and azathioprine may stabilize the course of neuromyelitis optica for a period of up to 18 months. Patients were initially treated with intravenous methylprednisolone (500 mg twice daily) for 5 days and then started on oral prednisolone (1 mg/kg). Prednisone was gradually tapered and then converted to an alternate day schedule, and continued for the full 18 months; on day 21, oral azathioprine was begun at 2 mg/kg. Clearly, confirmatory studies are needed. Anecdotal experience suggests that IFNs are not effective and, theoretically, glatiramer acetate might be contraindicated given the possibility that enhanced Th2 activity would be expected to worsen a humorally mediated disorder such as Devic's Disease (Duda *et al* 2000; Gold and Linington 2002). With recent publications describing antibody- and complement-dependent effector mechanisms of tissue injury (Lucchinetti *et al* 2002) and response to plasma exchange (Keegan *et al* 2002), it seems increasingly likely that immunosuppressive strategies focusing on reducing B-cell function should take preference in seeking to build on immediate improvements (see Chapter 16) and stabilize the longer-term clinical course. Cree *et al* (2005) administered rituximab, a chimeric murine/human monoclonal antibody that binds to the CD20 antigen and depletes B cells, to eight patients with Devic's disease in an open label, pilot trial. Treatment was well tolerated and seemed to suppress relapses. The treated patients generally improved (seven of eight) but – as the authors acknowledge – in the absence of controls, recovery might have been spontaneous. Lennon *et al* (2004) identified a serum autoantibody that may contribute to diagnostic certainty in the evaluation of Devic's disease (see Chapter 7). This IgG antibody has now been shown to bind to the aquaporin-4 water channel suggesting that Devic's disease may be an autoimmune channel disorder (Lennon *et al* 2005). This bioassay should enhance efforts to describe the full clinical spectrum of neuromyelitis optica and hasten the discovery of key antigens involved in triggering the disease and maintaining disease activity.

## Dose effects and comparison of different interferons

Placebo controls were uniformly used during the early period of clinical trials of interferons in multiple sclerosis. There were no 'head-to-head' studies comparing the relative efficacy of different drugs, doses and routes of delivery. This situation has subsequently changed (Table 18.7). Several direct comparisons of licensed and unlicensed products are available and more are under way. It is apparent, and in the main regrettable, that these studies are motivated primarily by competition for market share. Will they provide novel insights that lead to better treatment strategies?

The pivotal trials led to much speculation about the relative merits of subcutaneous injections of IFN-β1b three times weekly compared with the more convenient schedule of giving IFN-β1a by the intramuscular route once each week. The North American IFN-β1b trial showed that alternate day treatment reduced relapse rates by 28–33% in each of the first 3 years of use, and clearly demonstrated a dose effect. The pivotal IFN-β1a study did not report a reduction in relapse rate over the first year, and had a lesser effect in the second than already reported for IFN-β1b, yet it was granted approval by the FDA (United States) for its claim to reduce disease progression. Much like the pivotal North American IFN-β1b trial, PRISMS and SPECTRIMS indicated that a higher dose of interferon was perhaps more effective in reducing relapses than a lower dose when each was administered three times weekly. A study evaluating two doses (30 and 60 μg) of once weekly intramuscular IFN-β1a failed to support a dose effect except for MRI outcomes during the third year (Clanet *et al* 2002). Clanet *et al* (2004) extended the opportunity to these patients to remain on the same dose of IFN-β1a for up to 4 years (56% of the original cohort had completed 4 years of treatment at the time of publication). Again, clinical outcomes were similar between the two groups (30 μg or 60 μg weekly). The Once Weekly Interferon for Multiple Sclerosis Study (OWIMS 1999) showed that a higher dose of once weekly IFN-β1a influenced MRI features more than a lower dose, although neither had a convincing effect on clinical outcomes. Eighty-four percent of the OWIMS subjects agreed to remain on study for the duration of a 4 year extension trial. Freedman *et al* (2005b) reported that once

**Table 18.7** Recent randomized trials in relapsing–remitting multiple sclerosis

| Trial (number enrolled; follow-up) | Treatment | 1° Outcome | Comments |
|---|---|---|---|
| North American GA Extension Study (208; up to 6 years) | Glatiramer acetate 20 mg subcutaneous daily daily injection | Annual relapse rate: reduction reported | Patients enrolled in extension trial had fewer relapses and disability worsening than non-participants. Historical control group contained progressive patients |
| European-Canadian GA (239; 9 months) | Glatiramer acetate 20 mg subcutaneous daily injection vs. placebo | Total number of Gd+ lesions (29% reduction, p = 0.003) | Delayed, partial benefit: first seen by 6 months and many new lesions in GA group; proportion of patients with Gd+, $T_1$ black hole lesion volumes not significant and $T_2$ volumes continue to increase. Short follow-up |
| PRISMS-4 (506; 90% of initial study; 2 + 2 years) | After 24 months, placebo patients randomized to 22 μg or 44 μg IFN-β1a by subcutaneous injection × 3/week | Relapse count over 4 years (p = 0.001) | Unusual primary outcome; no chance for placebo cases to catch up; largest drop-out in 44 μg group. No adjustment for multiple comparisons. Almost achieves a benefit on disability benefit but effect is modest |
| INCOMIN (188; 1 year) | IFN-β1a 30 μg by intramuscular injection × 1 per week vs. 9 MIU IFN-β1b by subcutaneous injection on alternate days | Months 6–12, IFN-β1b superior reduction in relapse rate, proportion relapse-free and EDSS | Only radiologist blinded |
| EVIDENCE (677; 6–12 months) | IFN-β1a 30 μg by intramuscular injection × 1 per week vs. 44 μg by subcutaneous injection × 3 per week | Proportion relapse free favours high dose (75% vs. 63%) | Efforts to blind the evaluators but not patients. Short duration hard to evaluate |
| Tysabri (213; 1 year) | Tysabri 3 or 6 mg/kg by intravenous injection × 1 per month vs. placebo once per month | Fewer Gd+ lesions (p < 0.0001) | Effect disappeared when treatment stopped. Safety concern when given with IFN-β1a |

*Gd+ = gadolinium enhancing MRI lesions; IFN = interferon; EDSS = Expanded Disability Status Scale; MIU = million international units; Tysabri = humanized monoclonal anti-$\alpha_4$ integrin antibody. Adapted from Noseworthy and Hartung (2003) with permission.*

weekly IFN-β1a retains a slightly positive MRI effect with no clinical benefit in patients with relapsing–remitting multiple sclerosis. The results of recent direct comparisons (INCOMIN and EVIDENCE, see below) have been used to strengthen the claim that, although less convenient, exposure to interferon three times weekly outperforms weekly administration, at least for the first 6–12 months of treatment.

The INCOMIN study (Independent Comparison of Interferon Trial) randomized 188 relapsing–remitting patients with multiple sclerosis from 15 centres in Italy either to once weekly intramuscular IFN-β1a or alternate day subcutaneous injections of 8 MIU IFN-β1b, under single-blind (evaluator) conditions (Durelli *et al* 2002). The primary outcome measures were the proportion of relapse-free patients, and no new MRI lesions at 2 years. Both primary outcomes favoured the alternate day dose of IFN-β1b, and the magnitude of the effect became more evident in the second year of study (Figure 18.30).

In the EVIDENCE (Evidence of Interferon Dose–response: European North American Comparative Efficacy) trial, investigators from 56 centres in Europe and North America completed a randomized study directly comparing once weekly intramuscular IFN-β1a with high-dose subcutaneous (44 μg) three times weekly IFN-β1a in 677 patients with relapsing–remitting multiple sclerosis each having a baseline EDSS of <5.5 (Panitch *et al* 2002). This study was powered to demonstrate a treatment difference within the first 6 months of follow-up. The patients were not blinded but evaluators of clinical and MRI outcomes were unaware of the treatment randomization. The primary outcome was the proportion of relapse-free patients at 6 months, although patients were also evaluated at 1 year. At both 6 and 12 months patients receiving three times weekly IFN-β1a were more likely to be relapse free and with a reduced number of active MRI lesions (Figure 18.31). Fewer patients in the once weekly group developed neutralizing antibody (2% vs. 25%) and injection site reactions or liver enzyme elevations were also less frequent. Long-term safety data at ≥64 weeks confirmed that adverse events were more frequent with the high-dose group and were mainly attributable to the frequency of injection site reactions and hepatic and haematological abnormalities. Objectively, most events were rated as mild, and more serious adverse effects were equally distributed between groups (Sandberg-Wollheim *et al* 2005).

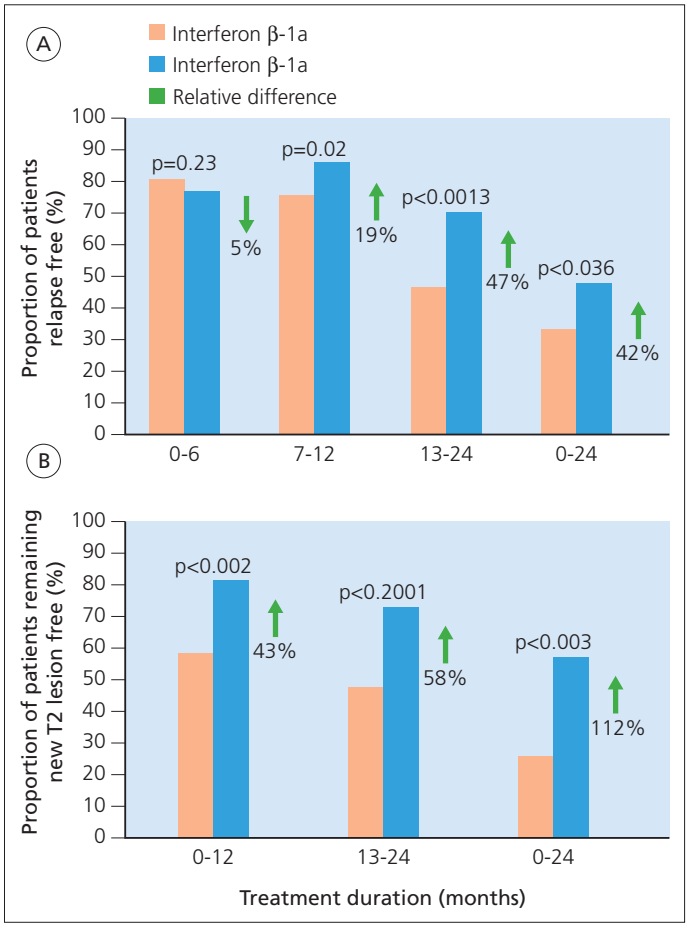



**Figure 18.30** Treatment of relapsing–remitting multiple sclerosis either with every other day subcutaneous IFN-β1b or once weekly intramuscular IFN-β1a (INCOMIN study). (A) Relative difference (proportion in IFN-β1b group minus proportion in IFN-β1a group divided by proportion in IFN-β1a group) between the proportion of patients free from relapses. (B) New proton density or $T_2$ MRI lesions in the treatment groups at different time points. Adapted from Durelli *et al* (2002). © 2002, with permission from Elsevier.

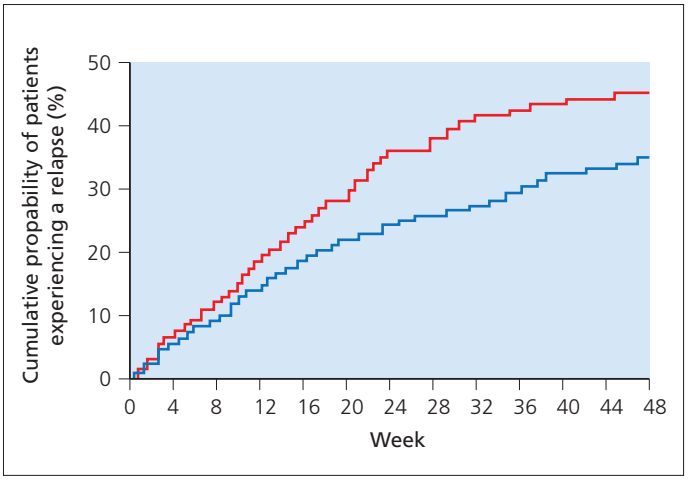



**Figure 18.31** Treatment of relapsing–remitting multiple sclerosis either with three times weekly subcutaneous IFN-β1a (Rebif; blue line) or once weekly intramuscular IFN-β1a (Avonex; red line; EVIDENCE Study). Kaplan–Meier curves illustrating the cumulative probability of patients experiencing a first relapse during the study. Adapted from Panitch *et al* (2002).

Proponents of once weekly interferon hold that the findings of these trials are suspect since in neither study were patients blinded to the treatment assignment. As has been the case with all trials performed to date, there is no mechanism in place adequately to define the long-term implications of these early efficacy claims, or the potential that neutralizing antibody formation will eventually compromise any treatment effect on disability. In 2004, more patients were receiving once weekly intramuscular IFN-β1a than other preparations – primarily because of convenience and more effective sponsor marketing, but also through physician preference given the lower incidence of neutralizing antibody formation and FDA approval for the putative reduction in disability.

The first systematic Cochrane review of interferons in relapsing–remitting multiple sclerosis appeared in 2003 (Filippini *et al* 2003a). The authors concluded that there was evidence only for a reduction in relapse frequency during the first year of treatment with no convincing benefit thereafter, and no effect on disability (Figures 18.32 and 18.33). As expected, this publication triggered considerable editorial discussion and correspondence centred, in large part, on methods used to conduct the systematic review (such as handling of drop-outs, comparability of studies, lumping trials of IFN-α and IFN-β, and ignoring MRI effects; Filippini *et al* 2003b; 2003c; M. Freedman *et al* 2003; Goodin 2003; Kappos and Kesselring 2003; Paty *et al* 2003; Rudick *et al* 2003). As with mitoxantrone, independent calculation of the 'number needed to treat' measure from each of the published trials turns out to be somewhat discouraging (Figure 18.34). In the setting of patients presenting with a clinically isolated syndrome, seven must be treated to prevent one patient developing clinically definite multiple sclerosis at 3 years. In the setting of relapsing–remitting multiple sclerosis, nine have to receive interferon for 1 year to prevent a single relapse, and eight patients must be treated for 2 years to prevent one patient from worsening by a single EDSS point. Although these numbers needed to treat may actually be superior to those quoted for other chronic medical conditions (see Sackett *et al* 2000), the high cost of interferon therapies and the apparent enthusiasm for their widespread use justify some reflection on cost–benefit ratios and health care economics. In a recently published systematic review, Rice *et al* (2005) concluded that the IFNs provide modest reduction in relapse risk for up to 2 years but there is insufficient evidence to judge efficacy beyond this time point. As with every systematic review, much hinges on an estimate of the behaviour of those lost to follow-up. In this example, if – to take a worst case – IFN-treated drop-outs worsened, the statistical benefit of treatment would no longer be judged significant.

## Adverse effects

In the pivotal trials, blinding was not thought to have been undermined by the local or systemic effects of subcutaneous IFN-β1b but was maintained less well in patients receiving intramuscular IFN-β1a (Avonex; 32% of patients were unblinded but the number of placebo cases correctly guessing the treatment code was not recorded). Now, several years on and with more

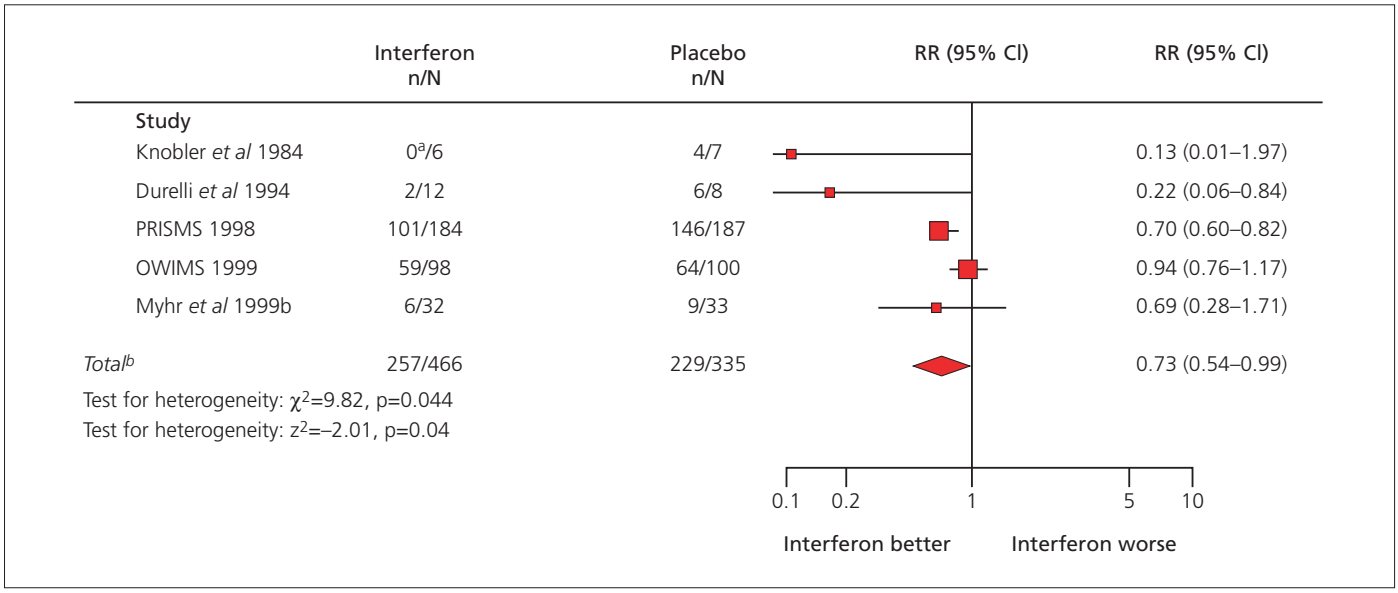



**Figure 18.32** Meta-analysis of patients who had at least one exacerbation during the first year of treatment. n/N = number of patients who had exacerbations/number of patients randomized. To estimate relapse rate, 0.5 was added to each cell of the 2 × 2 table for the trials. a = no patients with exacerbations in the IFN group; b = random effects model. Adapted from Filippini *et al* (2003a).

experience of these agents, we doubt that patients can be adequately blinded to the side effects of interferons. The main adverse effects of IFN-β1b and IFN-β1a are local injection site reactions (Figure 18.35), flu-like symptoms and hyperthermia at onset, and depression. Fortunately, there is no significant drug hypersensitivity. Based on the evidence from clinical trials, contraindications to the use of IFN-β are pregnancy, epilepsy and depression. Post-marketing experience in the United States indicates that patients in whom fatigue and depression occur prior to starting IFN-β1b, especially those with secondary progressive disease, often abandon treatment because of adverse effects (Neilley *et al* 1996). Events may be delayed for up to 29 months and usually consist of injection site reactions (Gaines and Varrichio 1998). The long-term risks of IFN-β1b are unknown.

With time, most patients are better able to tolerate the adverse effects commonly associated with the use of IFN-β (Walther and Hohlfeld 1999). Injection site reactions are more frequent with subcutaneous than intramuscular administration. These may become intolerable leading to discontinuation of treatment. Careful attention to technique (avoiding intradermal injections, excessive sun exposure, overly cooled solutions and nonsterile technique) and local icing of the injection site may help. Necrosis at the injection site is more common in women, especially if the medication is not warmed to room temperature before injection. Intramuscular injections seldom cause tissue reactions but abscess formation, although rare, may lead to significant morbidity. Many patients are able to tolerate the transient flu-like symptoms that frequently occur for the first 4–12 hours after each injection by administering the dose in the evening along with an oral anti-inflammatory agent (acetominophen or ibuprofen: G.P. Rice *et al* 1999; Rio and Montalban 2000). Occasionally it may be necessary to reduce the dose of interferon and to co-administer oral prednisone for a few weeks to improve compliance (Rio *et al* 1998). Patients often develop transient elevations of liver function tests, neutropenia and, less commonly, anaemia requiring dose reduction or a drug holiday.

We routinely measure liver function and a full blood count at baseline, after the first week and month of exposure and then every 3 months thereafter. Menstrual function may be affected, usually resulting in menorrhagia. The issue of depression remains controversial. We generally advise patients and family members that interferons may either expose or worsen underlying depression. They should remain alert to a change in mood that may require treatment. There are reports that spasticity may increase with interferons (Bramanti *et al* 1998; Frese *et al* 1999). Occasionally treated patients develop serological abnormalities suggesting the induction of autoimmunity, including antibodies to thyroid, nuclear and muscle antigens. There are several reports of treatment-induced thyroid dysfunction associated with the use of IFN-β in multiple sclerosis. The initial reported frequency varied from 0% to 34% (Colosimo *et al* 1997; Durelli *et al* 1998; 1999; Kivisakk *et al* 1998c; Monzani *et al* 1999; 2000; Rotondi *et al* 1998; Schwid *et al* 1997a). These trials involved small cohorts of patients treated for varying durations, and to us the overall estimated prevalence (23%) seems high based on personal experience, although that there is a genuine relationship is unambiguous (see below). A more recent study followed 106 patients receiving IFN-β for between 31 and 84 months (Caraccio *et al* 2005). Thyroid autoimmunity affected one-quarter of the patients. The majority were examples of hypothyroidism, half of which were transient. Hyperthyroidism occurred in one-fifth of the cases, and was always characterized by an initial hyperthyroid phase, followed by a plateau culminating in hypothyroidism. It also was often subclinical or transient. Clinical thyroid disease and the development of thyroid autoantibodies in isolation occurred most commonly in the first year after treatment. Females were preferentially affected, but thyroid disease was more persistent in males. The presence of thyroid specific antibodies at baseline (8.5%), the presence of subclinical hypothyroidism prior to

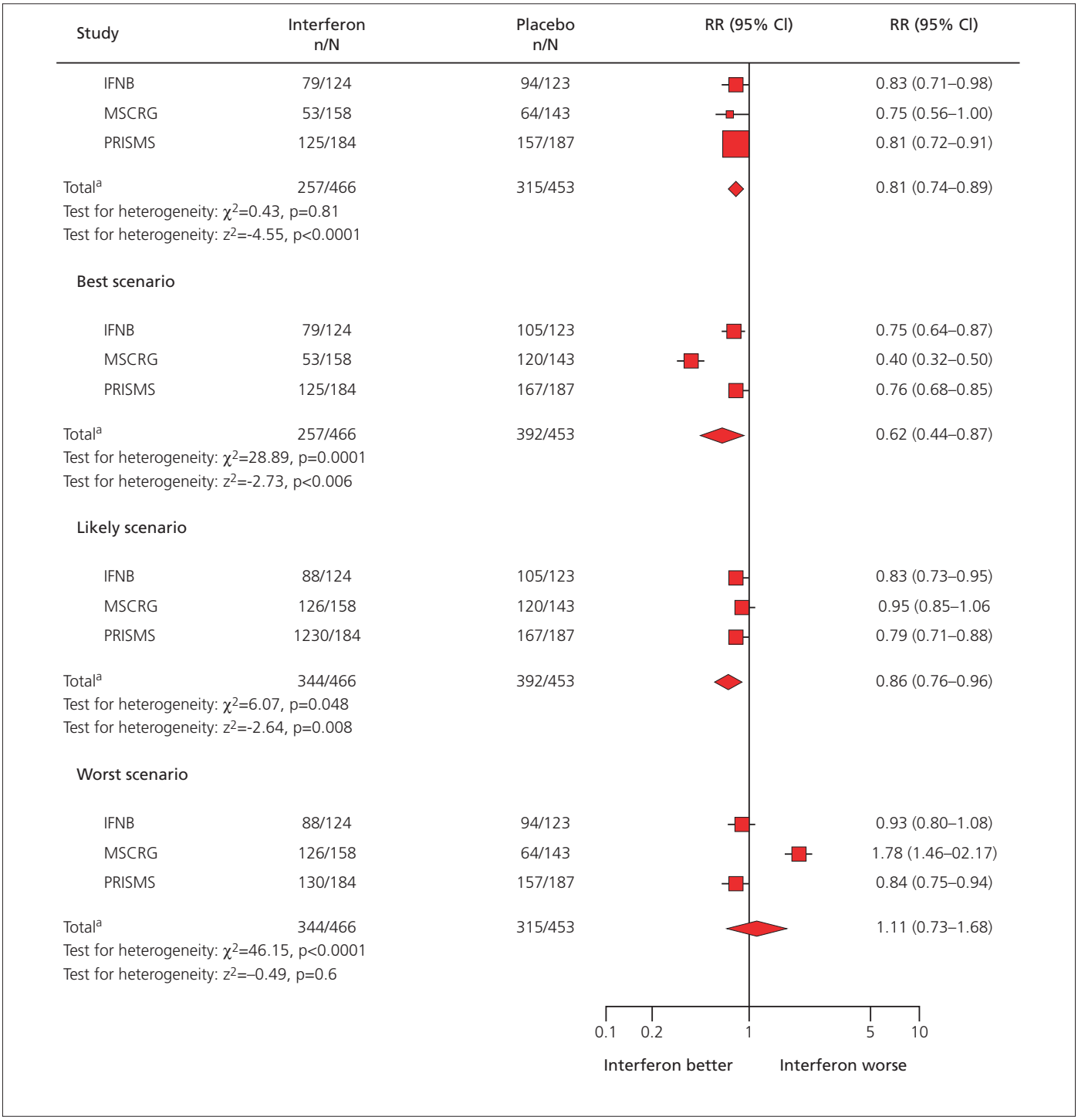



**Figure 18.33** Meta-analysis of patients who had at least one exacerbation during the first 2 years of treatment. n/N = number of patients who had exacerbations/number of patients randomized. a = random effects model. References: IFNB = IFNB Multiple Sclerosis Study Group (1993); MSCRG = Jacobs *et al* (1996); PRISMS = PRISMS Study Group (1998). Adapted from Filippini *et al* (2003a). © 2003, with permission from Elsevier.

starting treatment (2.3%: defined as raised thyroid stimulating hormone without abnormalities of serum thyroxine or triiodothyronine) or the development of thyroid-specific antibodies following treatment (23%) were the only predictive factors for the development of thyroid disease. There was no difference in frequency depending on exposure to IFN-β1a or IFN-β1b. There are isolated reports of treatment-related myasthenia gravis (Blake and Murphy 1997), systemic lupus erythematosus (Watts 2000), rheumatoid arthritis (Alsalameh *et al* 1998; Jabaily and Thompson 1997), inflammatory arthritis (Altintas *et al* 2002; Levesque 1999; Russo *et al* 2000), urticaria (D.L. Brown *et al* 2001), Raynaud's phenomena (Cruz *et al* 2000; Linden 1998b), worsening of psoriasis (Kowalzick 1997; Webster *et al* 1996), acute hepatitis (Christopher *et al* 2005) liver failure (E.M. Yoshida *et al* 2001), a fatal capillary leak syndrome (in a patient with pre-existing acquired C1 inhibitor

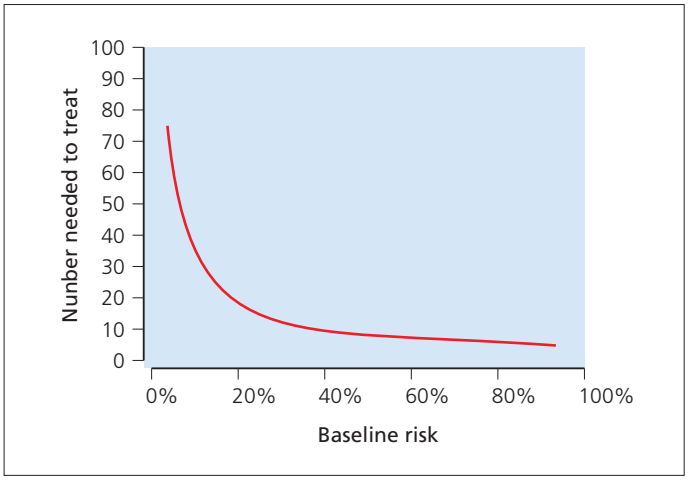



Figure 18.34 Number needed to prevent one patient having at least one exacerbation at 1 year in relation to baseline risks. Adapted from Filippini *et al* (2003a). © 2003, with permission from Elsevier.

deficiency; Niederwieser 2000; S. Schmidt *et al* 1999), intracerebral hemorrhage (Niederwieser *et* al 2001) and anaphylaxis (Clear 1999; Corona *et al* 1999). From amongst this catalogue, the one clear message is that patients with monoclonal gammopathy should not receive IFN-β as they may be at risk for developing a life-threatening capillary leak syndrome.

## Neutralizing antibodies to interferons

It is now revealed that up to 45% of patients on 8 MIU IFN-β1b develop neutralizing activity. In the original series, this usually occurred in the first year (34 of 124) with fewer examples thereafter (7 of 124 in year 2, and only 2 of 124 in year 3; IFNB MS Study Group and the UBC MS/MRI analysis Group 1995). In the trial of IFN-β1a (Avonex; Jacobs *et al* 1996), persistent neutralizing anti-interferon activity was seen in 14% of treated individuals by one year and 23% at two years. This compared with 4% in the placebo group, but the positive tests always disappeared with repeat testing. The tendency for neutralizing antibodies to be present transiently has since been confirmed, an early response but at low titre having predictive value for subsequent reversion to seronegativity (Gneiss *et al* 2004). Subsequent experience confirms the significant antigenicity of IFN-β1b and shows cross-reactivity between neutralizing and binding antibodies to IFN-β1b, IFN-β1a and naturally occurring IFN-β. At first, the clinical significance of neutralizing antibody responses remained uncertain (Kivisäkk *et al* 1997). Antibodies are detected by a cytopathic effect on virus-infected cells. Preliminary enzyme-linked immunosorbent assay screening has since been introduced and the prevalence of antibodies in more recent cohorts of patients treated with IFN-β1a is lower than previously published or that seen with IFN-β1b. For IFN-β1b, the original primary and secondary outcome measures have been re-analysed, stratified for the presence of neutralizing antibodies and different epochs within the initial 3 year period of exposure for comparisons of relapse rate, MRI activity and disability. This has generated much uncertainty (and spin) about whether the drug would be even more effective were it not for antibody development or, conversely, is doomed to short-term efficacy (at best) by immunogenicity.

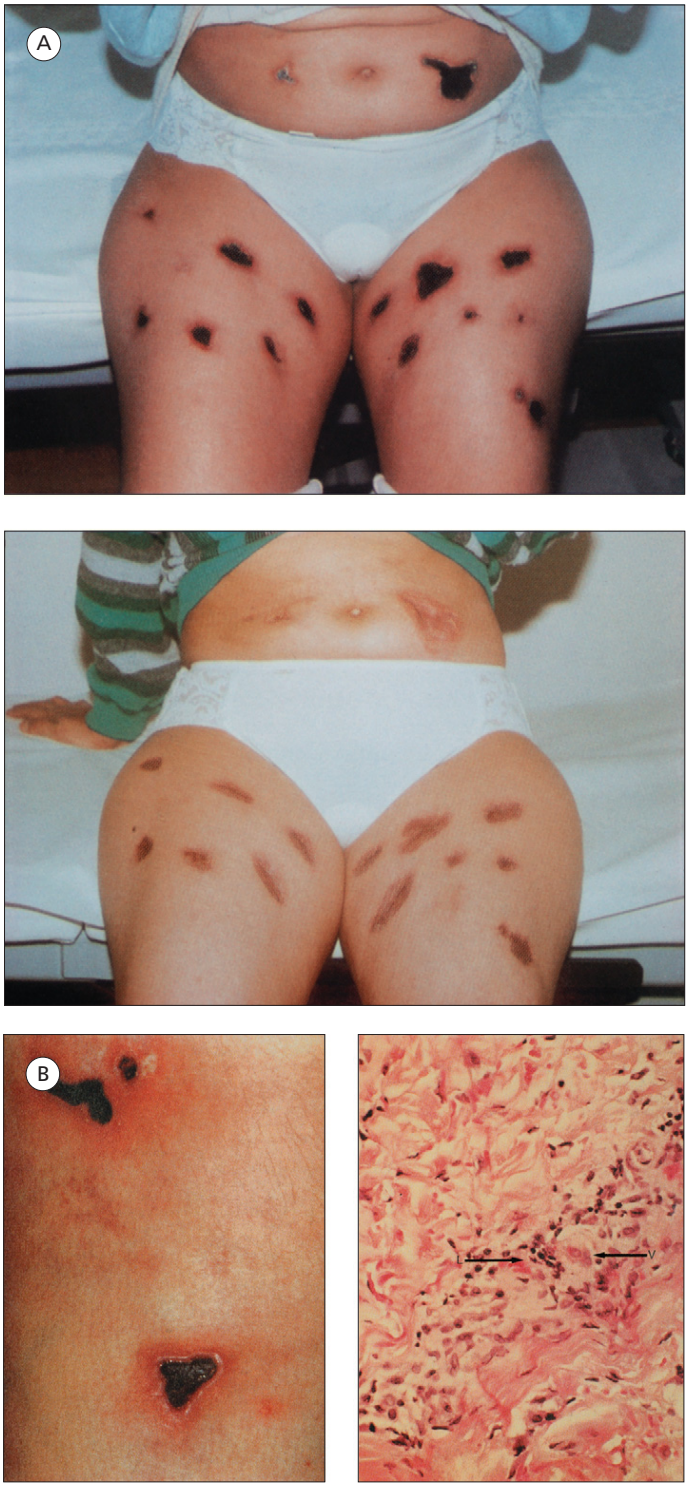



Figure 18.35 (A) Severe necrotizing lesions in a woman with multiple sclerosis undergoing treatment with IFN-β1b at onset (top panel) and on recovery (lower panel). (B) Macroscopic and microscopic appearance of an individual area of necrosis. From Albani and Albani (1997) with permission. © 1997, reproduced with permission of the BMJ Publishing Group.

In support of the first interpretation is the conclusion that patients who do not develop neutralizing activity have an even lower relapse rate than that reported for all IFN-β1b-treated patients. For the period 13–36 months, the attack rate was 1.06 per year in the placebo group compared with 1.08 per year in

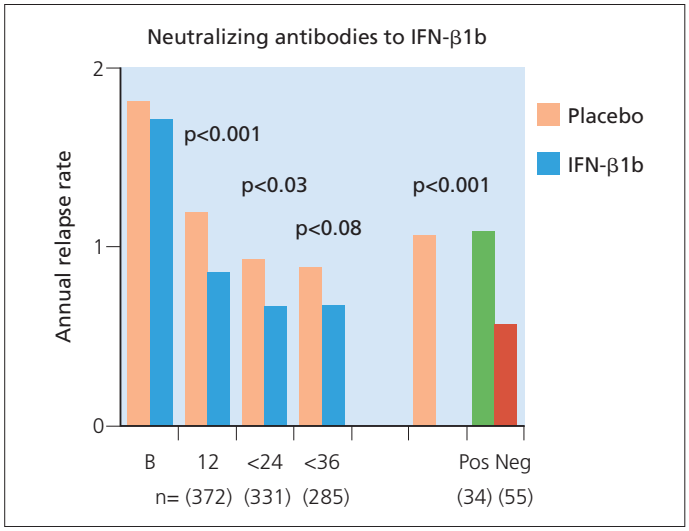



**Figure 18.36** Annual relapse rates at baseline (B), and on completion of years 1 (12), 2 (<24) and 3 (<36) in patients taking IFN-β1b; the annual relapse rate is also shown in a subgroup of patients with (Pos) and without (Neg) neutralizing antibodies compared with a cohort of controls studied for the same period. Adapted from the IFNB Multiple Sclerosis Study Group (1993; 1995). © 1993, 1995, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

the IFN-β1b-treated antibody-positive patients and 0.56 per year in those without neutralizing activity (Figure 18.36: IFNB MS Study Group and the UBC MS/MRI Analysis Group 1995). It follows that, at least in this series, the development of neutralizing activity is associated with a relapse rate which is greater than that reported for other treated patients. In fact, patients destined to develop neutralizing antibodies showed a higher relapse rate before neutralizing activity was detected. This increased further after the assay became persistently positive. For this reason, it has been proposed that patients who develop neutralizing antibodies may have a different profile of immune responsiveness which promotes both neutralizing activity and the disease process, culminating in the symptoms of multiple sclerosis. This formulation seems to us contrived.

In the early analyses of these trials, patients who developed neutralizing activity did not become more disabled than the remaining participants. In fact, the converse was true. This was seen as evidence that the development of neutralizing activity does not disadvantage patients in the longer term. However, taken with the increased relapse rate associated with neutralizing activity, this observation merely reflects the poor correlation between relapse and disability, and suggests that inactivity of IFN-β1b *in vivo* does not adversely affect the course of the disease – a conclusion prompting the response that IFN-β1b is therefore not a disease-modifying drug. The effects on MRI activity and total lesion load in patients developing antibodies parallel the observations relating to relapse rates.

To clarify these emerging issues, investigators using IFN-β1b in the pivotal study subsequently published a detailed report on the development of neutralizing antibodies (IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group 1996). They validated the cytopathic assay and confirmed that the original antibody results were not false-positives; although with a change in cut-off point for a positive titration result the prevalence dropped to 35%. Antibodies mainly, but not exclusively, developed in the first year and this complication was not dose dependent. Relapse rates differed depending on the presence of antibodies, as originally reported (IFNB Multiple Sclerosis Study Group 1995). There was more disease activity on MRI in patients who developed antibodies on high (but not low) dose IFN-β1b than the antibody-negative group, but the cumulative number of enlarging lesions was still less than in the placebo group. There was no detrimental effect on disability progression and antibody-positive patients had less disability progression than those patients who remained antibody negative. No new adverse events correlated with the development of neutralizing activity. In fact, beyond 18 months, fewer events occurred than previously reported in studies using IFN-β1b. Individuals who developed antibodies were no more or less likely than others on active treatment to discontinue IFN-β1b.

In the trial of IFN-β1a (Rebif; PRISMS 1998), all the adverse effects were as reported for other brands of IFN-β but they were no more prevalent. Specifically, neutralizing antibodies to IFN-β1a developed in 18% of treated patients and 1% of controls. Although initially reassuring, the extension study (PRISMS-4) did show a detrimental effect on relapse rate in antibody-positive patients (44 μg group, antibody-negative relapse rate was 0.50 per year compared with 0.81 per year in antibody-positive patients). The formation of neutralizing antibodies reduced the protective effect on relapse recurrence in the European trial of secondary progressive multiple sclerosis but did not influence disability progression (Polman *et al* 2003). Neutralizing antibody formation was shown to inhibit the MRI benefit from treatment in the SPECTRIMS trial (SPECTRIMS Study Group 2001).

The neutralizing antibody story has continued to unfold. Although there is still no definitive study of adequate size and duration to provide a final statement on this complex issue, the suspicion that antibody formation reduces both the biologic effect of IFN-β and the clinical and MRI evidence for efficacy have since increased. In a study of 754 Danish patients, Ross *et al* (2000) found that neutralizing antibodies are more common in patients receiving IFN-β1b than IFN-β1a; in patients treated with subcutaneous compared with intramuscular injections, and in those receiving three times weekly injections; compared to once weekly administration. Bertolotto *et al* (2002) found similar results based on a cytopathic effect assay in a study of 125 patients. They reported that those receiving IFN-β1a (Rebif) three times weekly developed neutralizing antibodies with a frequency between that reported for the other preparations (18 month results for persistently positive: IFN-β1b, 31%; subcutaneous IFN-β1a three times weekly, 15%; and intramuscular IFN-β1a once weekly, 2%). Also reviewing the nationwide Danish prescribing experience, P.S. Sorenson *et al* (2003) reported similar findings in 541 IFN-β-treated patients followed for up to 5 years. Using three techniques of varying sensitivity (the findings were similar regardless of the assays used), they found that approximately one-third of IFN-β-treated patients developed neutralizing antibodies in the first year of treatment. This percentage stayed largely unchanged with prolonged follow-up. However, there was considerable variability between the different preparations. Factors leading to a greater risk of neutralizing

antibody formation included exposure to IFN-β1b (compared with IFN-β1a), subcutaneous injection (compared with intramuscular; $p = 0.022$) and repeated dosing (three times weekly compared with once weekly; $p = 0.0001$). Antibody levels fell in the third year in some patients ($p = 0.023$), particularly those receiving IFN-β1b. The presence of neutralizing antibodies influenced the observed relapse rates in this study. Relapse rates were greatest during antibody-positive epochs (0.64–0.70 vs. 0.43–0.46; $p < 0.03$). They confirmed that antibody-positive patients relapse more often than those without antibodies (odds ratio during antibody positive periods: 1.51–1.58; $p < 0.03$) although this loss of protection is usually delayed. MRI data were not reported. These authors speculate that the reduction in prevalence of antibodies with time, and the associated fall in relapse rate may relate, in part, to changing avidity of the antibodies. Bellomi *et al* (2003) reported that the type of IFN-β exposure does not determine whether antibodies are lost with time.

The Danish series found no effect of antibody formation on disability progression as measured by the EDSS (P.S. Sorenson *et al* 2003). Approximately 50% of patients had deteriorated by 1.0 EDSS point (confirmed at 6 months) at the 42 month follow-up. Survival curves, stratified for the presence of neutralizing antibodies, seemed to separate thereafter, suggesting that antibody-negative patients accumulated disability more slowly after the 3 year follow-up, but the number of patients available for follow-up fell sharply after 3 years and this difference was not significant ($p = 0.14$). Taken together, the Danish investigators conclude that the development of antibodies does compromise the effect of IFN-β. They recommend that antibody status should be monitored in patients with active disease and suggest changing to another class of treatment (such as glatiramer acetate or mitoxantrone) in antibody-positive patients.

Oger *et al* (1997) reported that antibody formation correlated with high levels of immunoglobulin production in an *in vitro* immunoglobulin G secretion assay but others (Bellomi *et al* 2003; Rudick *et al* 1998a) were unable to identify markers that predict the development of antibodies. Lawrence *et al* (2003) developed a rapid, inexpensive radio-immunoprecipitation assay to measure binding antibodies to IFN-β. Using a cohort of 33 patients with relapsing–remitting multiple sclerosis, they reported that the assay is predictive both for the presence of neutralizing antibodies and reduced efficacy in preventing MRI outcomes. Gilli *et al* (2003) reported that neutralizing antibodies reverse the putative protective influence of IFN-β on reduction of matrix metalloproteinase-2 and -9 expression but do not influence endogenous levels of the tissue inhibitor (TIMP-1).

In a recent report, Petkau *et al* (2004) analysed the neutralizing antibody data collected during the pivotal North American IFN-β1b trial. They determined that neutralizing antibodies reduce the clinical benefit (relapse reduction) from both doses of IFN-β1b but the detrimental effect of these antibodies is more marked in those receiving the low dose (that is, relapse rates were higher by 28% for 1.6 MIU compared with 2% for 8 MIU: Figure 18.37A and B). They also reported that this reduction in efficacy reverses with restorations of antibody-negative status (60% who were once antibody-positive later had at least one antibody-negative value). Gilli *et al* (2003) reported that neutralizing antibodies developing during the course of treatment with each of the available interferons abrogated the effect of IFN-β on reducing matrix metalloproteinase-9 expression, suggesting a possible mechanism of action for these antibodies.

Against this background, the transactions of a conference devoted to antibody formation in multiple sclerosis have since appeared (Pachner 2003). Attendees reached consensus (>70% agreement) on many of the conclusions already discussed relating to antibody-mediated decrease in bioactivity. They called for more universal standards in the assays used to measure binding and neutralization, longitudinal data analyses to avoid the limitations of previously reported cross-sectional studies (Petkau 2003), and prospective efforts to identify strategies for reducing

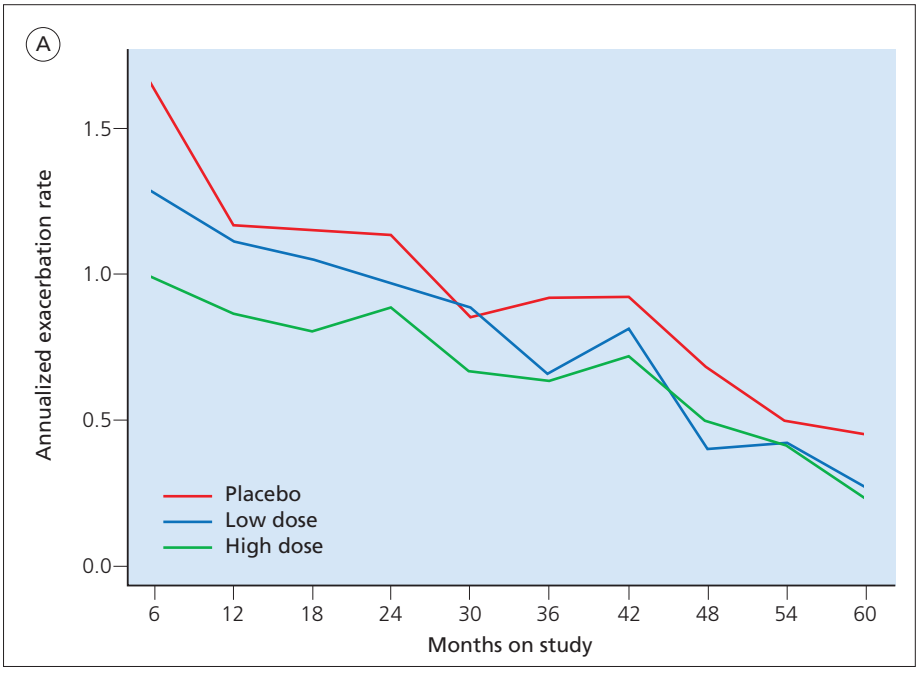



**Figure 18.37** (A) Annualized exacerbation rates in the preceding 6 month periods (number of exacerbations beginning in preceding 6 month period/number of patient years on study in preceding 6 month period). Adapted from Petkau *et al* (2004). © 2004, reproduced with permission of Hodder Education.

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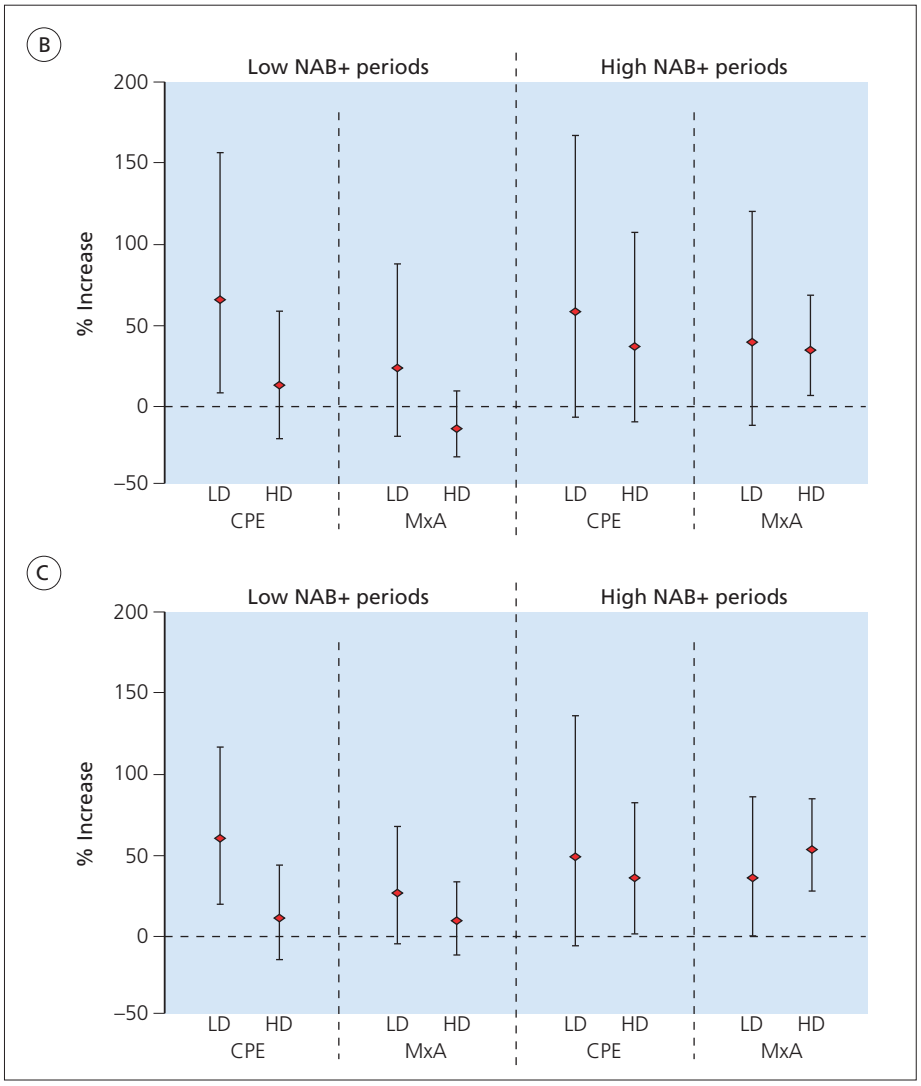



**Figure 18.37, cont'd** (B and C) Increase in exacerbation rate (and 95% CI) for eventually neutralizing antibody (NAB)+ subgroups in low NAB+ (confirmation required) and high NAB+ (no confirmation required) periods relative to NAB– periods: (B) 'Once positive, always positive' classification of NAB status. (C) 'All switches considered' classification of NAB status. LD = low dose; HD = high dose; CPE = cytopathic effect; MxA = myxovirus protein A. Adapted from Petkau *et al* (2004). © 2004, reproduced with permission of Hodder Education.

antibody formation in patients treated with IFN-β. Strategies for inhibiting the formation of antibodies so as to maintain the perceived efficacy of IFN-β1b include using higher doses, concurrent use of corticosteroids or other immunosuppressants, and switching brands – although the prevailing view is that antibodies to IFN-β1a and IFN-β1b cross-react. In 2005, there are still no proven strategies for reducing antibody formation. The interested reader is referred to a series of recent papers comprising the proceedings of an international consensus conference held in August 2002 (Bertolotto *et al* 2004; Billiau *et al* 2004; Deisenhammer *et al* 2004; Hartung and Munschauer 2004; Hartung *et al* 2004; Schellekens and Casadevall *et al* 2004; Vartanian *et al* 2004).

Malucchi *et al* (2004) recently reported on their non-randomized study of 78 patients treated with either subcutaneous IFN-β1b (Betaseron; n = 20), subcutaneous IFN-β1a (Rebif; n = 25) or IFN-β1b by intramuscular injection (Avonex; n = 33). Neutralizing antibody assays were performed every 3 months for up to 3 years. Their frequency was similar to previous reports in the literature (subcutaneous IFN-β1b, 35%; subcutaneous IFN-β1a, 20%; and intramuscular IFN-β1a, 3%). Relapses were most consistently reduced in the patients without antibodies; patients 'persistently positive' demonstrated less relapse suppression and a greater likelihood of EDSS worsening during the course of the study. In another recent report, Frank *et al* (2004) reported that subcutaneous IFN-β1b reduced the number of contrast enhancing lesions and the cumulative white matter lesion load over a period of up to 3 years in 30 patients using a baseline versus treatment crossover design. The MRI effect was reduced in antibody-positive patients. The authors suggested that IFN-β1b by subcutaneous injection reduced the progression of cerebral atrophy but, from our review of this paper, the benefit is less certain given the small sample size.

Thus, the issue of whether neutralizing antibodies matter is not settled. On one side of the debate is the theory that IFN-β is biologically inactive in the presence of neutralizing antibodies and so should not be prescribed. Antibodies very clearly reduce biological activity and seemingly reverse any effect on frequency of relapse, reducing antibody-positive patients to nearly the same risk of relapse as untreated controls. Several recent studies support the concept that neutralizing antibodies decrease the therapeutic effects of the IFN-βs (G.S. Francis *et al* 2005;

Giovannoni and Goodman 2005; Kappos *et al* 2005; P.S. Sorensen *et al* 2005). The observation that disability continues regardless of antibody formation suggests that this group of drugs provides little in the way of long-term disease modification. Others present these findings and their implications for efficacy and safety in the best possible light; they argue that the development of neutralizing activity has led to the true efficacy of IFN-β1b being underestimated; that neutralizing activity is not associated with additional adverse effects; and that, at worst, it may only make the drug harmlessly inactive.

## The licences for IFN-β

By 1996, approximately 35 000 patients in the United States were receiving Betaseron for ambulant, relapsing–remitting disease. The number of patients attending some centres who received a prescription was estimated at >50%. Presumably, there was some laxity in the policing of reimbursements by the insurance companies with a good deal of drift at the prescribing margins. The unofficial guidelines, drafted by neurologists involved in the clinical trials and with postmarketing experience, were orientated towards expanding the group eligible for a prescription and offered advice on managing difficulties which might arise, such as perceived lack of efficacy, without discontinuing treatment (Lublin *et al* 1996). In the first few months after a licence was granted for Avonex, the company claimed 15 000 prescriptions, with a proportion switching from IFN-β1b to IFN-β1a (Avonex), creating considerable confusion with respect to the carryover of clinical benefits, adverse effects and neutralizing antibodies. Because the clinical trials were published later and the granting of a licence was delayed, Rebif lagged in the United States market. In 2003, the approximate number of patients receiving these treatments in the United States (total 172 000 prescriptions) and Europe (94 000 prescriptions) respectively were: Avonex – 47% and 15% (94 500 total); Betaseron – 17% and 38% (65 500 total); Rebif – 10% and 31% (46 500 total); and Copaxone (see below) – 26% and 15% (59 500 total).

It did not take long for a debate to begin on the managed entry of the interferons in continental Europe and the United Kingdom, with jockeying for position on who should take the decision to prescribe and who pays (Walley and Barton 1995). In Europe, where Betaferon was granted a product licence in late 1995, Avonex in 1997 and Rebif in 1998, the professional analysis was much more measured than in the United States. The take-up of prescriptions was slower and in many countries this resulted from delay in establishing guidelines for clinical use, closely linked to decisions on funding. All forms of IFN-β and glatiramer acetate are currently provided in the United Kingdom through a Risk Sharing Scheme, organized by the Department of Health, in which patients on treatment will undergo annual EDSS evaluations for up to 10 years. From these long-term data, the price of the drug may in future be adjusted to meet an acceptable level of cost-effectiveness. Meanwhile, pressure from the neurological community and the commercial realization that the arguments with respect to efficacy and cost are not yet won has led to new trials, some already completed (see above). However, comparative studies with other immunosuppressive drugs, which the prescribing community would want to have available – such as the proposed ERAZMUS (EEC concerted action) trial comparing IFN-β1a (Avonex) with azathioprine and placebo in 1200 patients with early relapsing–remitting or secondary progressive multiple sclerosis, taking time to EDSS 3 over 4 years as the primary outcome measure, are commercially unattractive and have never materialized.

Information distributed by the pharmaceutical companies which make or market Betaseron in the United States recommends that

> *Betaseron™ (interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.*

In the European Community, Betaferon is currently indicated [European Agency for the Evaluation of Medicinal Products (EMEA) European Public Assessment Report (EPAR), Revision 5, 12 June 2003]

> *for the treatment of patients with relapsing-remitting multiple sclerosis and two or more relapses in the last two years. Betaferon is also indicated for patients with secondary progressive with active disease evidenced by relapses.*

In North America, Avonex

> *is indicated for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. Safety and efficiacy in patients with chronic progressive multiple sclerosis have not been established.*

Caution is advised in using Avonex in patients with a history of depression and in those with a prior history of epilepsy. Breastfeeding and Avonex-use should not be combined. In the European Community: Avonex is currently indicated (EMEA EPAR, revision 4, 24 February 2004)

> *for ambulatory patients with relapsing multiple sclerosis characterized by at least two recurrent attacks of neurologic dysfunction (relapses) over the preceding three year period without evidence of continuing progression between relapses. It slows the progression of disability and decreases the frequency of relapses over a two year period. Contra-indications are known hypersensitivity to IFN-β or human albumin, pregnancy, breast feeding, severe depression or suicidal ideation, and poorly controlled epilepsy.*

Avonex is also indicated for the treatment of patients who have experienced a single demyelinating event with an active inflammatory process if it is severe enough to warrant treatment with intravenous corticosteroids; if alternative diagnoses have been excluded; and if they are determined to be at high risk of developing clinically definite multiple sclerosis. The EMEA goes on to suggest that

*a high risk patient is one who has ≥ 9 T2 lesions on a baseline MRI and at least one new T2 or gadolinium enhancing lesion on a follow up scan performed at least 3 months later. Treatment should be discontinued in patients who develop disease progression*

In the United States

*Rebif™ (interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy of Rebif™ in chronic progressive multiple sclerosis has not been established.*

In the European Community, Rebif is currently indicated (EMEA EPAR, revision 6, 4 December 2003)

*for the treatment of patients with multiple sclerosis with two or more relapses within the last two years. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity.*

This licence is now updated to recommend 44 μg as the preferred dose.

In the climate which has emerged following the marketing of IFN-β, working in health care systems with competitive and limited resources, such as the United Kingdom, maintaining a balanced and responsible position, remains intermittently stressful but still of importance. Well-tried mechanisms for challenging decisions on prescribing, where medical and fiscal motives are easily confused, have already been exercised. It is somewhat ironic and, for some, frankly perplexing, that the introduction of a treatment that might have a disease-modifying effect in multiple sclerosis should have provoked so much apparent controversy. On one side of this debate are professional and lay enthusiasts who argue that this is the first useful drug treatment for a frightening and potentially disabling neurological disease affecting young adults. On the other, are those who have experienced previous short-lived therapeutic claims and, therefore, remain sceptical about the newly licensed therapies having more than a transitional role on the way to more effective remedies.

In the United Kingdom, all three interferon preparations are currently used according to the guidelines of the Association of British Neurologists (January 2001, see *www.theabn.org*) which require that there have been two or more clinically significant relapses in the previous 2 years in ambulant patients with relapsing–remitting multiple sclerosis and two disabling relapses as the main clinical feature of disease activity in ambulant patients with secondary progressive disease. The guidelines also suggest the following be considered as potential stopping criteria:

- the occurrence of two severe relapses within 12 months
- the development of secondary progression for >6 months
- the loss of ability to walk.

These somewhat rigorous stopping guidelines have not always proved feasible to apply in clinical practice (B.D. Dubois *et al* 2003). The EMEA reports provide a variety of recommendations for monitoring patients and deciding when treatment might be continued or discontinued. These reflect the uncertainties that exist concerning the long-term effectiveness of all the interferons and the frequent difficulties in determining for individual patients whether or not treatment is providing benefit. The use of IFN-β is contraindicated in young people aged <16 years, although the experience of treating a group of Italian children or adolescents is that the reduction in relapse rate is no less than in adults (Ghezzi *et al* 2005). The pivotal trials were usually confined to the 16–55 year age groups, and no upper age limit is included in the summary of product characteristics.

There is a critical need for thorough and transparent analysis of all the prescribing experience with each of these partially effective drugs to characterize, if possible, what determines 'responder' vs. 'nonresponder' status. To date, these analyses have not been possible as the informative clinical trial data are largely unavailable to investigators, being held *in camera* by the sponsors. Given the importance for all parties of identifying clinical and biological markers of response, both to predict who will respond and to clarify the magnitude and duration of a positive response, none of the approved drugs has yet been subjected to such comprehensive analysis. Indeed, investigators have yet to create clinical and MRI guidelines that are either consensus driven or, preferably, biologically meaningful. It remains uncertain whether the 'partial response' so universally reported in contemporary trials relates to a partial response for many or a biologically meaningful response for only a minority of patients. Consequently, patients and their physicians are left to speculate as to when drugs should be started, changed or stopped. This ambiguity has prompted some experts to suggest that since one cannot predict who may respond, virtually all affected individuals should be considered for treatment at the time relapsing–remitting multiple sclerosis is diagnosed (Van den Noort 1998). However, disbelievers amongst the prescribing community argue that the drugs are sufficiently limited in effectiveness as to make their use purely optional and determined more by the desire of the patient and physician to 'do something' rather than realistic expectation of a brighter neurological future.

## MOLECULES THAT INHIBIT T-CELL–PEPTIDE BINDING

The principle that immune responses can be manipulated by the use of peptides or other molecules that mimic closely the naturally occurring ligand for T-cell binding has shown that it is possible to promote clonal anergy. These strategies have therefore been applied to the treatment of multiple sclerosis.

### Oral myelin

One approach that has already received preliminary clinical application (Weiner *et al* 1993b) is inhibition of the autoimmune processes with oral antigen. Thirty patients, having two or more relapses in the previous 2 years, were treated with 30 mg of oral bovine myelin or placebo for 1 year. Six of the 15 myelin-treated patients had major attacks compared with 12 of the 15 placebo patients. There was no effect on disability, although a rather contrived subgroup analysis claimed a selective effect in DR2(15)-negative males. The clinical observations could not be

correlated with changes in the proportion or specificity of T-cell clones reactive to myelin basic protein, or its encephalitogenic peptides. In other contexts, oral feeding of antigen has been shown to favour the induction of T cells which secrete IL-4, TGF-β and IL-10 at low doses and to delete both Th1 and Th2 cells at higher doses (Y. Chen *et al* 1995). Although superficially attractive, the results of the pilot study always seemed to us overstated and few were surprised by the widely publicized news that the phase three trial of oral myelin (515 patients, 14 sites) showed no clinical effect. However, this negative study remains unpublished several years after the trial was stopped and seems destined never to be reported in full.

## Altered peptide ligands

Antigen-specific immunotherapy was dealt a further tough blow in 2000 when two phase two trials of altered peptide ligand therapy designed to interfere with T-cell responses were terminated early because of concerns about patient safety. In the first, use of the altered peptide ligand (CGP77116) was associated with clinical relapses and systemic hypersensitivity reactions that persisted despite dose reduction (Bielekova *et al* 2000). The trial was terminated after only eight patients were enrolled. The finding that two-thirds of patients who had clinical relapses after starting therapy were shown to have developed high T-cell precursor frequencies to the ligand and myelin basic protein peptide 83–89 suggested that the intervention incited clinical relapses. In the second study, three doses of the altered peptide ligand NBI5788 (5, 20 or 50 mg weekly by subcutaneous injection) were compared with placebo administration. The trial was stopped when nine of the 142 patients experienced hypersensitivity reactions. Immunological studies suggested that treatment induced a Th2 profile of immune response (Kappos *et al* 2000). This study was of insufficient duration to detect a clinically meaningful response but MRI monitoring suggested a possible benefit using the lowest dose of altered peptide ligand. D.E. Goodkin *et al* (2000) demonstrated that various doses of a complex of HLA-specific DR2 solubilized with the myelin basic protein peptide 84–102 (AG284) were well tolerated but the trial was not powered for an efficacy analysis.

## Copolymer-1 or glatiramer acetate (Copaxone)

Following the logic that immunological damage in multiple sclerosis is mediated by antigen-specific T cells, a synthetic peptide composed of L-alanine, L-glutamic acid, L-lysine and L-tyrosine was designed specifically to mimic the structure of myelin basic protein. Copolymer 1 [Cop-1, later renamed glatiramer acetate (Copaxone) by the sponsor upon approval of this agent for use in multiple sclerosis by the FDA in North America] was neither encephalitogenic nor toxic, and was shown to suppress experimental autoimmune encephalomyelitis (perhaps by inducing antigen-specific suppressor cells). It moved into clinical practice in the early 1980s (Abramsky *et al* 1977).

### *Clinical studies*

Bornstein *et al* (1982) first reported in detail on the therapeutic use in 16 patients with multiple sclerosis. In a subsequent blinded and placebo-controlled study of patients having two or more relapses in the previous 2 years, and EDSS scores of <6 at entry, randomization to active or placebo preparations was within EDSS bands (Bornstein *et al* 1987). Participants received subcutaneous Cop-1 for up to 2 years. A neurologist assessed disease activity, and analysis was on an intention to treat basis. Taking absence of relapse during the trial as the primary end point, a greater proportion of individuals in matched pairs randomized to Cop-1 were relapse free on completion than placebo cases (ten of 22 compared with two of 22 in whom the placebo partner but not the Cop-1-treated individual was free from relapse, and ten of 22 pairs in whom the course was concordant within individual pairs; $p = 0.039$: Figure 18.38A). There were 62 exacerbations in 23 placebo-treated patients compared with 16 amongst 25 Cop-1-treated individuals. Although the placebo group showed a reduction in relapse rate during the trial as part of the natural history, or regression to the mean, the difference between groups was 4.9 in the first year and 3.3 in the second, favouring treatment with Cop-1. Overall 14 of 25 treated patients were free from relapse compared with six of 23 in the placebo group ($p < 0.001$). An apparent difference in the rate at which Cop-1- and placebo-treated patients deteriorated (five of 25 and 11 of 23, respectively), which was especially marked in less affected individuals (EDSS <2 at entry), was not statistically significant. There was, however, a delay in time to progression by one EDSS point amongst Cop-1-treated patients (Figure 18.38B). Local injection site reactions seriously undermined blinding in this study and 29 of 40 participants (in whom information was available) correctly guessed treatment assignments (the authors suggest that unblinding was also influenced by the response to treatment). Subsequently, Bornstein *et al* (1991) completed a study of 106 patients with secondary progressive multiple sclerosis who had documented evidence for an increase in disability over the preceding 6–18 months. Treatment had no effect on the proportion of patients showing sustained progression by a further one EDSS point. Apart from local skin reactions at the injection site, Cop-1 was well tolerated.

The result of the above study was presumably influential in the decision to design a phase three trial involving patients with relapsing–remitting multiple sclerosis and using relapse rate as the primary outcome. This involved 251 patients randomized to Cop-1 (20 mg by daily subcutaneous injection for 2 years; $n = 125$) or placebo ($n = 126$; K.P. Johnson *et al* 1995). The relapse rate over 2 years in treated patients was $1.2 \pm 0.1$ compared with $1.7 \pm 0.1$ in controls (a 29% reduction giving annual rates of 0.6 and 0.8, respectively; $p < 0.007$: Figure 18.39A). More Cop-1-treated patients were free from relapse, and treatment also favoured a delay in time to relapse. With respect to disability, the proportions of patients taking Cop-1 who were unchanged, improved or worse by 1 EDSS point were 54%, 25% and 21% compared with 56%, 15% and 29%, respectively, in the placebo group (Figure 18.39B). Results of the pivotal North American trial led the FDA to approve Cop-1 for the reduction of exacerbations in patients with relapsing–remitting multiple sclerosis. (As noted above, following FDA approval for licensure the company renamed the agent glatiramer acetate or Copaxone.) A United Kingdom licence for the same indication followed in 2000 and in the rest of the European Union in 2001 (*www.tevapharm/com/copaxone/*). In the United Kingdom, the

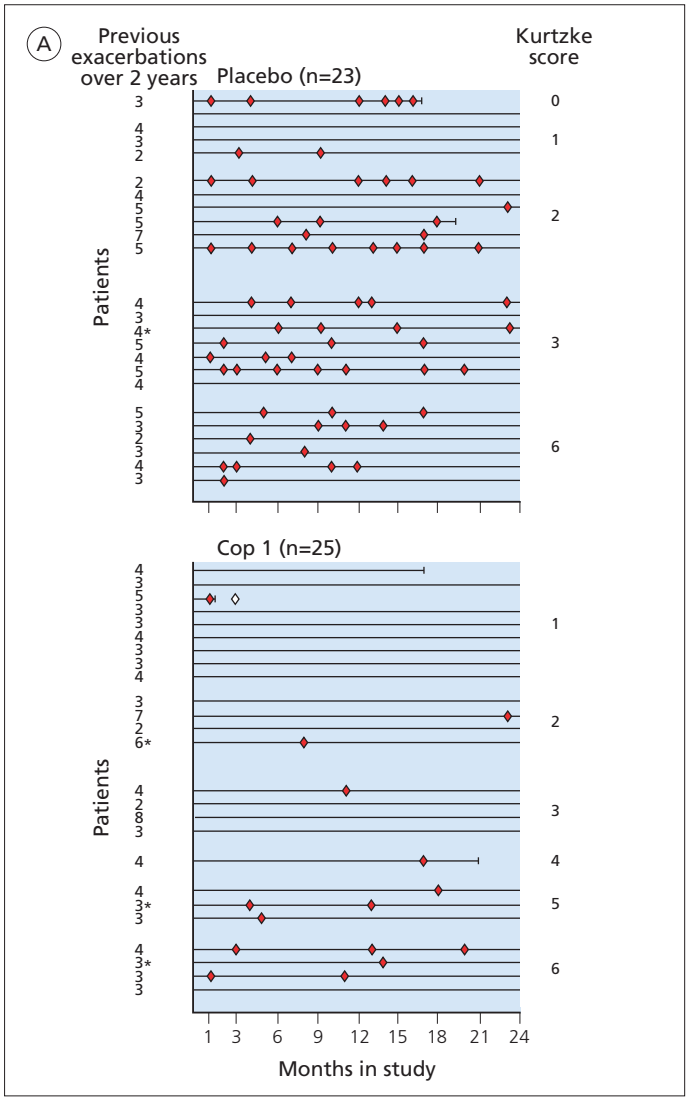



**Figure 18.38** Treatment of multiple sclerosis with copolymer-1. (A) Exacerbations occurring during the 2 years of the trial; each line represents a patient and each diamond represents an exacerbation. Patients are grouped according to their EDSS on entry. The number of pretrial exacerbations is indicated to the left. Discontinuous lines represent patients who withdrew before completion. The open diamond indicates an exacerbation occurring after withdrawal which was included as a study event. Patients who were not included in the matched-pair analyses are indicated by an asterisk. (B) Survival curves representing the probability of no worsening from the baseline EDSS; worsening was determined when first observed but was counted only if it continued for 3 months. Adapted from Bornstein *et al* (1987). © 1987, reproduced with permission of the Massachusetts Medical Society.

Association of British Neurologists guidelines on eligibility criteria for glatiramer acetate are:

- ambulant patients with relapsing–remitting multiple sclerosis able to walk at least 100 m without support (EDSS ≤5.5)
- at least two clinically significant relapses in the last 2 years
- age ≥ 18 years.

The pivotal North American glatiramer acetate (or Copaxone, see above) study has been continued. In a blinded extension for up to 11 additional months, there was no loss of effect on relapse rate. Sustained disability was seen in 23% of patients receiving glatiramer acetate compared to 29% of controls (K.P. Johnson *et al* 1998). The European–Canadian glatiramer acetate MRI study was designed to evaluate the effect of treatment on MRI features of disease activity in relapsing–remitting multiple sclerosis (Comi *et al* 2001b). Two hundred and thirty-nine patients with relapsing–remitting multiple sclerosis from 29 centres in seven countries were randomized to receive daily subcutaneous injections of placebo or glatiramer acetate (20 mg). Monthly MRI studies were performed for 9 months. This study demonstrated that treatment reduced the total number of gadolinium enhancing lesions (overall reduction, 29%; $p = 0.003$: Figure 18.40) although a large number of enhancing lesions were still seen in treated patients. This effect was first apparent after approximately 6 months of treatment (Figure 18.41). There was no difference, however, in the proportion of patients showing MRI contrast enhancements (although the specific data were not reported). Notably, only three treated patients remained free of contrast enhancing lesions during the 9 month study. $T_2$ volume continued to worsen in both groups but to a lesser degree in those receiving glatiramer acetate. The change in hypodense lesion volume was not significantly different between groups. Treatment also reduced the number of relapses but not for the first 6 months. A subsequent publication from this prospective study reported that treatment with glatiramer acetate reduced the proportion of the 1722 new contrast enhancing MRI lesions that developed into persisting hypodense $T_1$ 'black holes', at 7 months ($p = 0.004$) and 8 months ($p = 0.0002$) after they were first detected in the 239 participants (Filippi *et al* 2001a) but not at the 6 month assessment (Filippi *et al* 2002c; N.D. Richert 2002). These reports suggest

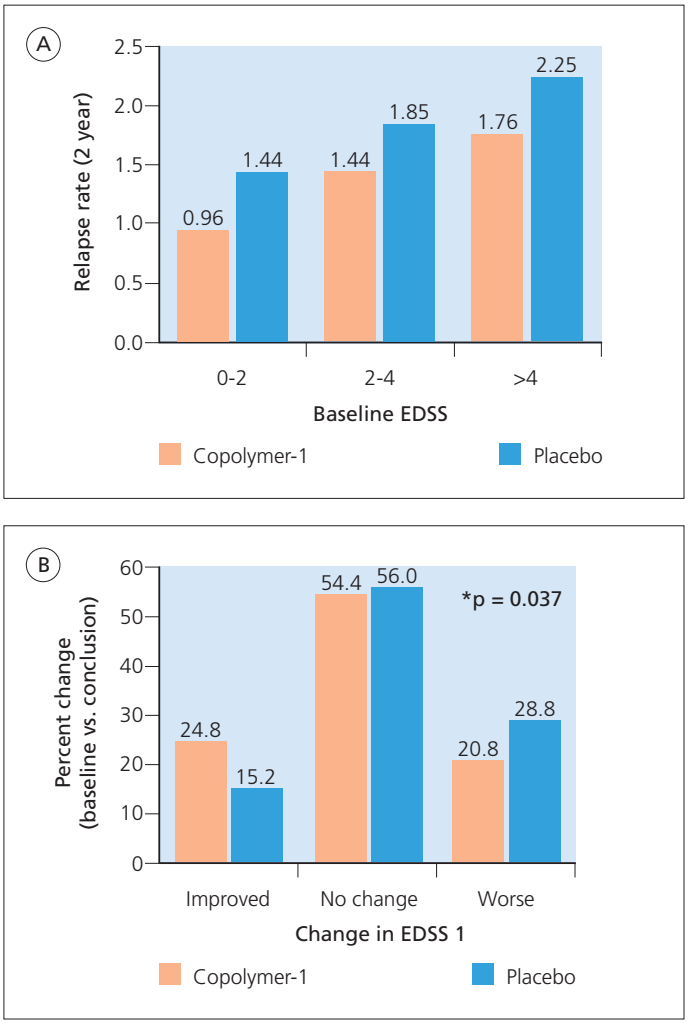



**Figure 18.39** Treatment of multiple sclerosis with copolymer-1. (A) Changes in relapse rate observed over 2 years, by baseline EDSS. Numbers above each bar represent the mean 2 year relapse rate for each group. (B) Percentage of patients who improved, were unchanged, or were worse by ≥1 EDSS points between baseline and the last (24 month) measurement (repeated measures ANCOVA). Numbers above each bar represent the percentage of patients in the respective copolymer-1 or placebo group. Adapted from K.P. Johnson *et al* (1995). © 1995, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

that glatiramer acetate has less immediate impact on MRI markers of inflammatory demyelination than IFN-β but may favourably affect the proportion of MRI lesions that develop significant axonal loss.

A 9 month, placebo-controlled trial of glatiramer acetate in 239 pateints with relapsing–remitting multiple sclerosis revealed a mean 0.7–0.8% reduction in central cerebral volume with no significant differences between the patient groups (Rovaris *et al* 2001c). The study showed a weak association between enhancing lesion numbers and atrophy. Rovaris *et al* (2002b) later designed a small, prospective study of glatiramer acetate on the formation of new $T_2$ lesions and (new and total) contrast-enhancing MRI lesions. This cohort of 20 patients with relapsing–remitting multiple sclerosis underwent monthly MRI studies during both pretreatment and posttreatment periods of observation (two sessions of monthly scans beginning 5 months before and then restarting 90 days after treatment with daily subcutaneous injections of glatiramer acetate, 20 mg). Patients were given both a standard and triple dose of gadolinium separated by 12–24 hours. Using MRI measures of disease activity based on pretreatment behaviour, the authors concluded that treatment reduced both new $T_2$ and new and total gadolinium enhancing lesion formation. The benefit was detectable within 4 months of starting therapy. In addition, glatiramer acetate reduced the number of contrast enhancing lesions using all doses of contrast enhancing agent. These observations suggested that, in the context of multiple sclerosis, glatiramer acetate may reduce the number of inflammatory lesions in situations of both mild and severe blood–brain barrier disruption – although this conclusion is necessarily based on an indirect measure of blood–brain barrier integrity.

A large, phase III, randomized, double-blinded, placebo-controlled trial designed to determine whether either of two doses of daily oral glatiramer acetate (5 and 50 mg) were superior to placebo in reducing relapse rate (primary outcome), MRI activity (secondary outcome) or disability (tertiary and other end points) was terminated after an interim analysis at 14 months suggested little likelihood of a positive outcome. The results are not yet published.

The clinical relapse rates of 85 patients with relapsing–remitting multiple sclerosis who switched from IFN-β1a (6 MIU by intramuscular injection for 18–24 months) to glatiramer acetate (20 mg by subcutaneous injection daily) either for reasons of perceived lack of efficacy (62 patients) or persistent intolerance to treatment-related side effects (23 patients) were evaluated by O.A. Khan *et al* (2001b). After a further period of 18–24 months prospective follow-up, the authors concluded that glatiramer acetate administration reduces relapse rate in patients previously not fully responsive to IFN-β. The degree of reduction is no less than in patients who responded but switched because of drug intolerance.

Although this result invites the conclusion that glatiramer acetate can rescue patients who fail on treatment with IFN-β, no definitive studies comparing the relative efficacies of these drugs are available although several trials are in progress. A comparison was made by O.A. Khan *et al* (2001c) of clinical outcomes at 18 months in a group of 156 patients with relapsing–remitting multiple sclerosis followed prospectively. In this open label, non-randomized and unblinded study, patients were permitted to choose no treatment (n = 33) or standard doses of intramuscular IFN-β1a (Avonex; n = 40), subcutaneous IFN-β1b (Betaseron; n=41) or glatiramer acetate (n = 42). At 18 months, 122 patients remained in the study (18/34 drop-outs were from the 'no treatment' group). Annual relapse rates were significantly reduced only by glatiramer acetate (0.49; p = 0.001) and subcutaneous IFN-β1b (0.55; p = 0.001) but not by intramuscular IFN-β1a (0.81) compared with the 'no treatment' group (1.02). Similarly, the percentage of relapse-free patients was significant only for glatiramer acetate and subcutaneous IFN-β1b (33% for both; p = 0.05; intramuscular IFN-β1a, 12%; no treatment, 7%). Mean change in EDSS also favoured these two treatment groups (IFN-β1b: –0.25, p = 0.010; glatiramer acetate: –0.44, p = 0.003; IFN-β1a +0.19, p = 0.452 compared with untreated patients: +0.60).

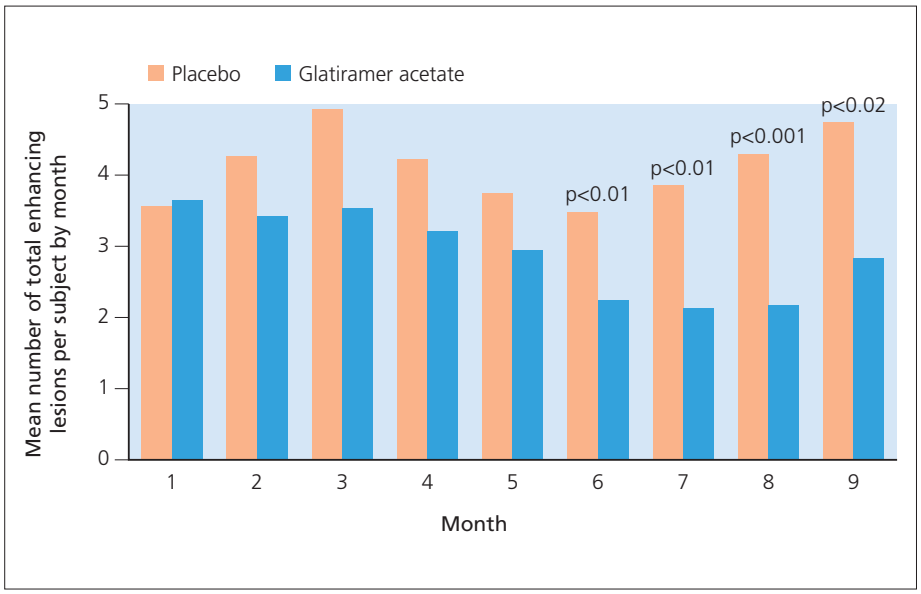



**Figure 18.40** European/Canadian trial of glatiramer acetate in relapsing–remitting multiple sclerosis. Median number of total enhancing lesions per subject observed at each month on study using the last observation carried forward. Repeated measures analysis favoured a treatment effect for glatiramer acetate (p = 0.003). Adapted from Comi *et al* (2001b). © 2001, reproduced with permission of John Wiley & Sons.

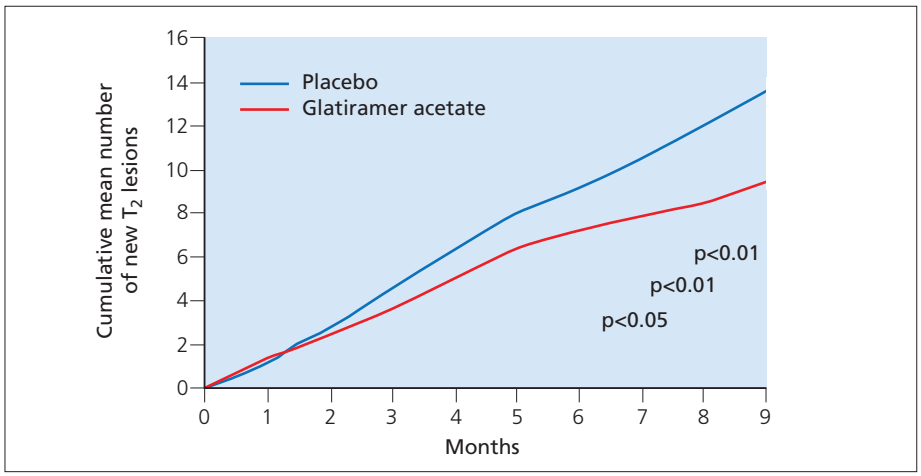



**Figure 18.41** European/Canadian trial of glatiramer acetate in relapsing–remitting multiple sclerosis. Cumulative mean number of new lesions observed on the $T_2$-weighted images at each month on study. Statistically significant differences first emerged after 5 months on treatment. Adapted from Comi *et al* (2001b). © 2001, reproduced with permission of John Wiley & Sons.

The impact of this study is clearly reduced by the design, but nevertheless it provides some evidence that, in practice, glatiramer acetate may have similar efficacy to IFN-β1b, and both are superior to IFN-β1a. A large, National Institutes of Health funded, phase three trial comparing IFN-β1a by once weekly subcutaneous injection (Avonex) and glatiramer acetate (Copaxone) given either alone or in combination (four treatment arms) to patients with relapsing–remitting multiple sclerosis is in progress in the United States (Fred Lublin, personal communication) An open label prospective study of modest size is already reassuring with respect to safety issues (Lublin *et al* 2001; 2002). Clearly, these turf wars are not yet settled.

Munari *et al* (2004; 2004b) completed a systematic review of glatiramer acetate and concluded that there is no conclusive evidence that this agent alters relapse or progression rate in patients with multiple sclerosis. The interested reader is referred to correspondence rebutting and supporting the methodological assumptions that led to this conclusion (Caramanos and Arnold 2005; Comi *et al* 2005; deJong *et al* 2005; Munari and Filippini 2005).

PROMISE was a massive, randomized, double-blind, placebo-controlled phase three study involving 943 primary progressive patients randomized in a 2:1 ratio either to receive glatiramer acetate or placebo. It was recently terminated after an interim analysis suggested futility (Wolinsky *et al* 2004). There were no safety concerns and doubtless post-hoc analyses will add greatly to our understanding of the nuances of testing therapies in this disease category. PROMISE was not fulfilled.

## *Adverse effects*

Glatiramer acetate is generally well tolerated. It is usually possible to initiate treatment at full strength (20 mg by subcutaneous daily injection) without dose titration. Although a daily subcutaneous injection is required, rarely do patients discontinue this drug because of intolerance. In the early reports (Bornstein *et al* 1982; 1987) and pivotal North American trial (K.P. Johnson *et al* 1995; 1998), there is comment on an unpredictable, sometimes frightening but transient and usually self-limiting systemic reaction (facial flushing, chest tightness, anxiety,

palpitations and dyspnoea) lasting for around 30 minutes immediately after an injection. This is experienced by up to 15% of patients (but not recurring in 50%) with an estimated frequency of one episode per 840 injections (K.P. Johnson *et al* 1998). It is important to warn patients but, although alarming, it is seemingly an innocent adverse effect. Approximately two-thirds of patients notice pain at the injection site. Local irritation may occur in 2–3% (K.P. Johnson *et al* 2000) but skin breakdown is very rare (Johnson *et al* 1998). Focal atrophy of subcutaneous tissue at injection sites and adjacent lymphadenopathy may develop (Windhagen *et al* 2001). Glatiramer acetate is not associated with laboratory abnormalities and routine blood studies are not needed to monitor its safety. There are no important drug interactions.

Treated patients may develop antibodies to glatiramer acetate. However, unlike the situation with neutralizing antibodies to IFN-β, experimental and clinical evidence does not suggest that these anti-glatiramer acetate antibodies reduce biological function (Teitelbaum *et al* 2003). This has been shown in assays that measure binding to MHC molecules, T-cell stimulation, interference of competition between glatiramer acetate and myelin basic protein peptide, cytokine production by glatiramer acetate-specific T-cell clones and *in vivo* inhibition of experimental autoimmune encephalomyelitis (Aharoni *et al* 1998; T. Brenner *et al* 2001; C. Farina *et al* 2002; Teitelbaum *et al* 1973; 1991; 2003).

## Mechanism of action

As for IFN-β, the precise mechanism(s) whereby glatiramer acetate influences the course of multiple sclerosis continues to be discussed (Dhib-Jalbut 2002; Neuhaus *et al* 2001; Yong 2002). Table 18.8 and Figures 18.42 and 18.43 itemize many of the key findings and provide references to the supporting literature. As discussed earlier, interferon administration is generally followed within weeks by a striking reduction in MRI evidence of blood–brain barrier disruption. This effect is much less dramatic following the administration of glatiramer acetate although MRI activity reduces gradually over a period of several months (see above, Comi *et al* 2001b). This may be explained by the finding that glatiramer acetate does not significantly inhibit T-cell migration (Dufour *et al* 2000; Prat *et al* 1999).

Each drug influences T-cell function (especially CD4 cells) in ways that both overlap and are distinctive. Each agent blocks T-cell activation and promotes Th2 (IL-4, IL-5, IL-10, IL-13 and TGF-β) cytokine production. Unlike IFN-β, however, glatiramer acetate induces the production of regulatory T cells in the periphery. These glatiramer acetate reactive cells cross the blood–brain barrier, respond to central nervous system myelin antigens by secreting Th2 (M. Chen *et al* 2001; Y. Qin *et al* 2000) and Th3 cytokines (Aharoni *et al* 2003) that inhibit Th1 cells, thereby effecting so-called 'bystander suppression'. Glatiramer acetate-reactive cells may also induce anergy (Gran *et al* 2000b).

Recently, abundant evidence has accumulated that glatiramer acetate-specific cells secrete brain-derived growth factors (Aharoni *et al* 2003; Kappos and Duda 2002; Ziemssen *et al* 2002) raising the intriguing possibility that this agent may enhance repair at the site of the multiple sclerosis lesion by inducing a degree of localized 'neuroprotective autoimmunity'.

**Table 18.8 Presumed mechanisms of action of glatiramer acetate (adapted from J. Zhang *et al* 2002 with permission)**

| |
|---|
| Modulates T-cell activation and/or proliferation |
| Competes for binding sites of MHC class II antigens (MBP, PLP, MOG: Ben-Nun *et al* 1996; Fridkis-Hareli *et al* 1994; Fridkis-Hareli and Strominger 1998; Racke *et al* 1992; Teitelbaum *et al* 1996; 2003) |
| May modify dendritic cell costimulation processes (Hussien *et al* 2001) or act as weak/partial T-cell receptor agonist (Wiesemann *et al* 2001) |
| Reduces proliferation of MBP-reactive T cells (Duda *et al* 2000; Karandikar *et al* 2002; Neuhaus *et al* 2000) |
| Actives both Th1 and Th2 cells (Zang *et al* 2003) |
| Increases ratio of anti-inflammatory (Th2) to proinflammatory (Th1) cytokines |
| Increases IL-10, IL-4, and IL-6 production (C. Farina *et al* 2001; Hussien *et al* 2001; Neuhaus *et al* 2001a) and decreases IL-12 production (Hussien *et al* 2001) |
| Increases and then decreases IFN-γ secretion with repeated antigen stimulation (Aharoni *et al* 1997) |
| Upregulates CD8+ T-cell responses (Karandikar *et al* 2002) |
| Induce regulatory Th2/3 cells that penetrate the central nervous system and express their anti-inflammatory cytokines and neurotrophic factors *in situ* in animal models of multiple sclerosis (Aharoni *et al* 2003) |
| Induces TNF-α and IFN-γ production (C. Farina *et al* 2001; Neuhaus *et al* 2000; Zang *et al* 2003) |
| Enhances production of brain-derived nerve growth factor (Ziemssen *et al* 2002) |
| Reduces monocyte (Weber *et al* 2004) and antigen-presenting cell function (S. Jung *et al* 2004; H.J. Kim *et al* 2004) |

*MHC = major histocompatibility complex; IL = interleukin; ; TNF = tumour necrosis factor; MBP = myelin basic protein; PLP = proteolipid protein; MOG = myelin oligodendrocyte glycoprotein; Th = T-helper cell.*

The idea that inflammation may enhance remyelination has attracted great interest in the experimental literature (Kipnis *et al* 2000; M. Rodriguez and Lennon 1990; Schori *et al* 2001; Schwartz 2001; Schwartz *et al* 1999; Schwartz and Kipnis 2001) and is discussed more fully in Chapter 10. Recently, M.S. Weber *et al* (2004) have reported that glatiramer acetate blocks monocyte reactivity *in vitro* using cells from treated patients. Both S. Jung *et al* (2004) and H.J. Kim *et al* (2004) have shown that glatiramer acetate also reduces the function of antigen-presenting cells. Together, these studies demonstrate that the mechanisms of action of glatiramer acetate extend well beyond the lymphocyte population of immune cells.

An enzyme-linked immunoadsorbent spot (ELISPOT) assay was developed by C. Farina *et al* (2002) that may correlate 'responder' status to glatiramer acetate. They created three immunological criteria (reduced proliferative response to glatiramer acetate, *in vitro* activation of IFN-γ-producing cells, and activation of IL-4-producing cells) and found that 13 of 15 clinical responders (87%) met two or all three criteria, compared with 22% of patients who appeared to be failing treatment. If correct, this assay may ultimately find more widespread use and lead to the development of other *in vitro* measures to inform treatment decisions.

Antibodies to glatiramer acetate develop within 3 months and may later diminish (T. Brenner *et al* 2001; C. Farina *et al* 2002).

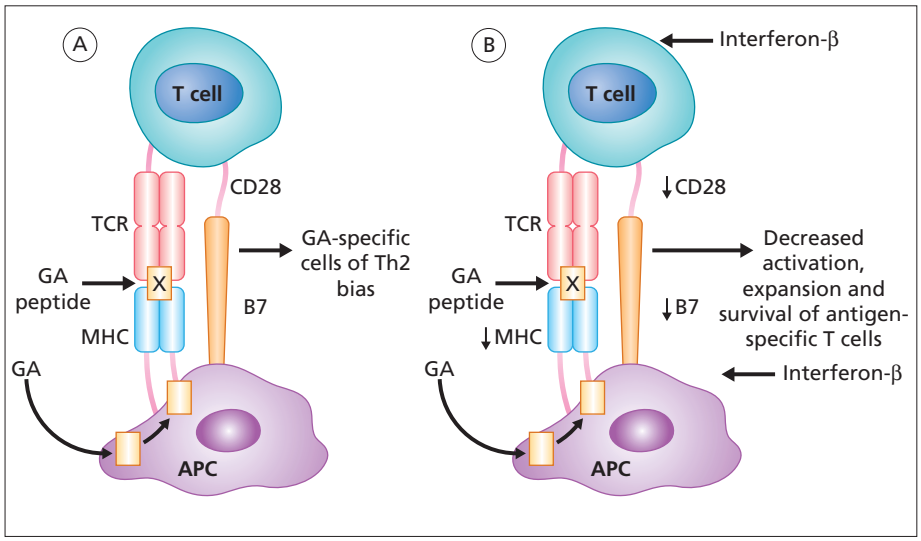



**Figure 18.42** Mechanisms of action of glatiramer acetate (GA) and beta-interferons on antigen presentation. (A) The high affinity of GA for the MHC groove or the uptake of GA by an antigen-presenting cell leads to the presentation of GA as an antigen and the generation of GA-specific Th2-biased cells. (B) IFN-β acts on its receptor on T cells and antigen-presenting cells. This decreases the expression of molecules needed for antigen presentation. Together with a further activity of interferon on T-cell expansion and survival, this leads to the decreased generation of antigen-specific T cells. X refers to an antigen-siting in the MHC groove; TCR = T-cell receptor. Adapted from Yong (2002). © 2002, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

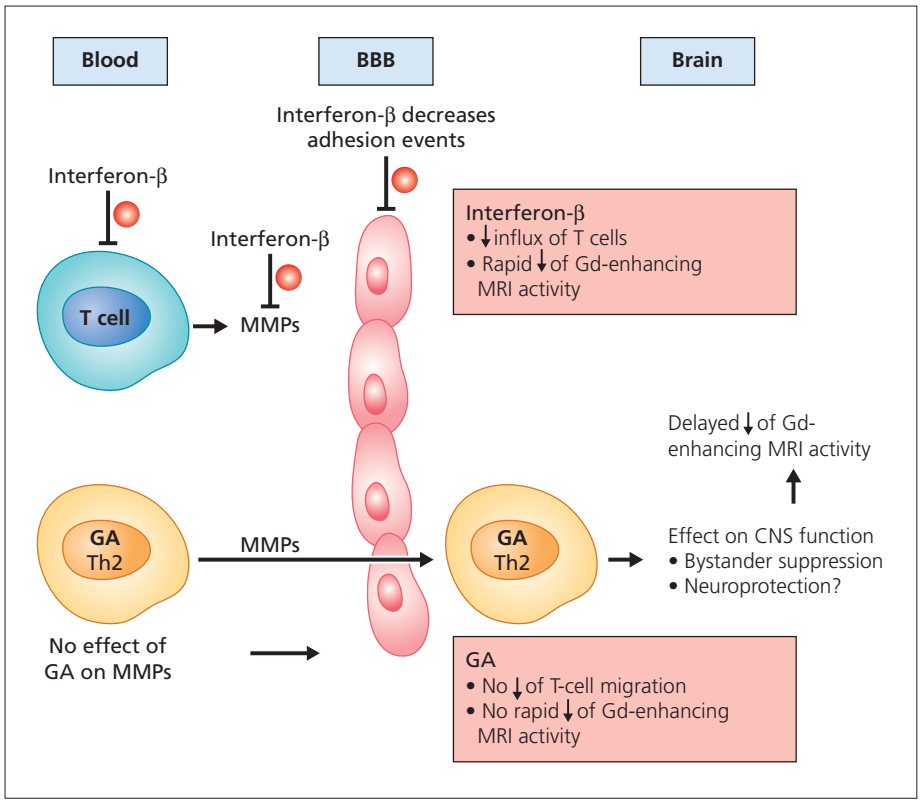



**Figure 18.43** Effects of glatiramer acetate (GA) and IFN-β on the blood–brain barrier (BBB) and within the central nervous system. IFN-β reduces the production of matrix metalloproteinases (MMP) by T cells and diminishes the adhesion of T cells to endothelium. These two effects reduce the influx of T cells into the central nervous system. GA-specific Th2 cells traffic into the central nervous system to produce local bystander immune suppression and possibly exert neuroprotection. Gd = gadolinium. Adapted from Yong (2002). © 2002, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

There is great interest in whether these antibodies reduce the clinical benefit of glatiramer acetate (see the discussion of the possible influence of neutralizing antibodies on clinical effects of the interferons). In a large series of *in vitro* and *in vivo* experiments, Teitelbaum *et al* (2003) reported that these antibodies do not seem to reduce activity. A subsequent study, however, reported that antibodies to glatiramer acetate reversed many of these putative activities, including the effect on T-cell proliferation and both pro- and anti-inflammatory cytokines (Salama *et al* 2003). More work is therefore needed to clarify these ambiguities.

Early work of great interest suggests that antibodies to glatiramer acetate induce remyelination in the Theiler's virus animal model of demyelinating disease (Ure and Rodriguez 2002). This finding parallels the observation that immunoglobulins directed against central nervous system antigens also induce abundant remyelination in this animal model (Bieber *et al* 2003; Ciric *et al* 2003; 2004; Mitsunaga *et al* 2002; M. Rodriguez and Lennon 1990) and raises the possibility that anti-glatiramer acetate antibodies may enhance repair of the lesion in multiple sclerosis.

In what ways might these two agents complement their mechanisms of action? Zang *et al* (2003a) showed that, when tested

together *in vitro*, IFN-β1a and glatiramer acetate act to antagonize their respective modes of action. Specifically, IFN-β1a blocked glatiramer acetate-induced T-cell proliferation and the drug-specific pattern of cytokine production was lost. Glatiramer acetate induced both Th1 (TNF-α and IFN-γ) and Th2 (IL-4 and IL-10) cytokines. Conversely, IFN-β inhibited Th1 cytokine production. Together, IFN-β reduced the number of IFN-γ-producing cells compared to glatiramer acetate alone – suggesting another type of antagonism between these two agents. Firm conclusions on the practical and immunological aspects of combination therapy seem premature.

### *The licence for Copaxone*

In the United States, information distributed by the pharmaceutical company that markets glatiramer acetate states that this agent is

> *recommended for reduction of the frequency of relapses in patients with relapsing remitting multiple sclerosis. It is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol and is not recommended for use in pregnancy. The safety and efficacy of glatiramer acetate is unknown in nursing women, in those with impaired renal function, in patients <18 years old, and in the elderly.*

Copaxone was approved for marketing in the United Kingdom and launched in December 2000 with the same general indications. This first approval in a major European market led to extension throughout the European Union by the end of 2001 under the European Mutual Recognition Procedure with the United Kingdom acting as reference member state.

## TREATMENTS THAT TARGET T CELLS

In view of the conditional benefits of immune suppression in the treatment of patients with multiple sclerosis, attention has turned to alternative means of interfering with the sequence of events that leads to tissue injury. The theoretical basis for designing therapies, the experimental evidence that they might work, such clinical evidence as there is for efficacy, and the reasons why theory does not always translate into clinical success were admirably reviewed by R. Hohlfeld (1997). These approaches include:

- the use of monoclonal antibodies that achieve much more precise immunological effects than nonspecific immunosuppressants
- reagents which block recognition between antigen-presenting cells and responder lymphocytes
- depletion of autoreactive lymphocyte populations by T-cell vaccination
- bone marrow transplantation.

The validity of these approaches has yet to be confirmed and most are conditional on whether the central hypothesis for the role of T cells in the pathogenesis of inflammatory demyelination is correct. Most of these therapies target circulating white blood cells, in particular lymphocytes, and so qualify as potential disease-modifying treatments in multiple sclerosis. We retain a brief discussion of the earlier studies as background to the current interest in this strategy.

### Anti-lymphocyte globulin

The first trial, assessing treatments designed to target circulating lymphocytes and adopting a double-blind and placebo-controlled protocol, was reported in 1982. Inevitably it was underpowered. Forty-three patients with relapsing–remitting multiple sclerosis were randomized to treatment with anti-lymphocyte globulin, azathioprine and prednisolone in combination for 1 month, followed by azathioprine (3 mg/kg) alone for a further 14 months, or placebo preparations. The reduction in relapse rate from 1.0 to 0.7 in the treated group, time to first episode and accumulation of disability all favoured an effect of treatment but the magnitude of these results did not impress the investigators, who reported their findings as offering no more than an indication for continuing to evaluate immunosuppression in the context of multiple sclerosis (Mertin *et al* 1982).

### Total lymphoid irradiation

Cook *et al* (1986) first compared total lymphoid irradiation given over 5 weeks with sham irradiation in a group of 45 patients with secondary progressive multiple sclerosis. They reported a beneficial effect on time to further sustained progression, especially over the first 12 months of the study. This clinical response was anticipated by a reduction in absolute lymphocyte count to $<850/mm^3$ and only these patients showed lower functional impairment scores for up to 4 years after the start of treatment. Wiles *et al* (1994) studied 27 patients (the plan was to study 56 but recruitment proved difficult) randomized to active or sham irradiation with 1980 cGy to the lymphoid system and spleen. There was no difference between groups in the clinical course over 2 years, other than a small improvement in bladder function. However, MRI activity was reduced. Three patients died – two, sham-treated, from respiratory complications of multiple sclerosis, and one, who received total lymphoid irradiation, from cardiac failure. Although these fatalities were not related to lymphoid irradiation, the treated group experienced more adverse effects than controls. Subsequently, Cook *et al* (1995) claimed that the concomitant use of corticosteroids further improved the effects of total lymphoid irradiation, and that this additional benefit correlated with the emergence of T cells having the $CD^+/CD3^-$ or $CD8^+/CD3^-$ phenotype. Mortality after total lymphoid irradiation was 1% compared with 14% in the sham-treated group. With EDSS scores at entry of >6.5, these were moderately severely affected patients at the outset.

### Monoclonal antibodies

With developments in therapeutic immunology came the opportunity to design small molecules and monoclonal antibodies targeting one component only of the immune system, and leaving the rest intact. In theory, chimaerization and humanization reduce the immunogenicity of therapeutic antibodies and allow courses of reagents having prolonged effects to be given repeatedly (Winter and Milstein 1991). A single pulse of treatment

can induce prolonged alteration in immunological behaviour long after the targeted immune population has been reconstituted (S. Qin *et al* 1993). Anti-CD6 (Hafler *et al* 1986), anti-CD2 (Hafler *et al* 1988), anti-CD3 (Weinshenker *et al* 1991b), anti-CD4 (Lindsey *et al* 1994a; 1994b; van Oosten *et al* 1997; Racadot *et al* 1993) and anti-CD52 (Moreau *et al* 1994; 1996) antibodies have all been administered to patients with multiple sclerosis. In some instances, anti-globulin responses and acute adverse effects limited the usefulness of these potential treatments and an additional problem has been modulation of the targeted lymphocyte antigen, allowing some cells to survive.

### Anti-CD6

Using a murine antibody which recognizes the T12 antigen (CD6) present on most (post-thymic) T lymphocytes (but neither chimaeric nor humanized), together with corticosteroids, Hafler *et al* (1986) reported clinical stabilization in six of 12 patients with secondary progressive multiple sclerosis (severe enough to require the recent use of a wheelchair in two cases) at 6 months in an open uncontrolled study. This effect was maintained for a further 3 months in three of these responders. Human anti-mouse antibodies developed within 7 days in seven of nine patients in whom assays were performed. Recovery of circulating T12 cells was rapid and there was evidence *in vitro* for antigen modulation. Studies of cerebrospinal fluid did not suggest that antibody had entered the central nervous system.

### Anti-CD3

Weinshenker *et al* (1991c) treated 16 patients, selected for recent rapid accumulation of disability or a high relapse rate, with 50 mg of an anti-CD3 monoclonal antibody (OKT3) over 10 days. Each received corticosteroids and non-steroidal anti-inflammatory drugs. One patient developed anaphylaxis within minutes of receiving the first dose of OKT3 and did not continue in the protocol. A variety of systemic symptoms occurred in all patients despite prophylactic measures (typical symptoms included hypotension, fever, nausea, vomiting, diarrhoea and skin rash). Six out of 16 deteriorated during the course of treatment but this alteration was transient in three. Two patients died from complications of severe multiple sclerosis between 9 and 12 months after enrolling in this trial. Overall, the authors were uncertain that the treatment provided any lasting benefit to this group of patients. At the 1 year follow-up examination, of the 15 patients who completed the treatment protocol, four had worsened by ≥ 1.0 EDSS points (including the two deaths), nine were unchanged (EDSS changed by ≤ 0.5 points) and two improved by ≥ 1.0 EDSS point. No conclusions could be reached in the three patients with relapses of whom one each improved, remained stable and deteriorated. A small number of serial MRI scans failed to show an effect on lesion load. Rapid but transient reductions in circulating lymphocytes and their subpopulations were observed. All patients developed high titres of human anti-mouse antibodies. The systemic manifestations of OKT3 administration are known to be cytokine mediated, to correlate with sequential release of circulating TNF-α and IFN-γ followed by IL-6, and to be suppressed with methylprednisolone (Pececs *et al* 1993). Each of the two patients studied by Weinshenker *et al* (1991c) showed a transient surge in circulating TNF-α and IFN-γ on the first day of treatment. Therapy was complicated by oral candidiasis, and two patients were thought on clinical grounds to have aseptic meningitis. Whilst not promoting the continued use of murine monoclonals in multiple sclerosis, Weinshenker *et al* (1991c) advocated the development of more specific and less toxic reagents, manipulated to restrict their immunogenicity.

### Anti-CD4

The first reported study using murine anti-CD4 monoclonal antibody therapy in multiple sclerosis (Racadot *et al* 1993) included 21 patients with disease progression or frequent relapse and showed no acute effects (good or bad). Clinical stabilization was claimed for 12 of 20 patients at 3 months and eight of the 20 at 6 months. No new relapses were documented. The reductions in circulating lymphocytes had returned to normal ranges within 90 days. A transient elevation was observed in circulating TNF-α, soluble TNF receptor and IL-6 but not IFN-γ, IL-1 or soluble CD8 and CD4 antigen. Unlike most other investigators, Racadot *et al* (1993) reported a detectable rise in cerebrospinal fluid TNF-α levels.

Lindsey *et al* (1994a) treated 29 patients in an open uncontrolled study with a chimaeric anti-CD4 antibody in doses ranging from 10 to 200 mg given as a single infusion, or over 3 days. The reduction in total circulating lymphocytes was partial and recovered within 6 months. The same pattern was observed for CD4 cells but without complete return to the normal range. Five patients developed anti-murine antibodies. Small improvements were noted in three of 26 patients undergoing clinical evaluation, but the majority remained unchanged (16 patients) or deteriorated (seven patients). Fourteen of 25 patients in whom serial scans were obtained had enhancing lesions on baseline MRI. One hundred enhancing lesions were seen on 91 scans obtained during follow-up, and 17 of 25 patients showed an increase in $T_2$-weighted lesions. The patients reported minor systemic symptoms and there was an increase in infections requiring treatment.

Most of these patients were subsequently considered for re-treatment on the basis that their CD4 count returned to >300 cells/mm$^3$ (Lindsey *et al* 1994b). Several were withdrawn or elected not to continue and one died suddenly after aspiration whilst eating. Twenty-one of the original cohort received up to three further treatments (a total of 36 courses were administered), responding with a drop in CD4 count on each occasion and sometimes showing prolonged lymphopenia. There seemed to be no increase in the development of anti-idiotype antibodies with this second exposure. One patient improved, three worsened, 16 remained unchanged and one was lost to follow-up. MRI activity was seen on ten of 16 scans before treatment and on 12 of 26 scans (from 16 patients) at follow-up (six of 17 in the subgroup with persistently low CD4 counts). Other than minor infections, some requiring treatment, and one episode of herpes zoster, there were few complications of repeated treatment. On the basis of these preliminary results, van Oosten *et al* (1997) randomized 71 patients, most with clinical and radiological evidence for disease activity, to treatment with chimaeric anti-CD4 or placebo under double-blind conditions.

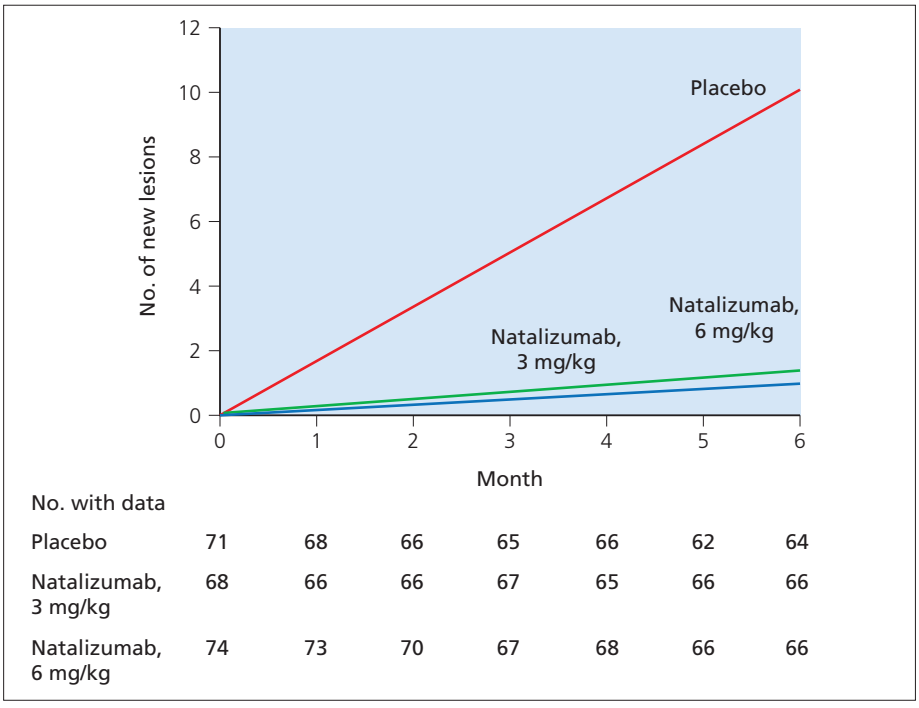
Although circulating CD4 counts were reduced, both groups showed persistent radiological activity (at around 1.5 new lesions per patient per month) although the number of clinical exacerbations was lower, by 41%, in the treated than placebo group. A mild cytokine release syndrome was apparent in these patients leading to withdrawal from the study in a few instances. Serial immunological observations in a subgroup of participants showed, as expected, reduced numbers of $CD4^+$ naive memory cells (which persisted for 12 months after treatment) but there was no effect on serum levels or on mitogen-stimulated release of TNF-α (Llewellyn-Smith *et al* 1997). These blood markers did not correlate with MRI activity.

### *Natalizumab (anti-VLA4)*

Lymphocytes and monocytes express $\alpha_4\beta_1$ integrin on their cell surface. This glycoprotein binds the endothelial VCAM-1 and thereby mediates cell adhesion and transendothelial migration. Natalizumab (initially marketed as Antegren, Elan Pharmaceuticals and Biogen) is a humanized monoclonal antibody that blocks the $\alpha_4$ integrin adhesion molecule and so reduces cell migration across the blood–brain barrier. Since serial gadolinium-DTPA enhanced MRI scans indicate breakdown of the blood–brain barrier as a consistent feature of new lesions (Kermode *et al* 1990), these properties suggested a potential therapeutic role during the active inflammatory stage of active multiple sclerosis. Data from the experimental autoimmune encephalomyelitis model of multiple sclerosis (Engelhardt *et al* 1998; van der Laan *et al* 2002) indicated that adhesion molecule inhibition might have therapeutic effects in inflammatory brain disease independent of the effect on cell migration. Natalizumab administration reduced new MRI activity in a placebo-controlled pilot study where two intravenous doses were given 1 month apart (Tubridy *et al* 1999; and see Schwid and Noseworthy 1999).

Against this background, D.H. Miller *et al* (2003a) reported a phase two randomized, double-blind, placebo-controlled study comparing two doses of natalizumab (3 and 6 mg/kg) administered intravenously once monthly for 6 months in 213 patients with relapsing–remitting multiple sclerosis. Both doses favourably influenced the primary end point (number of new MR lesions as determined by monthly scanning). Significantly fewer patients reported clinical relapses in the active treatment arms at 6 months (relapse-free: placebo, 62%; both active groups, 81%; $p = 0.02$: Figure 18.44). However, the apparent benefit of these treatments was not prolonged beyond the period of treatment. During the subsequent 6 months of follow-up, during which patients were untreated, those previously randomized both to the placebo and natalizumab groups, had essentially identical numbers of relapses and amounts of MRI activity. Treatment was well tolerated although there were a few allergic responses (including one episode of anaphylaxis causing bronchospasm and urticaria that responded quickly to emergency treatment with antihistamines), and perhaps a minor trend suggesting increased risk of infection (pharyngitis) in treated subjects. In a follow-up report, Dalton *et al* (2004b) demonstrated that gadolinium enhancing MRI lesions developing in the natalizumab-treated patients were less likely to develop into $T_1$ hypointense lesions ($T_1$ black holes) at 1 year than those present in the placebo patients. This report suggests that even a relatively limited period of treatment with this agent might have a degree of prolonged benefit on MRI behaviour. The clinical relevance of this finding remains to be determined.

These encouraging early findings led to further evaluation in two large phase III trials. Nine hundred and forty-two patients with relapsing–remitting multiple sclerosis, who had not received any other drug treatment for at least 6 months, were randomized to treatment with either natalizumab (300 mg) or placebo intravenously every 4 weeks for 28 months. A second placebo-controlled trial was designed to determine whether




| No. with data | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 71 | 68 | 66 | 65 | 66 | 62 | 64 |
| Natalizumab, 3 mg/kg | 68 | 66 | 66 | 67 | 65 | 66 | 66 |
| Natalizumab, 6 mg/kg | 74 | 73 | 70 | 67 | 68 | 66 | 66 |

**Figure 18.44** Treatment of relapsing–remitting multiple sclerosis with intravenous natalizumab (a humanized monoclonal antibody against anti-$\alpha_4$ integrin) at 3 mg/kg (blue line) and 6 mg/kg (green line). Cumulative mean number of new gadolinium-enhancing lesions on MRI while on treatment. However, in the subsequent 6 months, upon discontinuing treatment, the patients originally treated with the active antibody had equal numbers of relapses and MRI markers of disease activity to those originally randomized to placebo. Adapted from D.H. Miller *et al* (2003a). © 2003, reproduced with permission of the Massachusetts Medical Society.

prolonged administration of natalizumab provides additional benefit to weekly IFN-β1a in 1171 individuals who have already experienced at least one episode whilst on IFN-β1a. Preliminary data on safety, immunogenicity, pharmacokinetics and pharmacodynamics indicated that there were no unfavourable interactions between these therapeutic agents (Vollmer *et al* 2004a). In a similar but smaller trial, investigators randomized 110 patients treated with glatiramer acetate to monthly doses either of natalizumab or placebo for a period of 6 months.

Preliminary results of the first two studies described above, after patients had received treatment for a median duration of 13 months, led the Food and Drug Administration (*http://www.fda.gov/*) to license natalizumab (Tysabri) 300 mg by intravenous infusion every 4 weeks, late in 2004 for the 'reduction of clinical exacerbations in patients with relapsing forms of multiple sclerosis'. The advice on use in pregnancy is ambiguous ('only if clearly needed'); administration to individuals aged under 18 years is contraindicated; advice on the upper age limit is noncommittal. Although experience beyond 13 months was limited at that time, the only adverse effects of note were headache, arthralgia, infections and hypersensitivity reactions but these were infrequent and rarely limiting. In study 1, the annualized relapse rate was 0.25 in individuals receiving natalizumab compared to 0.74 in the placebo group; the percentages of patients remaining relapse free were 76% and 53%, respectively. In study 2, annualized relapse rate was 0.36 in patients receiving natalizumab compared to 0.78 (the same as placebo-treated cases from study 1) in those only being treated with IFN-β1a; the percentages of patients remaining relapse free were 67% and 46%, respectively – even less than the placebo rate for these individuals receiving IFN-β1a. As expected, the clinical results were matched by comparable reductions in disease activity using imaging surrogates. Again, there was no difference in the proportion or number of cases showing activity comparing the placebo group of study 1 and the IFN-β1a-only group of study 2 but this may reflect differences in the study populations. About 6% of patients developed a persistent antibody response to natalizumab that was associated with an apparent loss of clinical effectiveness. Clearly, these data do not provide support that IFN-β1a is effective in reducing clinical or MRI evidence of disease activity in patients who continue to report clinical relapses while receiving this agent.

The patients involved in the 2 year placebo-controlled trials are being followed in an extension study while on natalizumab; in order to obtain long-term data on effectiveness, tolerability and safety in addition to immunogenicity. The intention was to follow what happens to these patients in the 6–12 months after infusions cease, so as to determine whether this more prolonged antibody administration proves more durable against clinical and MRI indicators of disease activity than the results reported to date.

On 28th February 2005 the sponsors of Tysabri (Biogen Idec and Elan Pharmaceuticals) voluntarily removed this agent from clinical and research trial use because progressive multifocal leukoencephalopathy was reported in two patients treated with the combination of Tysabri and IFN-β1a (Avonex) for more than 2 years. A third case was soon reported in a patient treated with Tysabri for Crohn's disease (eight doses over a period of 18 months), again in the context of a randomized trial; the patient died from what initially was thought to have been a fatal glioma and later confirmed to be progressive multifocal leukoencephalopathy. This patient had been refractory to corticosteroids, azathioprine and other immunosuppressants – perhaps contributing to the risk of additional immunosuppression with this experimental agent. Two additional unconfirmed cases have been subsequently reported in the context of clinical trials for multiple sclerosis but, at the time of writing, the details are scarce. Tysabri-treated patients from these trials are now under close scrutiny to detect progressive multifocal leukoencephalopathy as early as possible and investigators are reviewing the available data to understand the mechanism(s) of presumed reactivation of the JC virus in this setting. As highlighted earlier, these events remind us of the potential risks inherent in clinical trials (Drazen 2005). It remains uncertain that this once-approved therapeutic agent will resurface for use in multiple sclerosis and other inflammatory disorders.

### *Anti-Vβ5.2/5.3⁺ T cells*

In a study designed to determine whether administration of the humanized monoclonal antibody ATM-027 (with specificity for Vβ5.2/5.3$^+$ T cells) would reduce MRI measures of disease activity, Killestein *et al* (2002b) stratified relapsing–remitting patients by HLA-DR2 status to receive monthly intravenous infusions either of the antibody (n = 47) or placebo (n = 12). The dose was titrated to deplete the target T cells. Treatment successfully suppressed the Vβ5.2/5.3$^+$ T-cell population and was well tolerated. There was a trend suggesting a reduction in MRI activity (lesion count, volume of enhancing lesions) but this result did not achieve the goal of the study.

### *Anti-CD52*

Campath-1H may emerge as an important treatment for multiple sclerosis. From the clinical science perspective, its credentials are already established. Clinical observations provided the stimulus for basic research that has illuminated key aspects of the pathogenesis (Coles *et al* 1999a; Moreau *et al* 1996; Redford *et al* 1997; K.J. Smith *et al* 2001; Wilkins *et al* 2003). In turn, these are now being recycled into clinical practice and with provisionally encouraging results. Campath-1H is a humanized monoclonal antibody suitable for therapeutic use that targets the CD52 antigen present on all lymphocytes and a proportion of monocytes. As a result of its isotype, Campath-1H is exceptionally good at activating complement and mediating antibody-dependent cell-mediated cytotoxicity (M.Q. Xia *et al* 1993). CD52 does not lose its potential for lysis through modulation by antibody. Lymphopenia is rapid and prolonged following a pulse of treatment since the CD52 antigen is expressed in high density on the target cell membrane (Hale *et al* 1990). The median times to recovery of baseline counts for CD3, CD4, CD8 and total lymphocytes are 51, 61, 30 and 66 months, respectively. Conversely, B-cell numbers return more rapidly and tend to overshoot above baseline but rarely rise above the upper limit of the normal range. Although a single treatment does not elicit an anti-globulin response, this may not be the case if repeated courses of antibody are given. Campath-1H has been studied in three cohorts of patients with multiple sclerosis treated on an open label basis.

The change in MRI evidence for disease activity following treatment with Campath-1H established that a reduction in the

availability of circulating lymphocytes is associated with a more or less complete cessation in new lesion formation and prompted the further evaluation of Campath-1H as a possible disease-modifying treatment (Moreau *et al* 1994). A second cohort of 36 patients with secondary progressive multiple sclerosis (duration of the progressive phase, 3.6 ± 2.6 years; mean EDSS 5.8 ± 0.8; increase in disability in the year before treatment, ≥ 1 EDSS point; annual relapse rate, 0.7 per patient per year) confirmed that radiological evidence for disease activity was suppressed by >90% for at least 18 months (Coles *et al* 1999a; Paollilo *et al* 1999). Relapse rate, expected to decline as part of the natural history of multiple sclerosis in the secondary progressive phase, changed from 0.7 per patient per year before treatment to an annualized rate of 0.02 per patient per year at mean follow-up of 6.7 (SD ± 2.1) years. When 13 patients from this original cohort were re-examined 5.8 years (± 0.5) after their last scan (which was itself 18 months after Campath-1H), there was no evidence for an increase in proton density or $T_1$ lesion volume in the intervening period.

However, dissociation emerged between this suppression of inflammation and disease progression. Disability increased by +0.2 EDSS points per patient per year. Although this represents a statistically significant reduction in rate of progression compared to the year before treatment ($p < 0.001$), the toll of incremental progression over time has led to substantial accumulation of disability with no overall benefit from treatment (Figure 18.45). Disease progression was associated with brain atrophy. Patients who progressed from baseline at the first follow-up interval (18 months) showed reduced brain volume at the time of treatment with Campath-1H by comparison with patients showing initial stability of clinical progression. Those who progressed early had most inflammatory activity prior to treatment. Furthermore, despite continued suppression of cerebral inflammatory activity, this poor prognosis group with atrophy at the time of treatment and early disease progression demonstrated sustained reduction in brain volume and altered MR spectroscopy (*N*-methyl-aspartate) indicating progressive axonal loss. After 7.5 years, mean percentage change in cerebral volume was –0.48% (± 0.46) per year. The mean absolute change was –1.37 (± 1.28) mL/year ($p = 0.002$). Two patients in this group had measurable cerebral atrophy despite clinical stability. Early loss of brain volume was an indicator of sustained atrophy. The six of 13 patients who had already shown increased cerebral atrophy at 18 months after Campath-1H had a mean further loss of 2.13 mL per year (± 0.65), compared to only 0.7 (± 1.4) mL per year in those whose cerebral volume was stable for the initial 18 months after treatment ($p = 0.042$). The lesson is clear. Once the cascade of events leading to tissue injury is established, effective suppression of inflammation does not limit brain atrophy or protect from clinical progression.

Against this background, a third cohort consisted of 22 patients with active relapsing–remitting multiple sclerosis, a short clinical history and no disease progression (Coles *et al* 2005). As a group, they had experienced a total of 133 relapses over 60 patient-years of combined disease history before treatment, giving an annual relapse rate of 2.2 per patient. This rose to 2.94 per patient in the year before Campath-1H. The cohort included 17 drug naive patients and five who had already failed treatment with IFN-β. After treatment this cohort has had five investigator-confirmed episodes, giving a relapse rate of 0.14, and representing a 94% reduction in relapse rate (Figure 18.46). By comparison with many of the pretreatment episodes, all but one was clinically mild with full spontaneous recovery and leaving no stepwise increase in EDSS.

It is instructive to compare the accumulation of disability in the relapsing and progressive groups (Figure 18.47). In the year before treatment, the relapsing patients showed a mean annual increase of +2.2 EDSS points. Mean annualized changes over the periods 0–6, 6–12 and 12–24 months were –2.4, –0.6 and –0.4, respectively. This compares with –3.8, –0.6 and –0.2 in the relapsing–remitting cohort (excluding the more advanced group of patients who had failed previous treatment with IFN-β). Nine of 15 patients observed at 1 year had an improved EDSS. All but one of the others was stable, and the mean effect was an improvement by 1.2 points compared to baseline. This improvement was sustained in the nine patients observed at 24 months, whose mean EDSS was –1.3 points from baseline. One patient had a sustained deterioration from EDSS 6.0 to 6.5 within the first 3 months after Campath-1H, but no subsequent change in disability. This stabilization of disability stands in marked contrast to the group with secondary progressive multiple sclerosis.

Patients treated for multiple sclerosis with Campath-1H experience an acute cytokine release syndrome with severe but temporary rehearsal of previous clinical features - specific manifestations varying with previous clinical features (see Chapters 10 and 13; Figure 18.48; Moreau *et al* 1996). Pretreatment with corticosteroids abolishes or minimizes these neurological exacerbations. Infections that may represent adverse effects of Campath-1H are mild and relatively infrequent given the profound and prolonged depletion of lymphocytes. These include spirochaetal gingivitis (at 10 days), measles (at 11 days), herpes zoster (three instances; at 6 and 9 months, respectively), varicella zoster (at 2 years), recurrent aphthous mouth ulcers (from 6–9 months), pyogenic granuloma (at 22 months), and listeria meningitis after eating soft cheese at 2 weeks. One patient with secondary progressive multiple sclerosis (EDSS 8.5) died of sepsis 7 years after Campath-1H treatment.

The principal adverse effect of Campath-1H therapy in patients with multiple sclerosis is Graves' disease (Coles *et al* 1999b). One patient had experienced Graves' disease prior to Campath-1H treatment and, to date, 15 new cases have been observed after treatment in the remaining 57 patients (27%), with one additional case of autoimmune hypothyroidism. One patient in the relapsing–remitting group developed acute renal failure as a result of Goodpasture's syndrome, with no lung involvement. This occurred 10 months after treatment with Campath-1H and was associated with the development of high titre anti-glomerular basement membrane antibodies, which were not detectable in serum taken before Campath-1H treatment, nor 1 month before her illness. Systematic screening of sera from all other patients for autoantibodies against glomerular basement membrane, reticulin, gastric parietal cell, endomysial, anti-acetylcholine receptor and anti-voltage gated calcium channel have shown no abnormalities. One patient has developed positive anti-double-stranded DNA antibodies without any clinical evidence of systemic lupus erythematosus, impaired renal function, or arthritis. Another patient with a positive family history of coeliac disease had elevated positive IgA and IgG anti-gliadin antibodies, without IgA tissue transglutaminase antibodies, in a single serum sample at 1 month after Campath-1H.

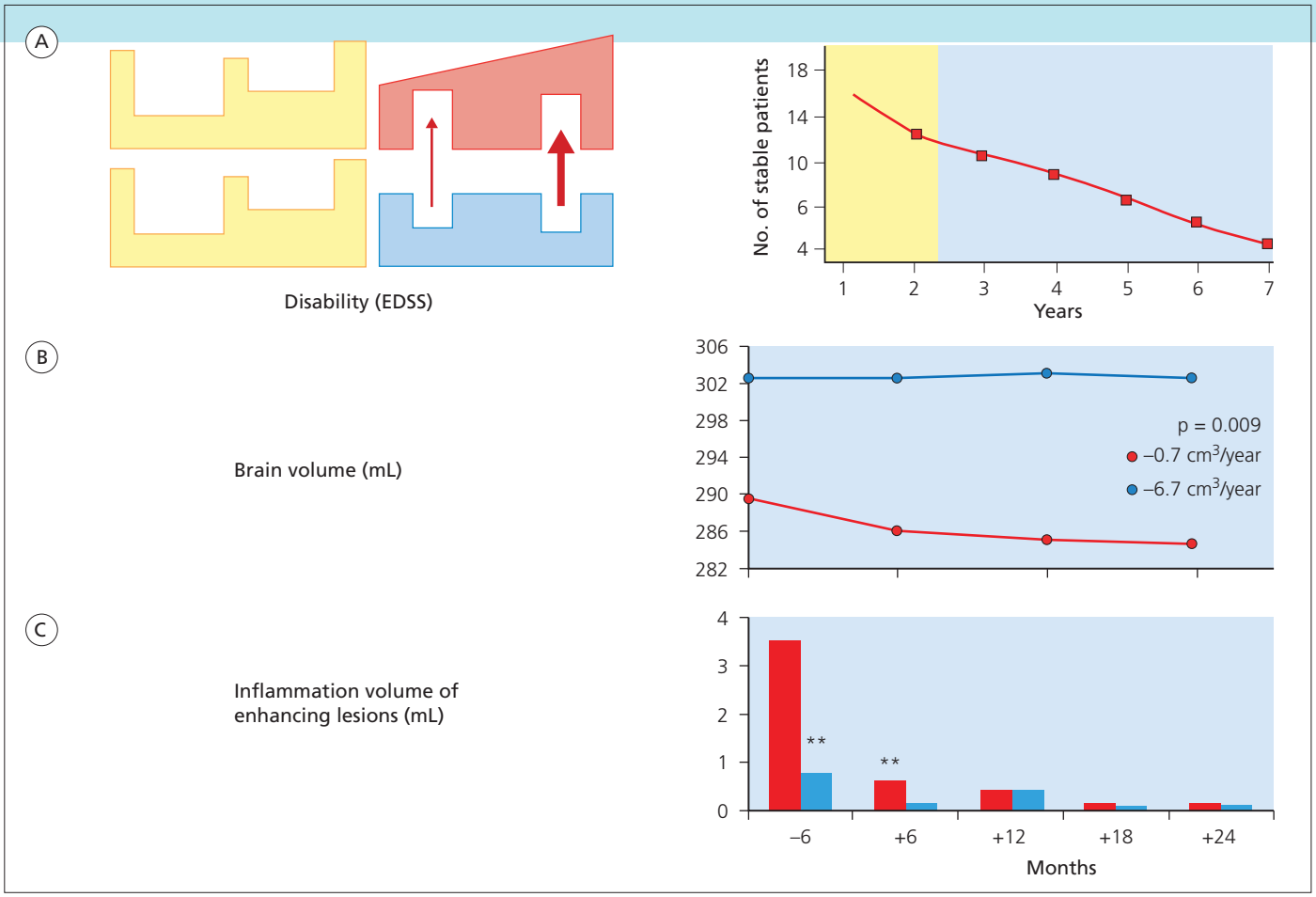



**Figure 18.45** Correlation between brain atrophy and progression of disability in patients with secondary progressive multiple sclerosis showing substantial reduction in new lesions after treatment with Campath-1H. Adapted from Coles *et al* (1999a). © 1999, reproduced with permission of John Wiley & Sons.

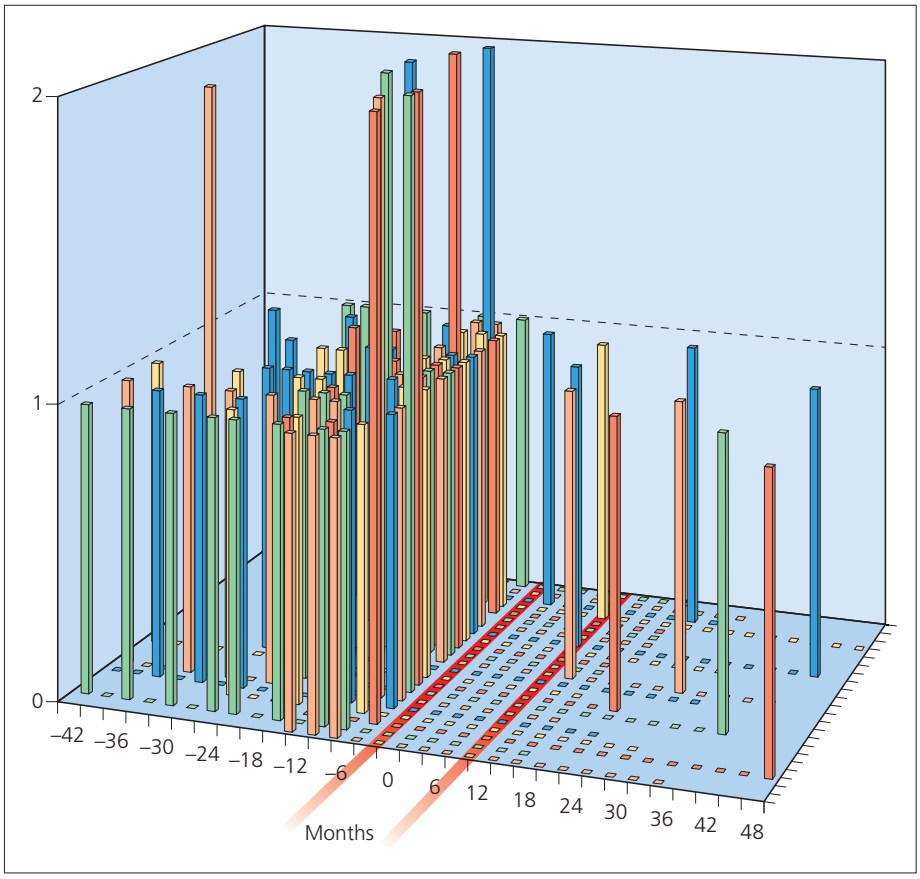



**Figure 18.46** Reduction in new episodes following treatment with Campath-1H in patients with active relapsing–remitting multiple sclerosis. Adapted from Coles *et al* (2005).

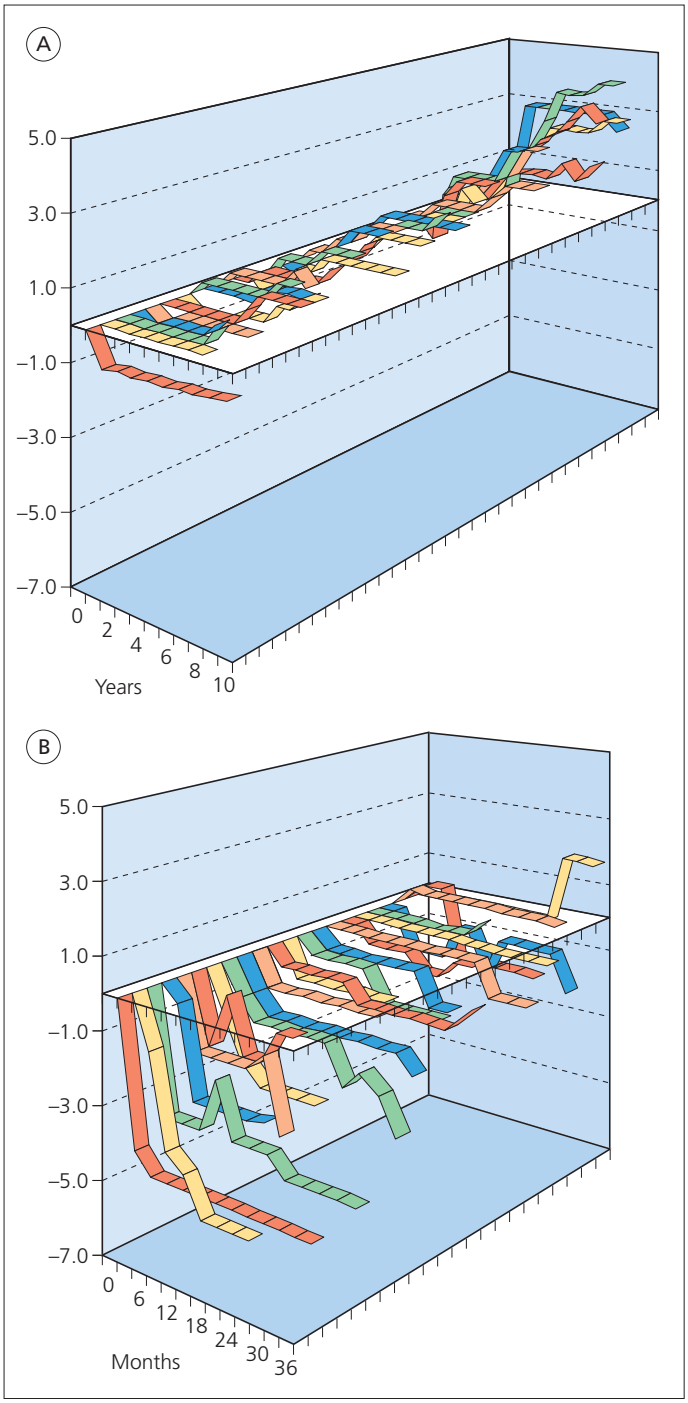



**Figure 18.47** Comparison of serial change in disability (EDSS) in 36 patients with secondary progressive multiple sclerosis and 22 with early active relapsing–remitting disease. Adapted from Coles *et al* (2005).

These were undetectable in both the subsequent serum samples and those taken before treatment. Recruitment closed in April 2004 for a phase II multicentre randomized study comparing two doses of Campath-1H (60 mg and 120 mg over 5 days at baseline, repeated at 1 and 2 years) with IFN-β1a (Rebif; 22 μg three times weekly increasing at 1 month to 44 μg three times weekly by subcutaneous injection) in patients with early clinically active relapsing–remitting multiple sclerosis. The primary outcome is time to sustained disability as determined at 3 years. A press release issued by the sponsors in September 2005 reporting the first interim analysis indicates at least a 75% treatment effect on relapse rate, and >60% on sustained accumulation of disability, each at 1 year, compared with Rebif. These preliminary results appear to confirm the high efficacy of Campath-1H but, as before, the major adverse effect relates to autoimmunity with three cases of idiopathic thrombocytopaenic purpura, one of which proved fatal

### *Anti-CD25 (daclizumab)*

There are few studies that systematically address the management of patients failing to respond adequately to approved therapies. In an uncontrolled series, Rose *et al* (2004) treated 19 patients, 17 of whom were not responding to other therapies, for between 5 and 25 months with daclizumab and claimed that all showed reduced MRI activity, compared with pre-treatment images, and 'sustained clinical improvement (10) or 'stability' (9). In a recent report, Bielekova *et al* (2004) administered a humanized monoclonal antibody (daclizumab) directed against the IL-2 receptor on activated T cells (IL-2Rα-chain; CD 25) to 11 patients with multiple sclerosis who appeared not to be responding to IFN-β1b treatment. All patients continued to receive IFN-β1b therapy during this study. 'Failure to respond' was defined as either one or more relapses or continued progression of ≥ 1.0 EDSS worsening over a period of 18 months on IFN-β1b treatment. Patients were selected for participation if they demonstrated ≥ 0.67 new MRI lesions per month during a 4-month period on IFN-β1b treatment. Treatment was given as 1.0 mg/kg per intravenous dose at baseline and week two, and then five additional infusions given at 4-weekly intervals. This agent was well tolerated although there were more infections and liver enzyme elevation over the period during which the antibody was given. There was a 78% reduction in new contrast enhancing lesions compared with baseline that began approximately 6–8 weeks after the first antibody infusion. One patient seemed to respond only to a higher dose (2 mg/kg per dose administered every 2 weeks). Secondary measures of benefit included a reduced relapse rate, better motor performance on the nine-hole peg test, improved scores on the Scripps Neurological Rating Scale, and reduced volume of contrast enhancing lesions. Further studies are planned.

## T-cell vaccination

One therapeutic approach has been to eliminate antigen-specific autoreactive T cells by vaccination with X-irradiated cells primed against myelin basic protein. It was J. Zhang *et al* (1993) who first showed that inoculation of myelin basic protein reactive T cells induces responses that deplete circulating antigen-specific T cells, confirming that clonotypic interactions regulating autoreactive lymphocytes can be induced in humans by T-cell vaccination. Subsequently, in a small pilot study involving eight patients, five showed a reduction in relapses from a total of 16 to three in the 2 years before and after treatment, whereas controls showed no apparent reduction (12 and 10 before and after treatment). These clinical changes were accompanied by a difference in MRI lesion load of +8% and +39.5%, respectively. Clinical and MR indices of disease activity worsened in three patients in whom

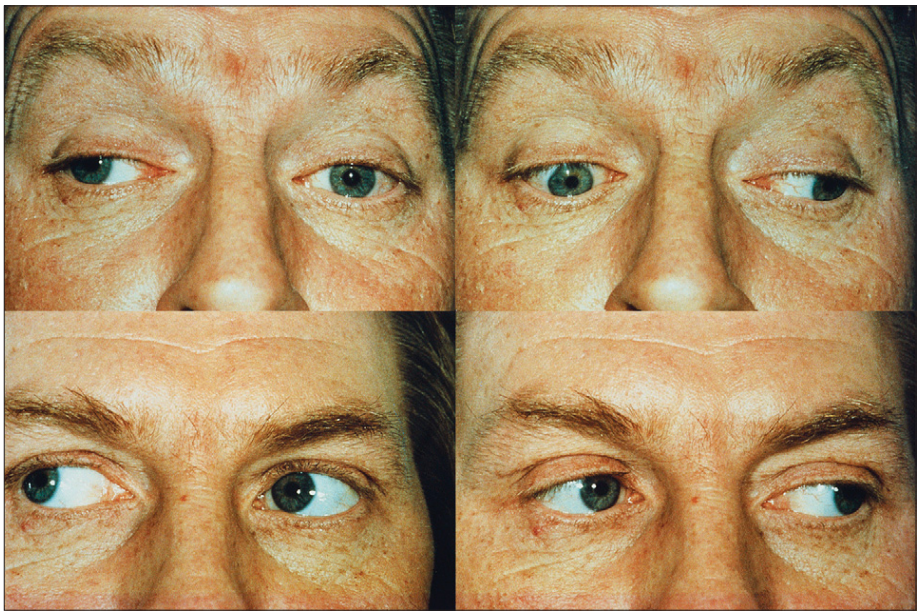


**Figure 18.48** Recurrence of internuclear ophthalmoplegia with complete recovery developing in a patient during (top) and after (bottom) the first infusion of CAMPATH-1H. From Moreau *et al* (1996) with permission.

autoreactive T cells (showing different antigenic specificity) reappeared after vaccination (Medaer *et al* 1995).

Building on their earlier experience with experimental autoimmune encephalomyelitis (see Chapter 11) and clinical laboratory studies, Vandenbark *et al* (1996a) immunized 23 HLA-DRB1*1501-positive patients with T-cell receptor Vβ5.2 (residues 38–58 in two variations, with and without a tyrosine to threonine substitution at position 49), or placebo (n = 6) peptides on 14 occasions over 1 year. T-cell responses were more predictable and rapid with the substituted than natural peptide but were difficult to sustain in both groups. Several who were vaccinated continued to show T-cell reactivity on completion. However, there was a reduction in myelin basic protein reactivity which also correlated with altered disease progression. An unusually high number of patients with primary progressive multiple sclerosis was included (eight of 23 patients) and neither these nor the secondary progressive cases showed a clear clinical benefit (or deterioration) from the vaccination protocol (those who responded immunologically remained unchanged by comparison with all other participants, both placebo-treated and nonresponders; p = 0.02). Peptide-specific T-cell clones tended to show Th2 cytokine profiles (predominant production of IL-10) in contrast to the Th1 features of their myelin basic protein-specific T-cell clones.

## Bone marrow and stem cell transplantation

Bone marrow transplantation following immune ablation has received much attention in recent years. More research is needed before it is clear whether this is a useful approach to treatment, and sufficiently safe to justify whatever clinical dividend emerges in due course. Currently patients either with advanced secondary progressive multiple sclerosis or refractory, aggressive relapsing–remitting disease are being assessed. If efficacy is established, the next step may be to assess whether patients who are at an earlier stage of the disease, but can genuinely be predicted to have a poor prognosis, should be selected for further trials. In the context of multiple sclerosis, the term stem cell transplantation is currently used primarily to refer either to bone marrow or peripheral blood autologous stem cell transplantation applied in the setting of immune system ablation. Experimental work with neural stem cells is moving quickly in model systems but is not yet applied to patients. The rationale for stem cell transplantation in all immune-mediated disorders is the premise that after near complete ablation of the host immune system (full ablation is not currently possible), the reconstituted immune system will be reprogrammed, resulting either in prolonged remission or amelioration of immune-mediated attack on the host. However, it remains to be established whether therapy depends more on the immunosuppressive induction with autologous stem cell rescue than these strategies for immune tolerance to autoantigens. Whatever the precise mechanisms, preliminary evidence in experimental animal model systems and multiple sclerosis is considered promising (Burt *et al* 1995; 1997).

Allogenic stem cell transplantation requires an HLA identical donor and, as such, has rarely been feasible for patients with multiple sclerosis. With advances in umbilical cord blood screening methods for bone marrow donors and cord blood banks, it will soon theoretically be possible to identify HLA compatible donors for haematopoietic stem cell transplantation (Laughlin *et al* 2001). Bone marrow harvesting requires a general anaesthetic, yields few T cells and is associated with a longer reconstitution time. Currently, most programmes therefore harvest autologuous stem cells from peripheral blood (as opposed to bone marrow) since this requires only a brief exposure to the risks of bone marrow suppression (Comi *et al* 2000; Tyndall and Koike 2002). Currently, peripheral blood stem cell harvesting is achieved using high-dose cyclophosphamide (2–4 g/m$^2$) either alone or with granulocyte colony-stimulating factor (G-CSF). G-CSF has been used without cyclophosphamide but may increase the likelihood of triggering an exacerbation of multiple sclerosis. This occurred in four of ten

patients receiving G-CSF for peripheral blood stem cell harvesting (Openshaw *et al* 2000a). Three patients responded to methylprednisolone but one relapse proved fatal. These investigators reportedly now administer methylprednisolone together with recombinant G-CSF and do not use G-CSF after the patient is transplanted. There are several options for cytotoxic drug conditioning, including BEAM (*B*CNU, *E*toposide, cytosine *A*rabinoside, and *M*elphalan) alone or with anti-thymocyte globulin. Others use cyclophosphamide together with total body irradiation and a combination of busulfan and cyclophosphamide. The field has moved away from T-cell purging as there is no clear advantage and the risks of infection in the setting of T-cell depletion are high.

During the mobilization phase, patients may experience fever, seizures and infection. Allergic reactions to cyclophosphamide, G-CSF or the stem cells may occur during the intervention. Following transplantation, patients can experience allergic responses to anti-thymocyte globulin. Mucosal infections, prolonged fever, bleeding, neutropenia, thrombocytopenia, neurotoxicity and autoimmune thyroiditis (as with Campath-1H) are all encountered. Late complications, especially in T-cell-depleted grafts, include serious infections (such as aspergillosis), veno-occlusive liver disease, thrombotic thrombocytopenic purpura, hypogonadism, cataract formation, and the development of malignancy related to the prolonged period of immunosuppression (Fassas *et al* 2000). Although autologous peripheral blood stem cell transplantation has a lower risk than allogenic transplantation, mortality rates are still reported to be in the 5% range or slightly higher. This relatively high risk of a fatal complication for an experimental therapy given in the context of a chronic, rarely life-threatening disorder places the burden on proof of superiority for those conducting this work.

The numbers of cases treated worldwide is ever increasing. In 2000, it was estimated that 74 patients with multiple sclerosis had been transplanted. This had risen to 109 by the third quarter of 2002, and approximately 200 people with multiple

**Table 18.9 Published results with haematopoietic stem cell transplantation in multiple sclerosis**

| Investigator | Conditioning and immune ablation | Comments |
|---|---|---|
| Mancardi *et al* 2001 (ten patients; five Italian sites) | 30–40 days following BEAM | Median follow-up only 18 months. Most stable. No Gd+ or new $T_2$ lesions. Atrophy (1 year) and oligoclonal bands continued at 2 years |
| Kozák *et al* 2002 (15 patients) | BEAM-ATG. 9/15 also received *ex vivo* T-cell depletion of graft | One death from progressive multiple sclerosis. Median follow-up 20 months with 11/15 stable or improved |
| Saiz *et al* 2004 (15 patients) | BCNU, high-dose cyclophosphamide, ATG and T-cell-depleted grafts | 3 year median follow-up: 46% free of disease activity. No deaths. 4/14 continued to relapse (3 of these at multiple times). MRI no new lesions but atrophy continued |
| Openshaw *et al* 2000b (five patients) | Busulfan, cyclophosphamide and T-cell-depleted blood autografts | One died early post-transplant; histology showed macrophages but few T cells surrounding demyelinated plaques |
| Nash *et al* 2003 (26 patients; four United States sites) | Prednisone 1 mg/kg/day by mouth, TBI 2Gy × 4 doses, cyclophosphamide 60 mg/kg × 2 doses, horse ATG 15 mg/kg/daily × 6 doses, GCSF 5 μg/kg/daily by intravenous injection | 27% progressed by ≥ 1.0 EDSS at 3 years. Four new Gd+ lesions. Nine of 12 still had oligoclonal bands. One died with EBV-PTLD. Two relapses during mobilization, one proving fatal; 91% survival at 3 years |
| Burt *et al* 2003 (21 patients; three United States sites) | Cyclophosphamide 60 mg/kg iv, TBI with lung shield, 150 cGy bid on days –3, –2, –1 | No transplantation-related deaths. Two died from progressive multiple sclerosis after 13–18 months. Eight of 12 at EDSS >6 worsened. All nine of nine at EDSS < 6 remained stable |
| Kimiskidis *et al* 2002 (35 patients) | Cyclophosphamide, G-CSF, BEAM, busulfan | G-CSF may have caused radiological deterioration. Subclinical MRI activity persisted in five patients. MRI atrophy progressed at 12 and 24 months. Two cases developed post-transplantation autoimmunity: thyroiditis (1) and refractory factor VIII-inhibitor (one with massive haemorrhage and death). Progression-free survival, 67% at 5 years |
| Fassas *et al* 2002 (85 patients; nine European sites and one United States site) | BEAM for 54/85<br>93% peripheral blood stem cell transplants (BMT 7%)<br>60% had *ex vivo* graft T-cell depletion | Median 16 months follow-up. 27% worsened in early post-transplant period. Seven of 85 (8.2%) died; two from progressive multiple sclerosis with high pretransplantation EDSS scores; five from toxic causes – four infections and one from heart failure. 3 year death rate was 10%; 20% progressed and 21% improved by ≥1.0 EDSS. MRI active after TPT in 8%. 74% progression-free survival at 36 months |

*BEAM = BCNU, etoposide, cytosine arabinoside, melphalan, rabbit ATG (anti-thymocyte globulin); TBI = total body irradiation; G-CSF = recombinant human granulocyte colony-stimulating factor; PTLD = post-transplantation lymphoproliferative disorder; EBMT Study = European Group for Blood and Marrow Transplantation Study.*

sclerosis had been transplanted by mid-2003. A position paper summarizing the opinion of selected European multiple sclerosis specialists has been published making recommendations for each step in this complex therapeutic programme (Comi *et al* 2000). The published results to date are summarized in Table 18.9. As noted, the numbers are small, the follow-up is modest and the evidence for clinical benefit is minimal to date. Several studies have shown MRI evidence for stability or apparent improvement, although serial MRI studies have shown that cerebral atrophy continues to progress after transplantation. Again, it is unclear to what extent the reduction in new MRI lesions relates to the transplant procedure rather than the profound degree of immunosuppression associated with induction.

In the trial reported by Nash *et al* (2003), death from post-transplantation lymphoproliferative disorder was attributed to a change from horse to rabbit anti-thymocyte globulin in the high-dose immunosuppressive therapy protocol. A second death was attributed to a relapse of multiple sclerosis during mobilization (another episode in a second patient during mobilization reversed within 6 months). Thirteen of the first 18 patients developed a fever and rash, sometimes associated with neurological worsening ('engraftment syndrome'). Burt *et al* (2003) reported two late multiple sclerosis-related deaths, and EDSS progression in eight of 12 patients with baseline EDSS scores of 6.0 or higher. They concluded that intense immunosuppression with total body irradiation and haematopoietic stem cell transplantation should not be offered to patients with advanced progressive multiple sclerosis. Conversely, in a retrospective review of bone marrow transplantation, Fassas and Kimiskidis (2003) conclude that the early results are encouraging despite the morbidity and mortality experienced in their protocol. In a recent update of the series from Barcelona, Saiz *et al* (2004) reported on their experience of autologous stem cell transplantation after a course of high-dose chemotherapy. As outlined in the accompanying editorial (Freedman and Atkins 2004), at 3 years median follow-up, four of 14 patients continued to experience relapses (several each in three individuals) suggesting incomplete or ineffective suppression of disease activity although 46% were disease free. This protocol seemingly prevented the development of new contrast enhancing lesions and was followed by reductions in $T_2$ lesion load. In parallel, however, there was progressive brain atrophy. It remains to be determined whether the reduction in brain volume reflects true progressive atrophy or is fully explained by a reduction in active inflammation. The current status of autologous haematopoietic stem cell transplantation in multiple sclerosis is reviewed elsewhere (Blanco et *al* 2005; Burt *et al* 2005). Muraro *et al* (2005) recently reported that there is an important change in the immune profile of T cells 2 years after stem cell transplantation in patients with multiple sclerosis. Post-transplantation there are fewer memory T cells and a greater diversity of expressed T cell receptors, suggesting that delayed benefit may extend beyond that explained by lymphocyte depletion. The trials in progress will bring more insights but each is relatively small and insufficiently powered to prove definitive.

## AGENTS INHIBITING MACROPHAGES AND THEIR MEDIATORS

Drugs that inhibit the function of macrophages (and microglia), or the release of their mediators, have been evaluated in multiple sclerosis although it is unclear whether these studies are primarily motivated by attempts to modify the course of the illness or merely to suppress symptoms.

Monoclonal antibodies targeted against TNF-α have been used in rheumatoid arthritis and appear to stabilize joint symptoms for several months. We have used very short pulses of humanized soluble TNF receptor for the specific purpose of suppressing the cytokine release syndrome associated with the use of Campath-1H without apparent benefit or adverse effect (Coles *et al* 1999a). In a randomized, double-blind, placebo-controlled study of a recombinant soluble TNF-α receptor p55 immunoglobulin fusion protein (lenercept), Arnason *et al* (1999) demonstrated that this agent is associated with an increase in disease activity (earlier, more frequent and possibly more severe clinical relapses) than placebo (Table 18.10). The drug was poorly tolerated (headaches, nausea, abdominal pain; Schwid and Noseworthy 1999). A previous small study had also demonstrated an increase in MRI markers of disease activity in

**Table 18.10 Number, duration and annual rate of exacerbations during the Lenercept multiple sclerosis trial**

| No. of patients | Placebo 43 | Lenercept (mg) 44 (10 mg) | 40 (50 mg) | 40 (100 mg) | p value |
|---|---|---|---|---|---|
| Patients with ≥1 exacerbation through week 24 | 15 | 21 | 28 | 27 | 0.003[a] |
| Patients with ≥1 exacerbation through week 48 | 22 | 26 | 32 | 32 | 0.007[b] |
| Exacerbations with onset ≤ week 24 | 22 | 28 | 37 | 33 | |
| Duration (days) of these exacerbations | 28.3 | 38.6 | 41.6 | 42.0 | 0.62[c] |
| Range (median) | 28 (1–91) | 31 (6–189) | 31 (6–201) | 25 (4–261) | |
| Annualized exacerbation rate | 0.98 | 1.0 | 1.64 | 1.47 | |

*a Chi-square tests: global.*
*b Kruskal–Wallis test.*
*c Kaplan–Meier (KM) (means and medians are estimated from the KM curves).*

response to anti-TNF-α monoclonal antibody (van Oosten *et al* 1996b). In addition, 17 patients are reported to have developed signs and symptoms suggesting central nervous system demyelination after treatment with the anti-TNF-α agent etanercept, and two patients have had similar reactions to infliximab administration (Mohan *et al* 2001). As such, despite the theoretical arguments in favour of its use, anti-TNF-α strategies do not appear to have a therapeutic future in multiple sclerosis.

A few preliminary results are available on the use of macrophage inhibitors in multiple sclerosis but the choice (or availability) of agents is such that their therapeutic role remains largely unexplored. Deoxyspergualin suppresses the maturation of lymphocytes and also inhibits production of oxygen radicals by macrophages. It received attention amongst multiple sclerosis sufferers through publicity surrounding an individual case and on the basis of effects in experimental autoimmune encephalomyelitis (Schorlemmer and Seiler 1991). Deoxyspergualin was subsequently evaluated in a placebo-controlled study in which 2 or 6 mg/kg deoxyspergualin was given intravenously for 1 month as 5 day pulses (Kappos *et al* 1994). Preliminary results showed no effect on the pretreatment level of disease activity assessed by MRI but the clinical evaluation remains unpublished. Different doses of pentoxifylline were given to 14 patients by L.W. Myers *et al* (1998) to identify that which best suppressed TNF-α production in both a bioassay and enzyme-linked immunosorbent assay. These were sensitive assays since TNF-α was detected in the majority of cerebrospinal fluid samples before treatment. There was no immunological effect of treatment at any dose and almost all the patients deteriorated, objectively and subjectively. MRI abnormalities continued to accumulate. van Oosten *et al* (1996b) also were unable to demonstrate any effect of pentoxifylline (800–1200 mg daily for 4 weeks) on a range of Th1 and Th2 cytokine productions in 20 patients with multiple sclerosis. By contrast, Rieckmann *et al* (1996) showed *in vitro* and *in vivo* suppression by pentoxyfilline (1600 mg/day by oral administration) on TNF-α and IL-12 production, with corresponding stimulation of IL-10 and IL-4 in patients with relapsing–remitting multiple sclerosis.

Nineteen patients (nine with primary progressive and ten with secondary progressive disease) were treated by S.G. Lynch *et al* (1996) using the iron chelator desferroxamine by subcutaneous infusion for 14 days to enhance iron chelation and prevent hydroxyl radical formation. The study was open and uncontrolled and rather little can be learned from the claim that nine, six and three and three, five and six patients improved, were unchanged or worsened by >1 EDSS point at 6 and 12 months, respectively. The same reservations apply to an earlier study of 12 patients with more marked disabilities (EDSS 5.5–8) of whom seven, four and three improved, stabilized or worsened in the 3 months after treatment with desferroxamine (Norstrand and Craelius 1989).

## RECENT MISCELLANEOUS TREATMENTS

The National Multiple Sclerosis Society (of the United States) keeps a checklist on trials in progress. The most recent version lists more than 150 current clinical trials (*http://www.nationalmssociety.org/Clinical%20Trials.asp*). Several are likely to be completed in the near future and new options for treatment or fresh insights into preferred strategies for the timing and choice of interventions may be provided. A few new faces are already on the street.

### *Statins*

As outlined in recent editorials (D. Baker *et al* 2003; Neuhaus *et al* 2004), statin drugs are attracting interest in both the scientific and lay literature as potential treatments for multiple sclerosis, and for several reasons. Statins have a wide variety of immunoregulatory effects, are relatively inexpensive, generally well tolerated and available as oral agents. Lovastatin was shown to be partially effective in acute experimental autoimmune encephalomyelitis (Stanislaus *et al* 2001). Neuhaus *et al* (2002) demonstrated that simvastatin, mevastatin and lovastatin each had significant immunosuppressive activities in humans, including treatment-induced reduction in the proliferation of stimulated peripheral blood mononuclear cells, reduced adhesion molecule expression (CD54; ICAM-1), altered Th1/Th2 cytokine profile (paradoxically favouring a so-called 'proinflammatory profile'), reduced matrix metalloproteinase-9 levels and expression of B-cell and T-cell cytokine receptors. In further animal studies, Youssef *et al* (2002) showed that oral atorvastatin promoted a Th2 anti-inflammatory cytokine profile, reduced the expression of MHC class II and costimulatory molecules, and prevented the development of chronic experimental autoimmune encephalomyelitis. There are probably multiple mechanisms whereby statin drugs affect the immune response but inhibition of mevalonate with subsequent reduction in isoprenoids (and, hence, reduced post-translational isoprenylation of proteins) may be important (D. Baker *et al* 2003). In an open label trial of 30 patients with multiple sclerosis, Vollmer *et al* (2004b) reported an effect on contrast enhanced MRI indicators of disease activity (reduction in 44% by number and 40% by volume of contrast enhancing lesions) at months 4, 5 and 6 following the administration of simvastatin (80 mg orally per day) compared with pretreatment data. This small study did not demonstrate a reduction in relapse rate but patients were only followed for 6 months. Being unblinded, the study did not adequately address the possibility of regression to the mean. Exploratory immunological studies did not demonstrate an impressive *in vitro* effect. Much more work is clearly needed to raise the status of statins as a disease-modifying treament in multiple sclerosis.

### *Estriol*

Pregnancy provides an important, though transient, benefit for patients with relapsing–remitting multiple sclerosis (see Chapter 4). This example from nature has long provoked interest in estrogen therapy as a potential treatment option. Sicotte *et al* (2002) completed a small open label trial of daily high-dose oral estriol administration (8 mg/day – an amount designed to simulate pregnancy levels) in 12 women (six each with relapsing–remitting and secondary progressive multiple sclerosis). The relapsing–remitting cohort, but not those with secondary progressive multiple sclerosis, experienced a reduction in MRI evidence for disease activity (number and volume of gadolinium-DTPA enhancing lesions). This result was unexpected since the natural history of gadolinium enhancing lesions appears similar in both clinical subgroups and the response to

other therapies such as IFN-β has been similar. Treated relapsing–remitting patients also demonstrated reduced immune function compared with pretreatment values (such as reduced delayed-type hypersensitivity to tetanus and serum levels of IFN-γ). MRI and immune functions returned to pretreatment levels when estriol was discontinued. The authors do not discuss safety issues other than to say that 'pregnancy levels' of estriol were associated with uterine bleeding requiring endometrial biopsy. They recommend that future trials consider combining estriol with progesterone to prevent uterine endometrial hyperplasia. Other safety issues known to be associated with high-dose estrogen therapy would need to be considered carefully in future trials (including effects on thromboembolic disease, migraine, breast cancer, endometrial hyperplasia and cancer, menstrual irregularity, gallbladder disease, cholestatic jaundice, pancreatitis and hypertension).

### *Minocycline*

Based on its anti-inflammatory properties, acting through the inhibition of matrix metalloproteinases, and evidence for efficacy in experimental autoimmune encephalomyelitis (Popovic *et al* 2002), minocycline seems set for thorough evaluation as a treatment for multiple sclerosis. Metz *et al* (2004) treated 10 patients with relapsing–remitting disease, observed to have a mean number of episodes during the previous 2 years of 2.6 (range 2–4 over the 2 years) with minocycline (100 mg twice daily for 6 months); interim analysis of this uncontrolled series showed no change in the frequency of episodes but mean total enhancing lesion number changed from 1.4 per scan before treatment to 0.2 lesions per scan whilst receiving minocycline, representing > 84% reduction; however, these data (before and after treatment) depended exclusively on the experience of only five patients.

## POSTSCRIPT

We have reviewed much that has gone into recent efforts to develop more effective therapies for people with multiple sclerosis. Clearly progress has been made but more is needed. We are cautiously optimistic that the decade ahead will bring even more hopeful news for our patients and trust that progress will accelerate. We say this, fully aware of the vast investment in biomedical research worldwide and the tremendous collaborative spirit that is evident in the work already accomplished and currently under way. We are encouraged by the creativity of the scientific community and anticipate that continued productive collaboration across the research and biotechnology communities will pay further dividends. The currently available, licensed medications demonstrate favourable effects on relapse rates and on MRI indicators of (presumably inflammatory) disease activity. We do not yet know for certain that treatment delays clinical disability progression or the progression of brain and cord atrophy. We strongly suspect that the progression of clinical disability often developing as the years pass is largely attributable to gradual loss of axonal number and function. This assumption brings great hope that meaningful benefits will follow closely on our increased understanding of the factors that determine axonal loss. Until such time as the 'breakthrough' arrives, we must remain objective and humble about what is known and what is not. We must continue to ask the right scientific questions and demand useful answers even if these are hard to acquire. Patients have a right to be informed about the knowledge base and zones of ignorance in multiple sclerosis. They should understand fully the limits of our ability to control the course of their illness and be encouraged to participate actively in debating the merits and demerits of existing and new treatments.

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