DRUG FOCUS

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Editor's Choice

Current and future disease-modifying therapies in multiple sclerosis

S. Y. Lim, C. S. Constantinescu

Linked Comment: Sharrack and Jenkins. *Int J Clin Pract* 2010; 64: 532–4.

SUMMARY

The development of disease-modifying therapies (DMT) in multiple sclerosis (MS) has rapidly evolved over the last few years and continues to do so. Prior to the United States Food and Drug Administration approval of the immunomodulatory agent, interferon-β1b in 1993, no other drug had been shown to alter the course of the disease in a controlled study of MS. At present, there are five licenced disease-modifying agents in MS – interferon-β1b, interferon-β1a, glatiramer acetate, natalizumab and mitoxantrone. All have shown significant therapeutic efficacy in large controlled trials. However, current therapies are only partially effective and are not free from adverse effects. Moreover, available DMTs are overwhelmingly biased in favour of those with relapsing-remitting disease. Effective treatment for progressive MS is severely limited, with only interferon-β1b and mitoxantrone having licenced use in secondary progressive, but not primary progressive disease. Monoclonal antibodies, such as natalizumab selectively target immune pathways involved in the pathogenic process of MS. Alemtuzumab, daclizumab and rituximab are other notable monoclonal antibodies currently undergoing phase II and III trials in MS. Alemtuzumab has so far shown promising therapeutic benefit in relapsing disease, although immunological adverse effects have been a problem. Oral therapies have the benefit of improved tolerability and patient compliance compared with current parenteral treatments. Cladribine and fingolimod (FTY720) have shown encouraging results in their phase III clinical trials. It is also worth noting the evidence for starting DMT in patients with clinically isolated syndrome, whereby early treatment has shown to delay the onset of clinically definite MS in separate phase III studies.

Review Criteria

Trials chosen for our review were the pivotal and newer studies of licenced treatments for MS and those of promising disease-modifying therapies, which had completed or are at least currently in phase II testing. We conducted an on-line literature search using PubMed for relevant studies and clinical trials. We also referred to abstracts from recent international conferences, individual drug-makers' websites and http://clinicaltrials.gov for further details and updates on said trials.

Message for the Clinic

Evidence from clinical trials suggests that treatment with DMT in the appropriate MS patients improves disease activity and severity. In addition, treatment can delay the onset of clinically definite MS in patients presenting with their first attack of demyelination. A number of DMTs are currently being developed with the prospect of having comparable or improved therapeutic efficacy, safety profile and tolerability to existing therapies, broadening our future therapeutic options.

Division of Clinical Neurology, University of Nottingham, Nottingham, UK

Correspondence to:
Professor Cris S. Constantinescu, Division of Clinical Neurology, B Floor, Medical School, University of Nottingham, Nottingham NG7 2RD, UK
Tel.: + 44 115 975 4598
Fax: + 44 115 970 9738
Email: cris.constantinescu@nottingham.ac.uk

Disclosure

CSC has received research support, consultancy fees, travel support or speaker fees from Teva, Biogen Idec, Bayer Schering, Centocor, Merck-Serono, and GlaxoSmithKline, Roche, UCB, GW Pharmaceuticals, and Cephalon. SYL has been supported by an unrestricted grant from Teva.

Introduction

Multiple sclerosis (MS) is a chronic, potentially disabling, immune-mediated inflammatory demyelinating disease of the central nervous system (CNS). The multifocal nature of the disease manifests clinically as a range of sensorimotor, cerebellar, visual, sphincteric, cognitive, and neuropsychiatric symptoms. Most patients present with a relapsing and remitting course, which is characterised by recurring attacks of acute neurological deficits or exacerbations of existing deficits (relapses) followed gradually by partial or full recovery (remission). Although the clinical course may vary considerably between individuals, secondary progression eventually occurs in the majority, characterised by irreversible, progressive disability (1). The immune pathogenesis of MS is thought to be heterogenous, with recent studies showing the involvement of distinct subsets of T-cells (2), and the crucial role of B cells and antibodies (3). The exact aetiology is unknown, although it is likely to stem from the loss of immune regulation, leading to the breakdown of immune tolerance, influenced by genetic susceptibility. Focal CNS inflammation, demyelination, axonal loss and eventual neuronal death are typical features although pathologically there is heterogeneity.

Multiple sclerosis is a challenging disease to treat, not least because of its significant heterogeneity and unpredictable clinical course. Traditional immunosuppressants such as cyclophosphamide and azathioprine have been used in MS for some time, showing a variable degree of benefit (4–6). However, the risk of serious infections amongst other significant side effects, and the emergence of new immunomodulatory drugs, has limited their use.

Immunomodulatory agents, which became available from the early 1990s, aim to prevent relapses, minimise disability and may reduce disability

progression (particularly relapse-related disability) without significant immunosuppressive effects. The immunomodulatory agents interferon (IFN)-β1a, 1b and glatiramer acetate are first-line therapy in MS. For more severe disease, second-line therapy consisting of the monoclonal antibody natalizumab and cytotoxic agent mitoxantrone are used.

Increasingly, new and novel therapeutic agents are being trialled in MS centres worldwide. These include monoclonal antibodies and oral agents for relapsing and progressive forms of the disease. In this non-systematic review, we outline the existing disease-modifying agents; briefly discuss the promising new drugs currently in development and look at the current evidence for disease-modifying therapies (DMT) in early MS.

Existing treatments

Interferon-β and glatiramer acetate

Two formulations of interferon treatment are available: IFN-β1b (Betaferon; Schering AG, Berlin, Germany or Betaseron; Berlex, Montville, NJ) and IFN-β1a (Rebif; Merck Serono, Geneva, Switzerland and Avonex; Biogen Idec, Zug, Switzerland). Both are type 1 interferons, which share anti-inflammatory and antiviral properties, but differ slightly in their pharmacodynamics and pharmacokinetics (7). IFN-β has been shown to inhibit T-cell activation and reduce blood brain barrier permeability to inflammatory cells, although it in itself may not cross the blood brain barrier (8). Avonex is given intramuscularly once a week (30 μg), Betaferon or Betaseron subcutaneously on alternate days (0.25 mg) and Rebif subcutaneously three times a week (22 or 44 μg).

Glatiramer acetate (Copaxone; Teva Neuroscience, Kansas City, MO) is a synthetic co-polymer structurally similar to myelin basic protein (MBP), a major component of myelin (9). It is given as a daily subcutaneous injection (20 mg). It is thought to produce anti-inflammatory effects mainly via functional inhibition of MBP-reactive T-lymphocytes and induction of Th 2 (T helper) lymphocytes in the CNS (10,11).

Pivotal phase III studies of IFN-β and glatiramer acetate have all demonstrated a significant reduction in relapse rate (by approximately 30%, see Figure 1) and improvement in magnetic resonance imaging (MRI) measures of disease activity in relapsing-remitting MS patients (12–15). These were conducted as 2-year, double-blinded, randomised, placebo-controlled, multicentre trials. It is difficult to perform an accurate cross-trial comparison of the pivotal studies because of the differences in the study design and patient population, but this has nonetheless been systemically analysed and reported in detail elsewhere (16,17).

Recent head-to-head comparison trials, specifically the REGARD (Rebif 44 μg vs. Copaxone)(18) and BEYOND (Betaferon/Betaseron vs. Copaxone)(19) trials give a more accurate view of the comparative efficacy between these drugs. They have so far shown largely similar efficacy between the IFN-β treatments and glatiramer acetate. The REGARD trial evaluated the efficacy of three times a week 44 μg subcutaneous IFN-β1a compared with daily subcutaneous 20 mg Copaxone in 764 patients with relapsing-remitting multiple sclerosis (RRMS) (18). No significant difference was noted between both treatments in the study end-points, which included time to first relapse and change in the volume of T2 and contrast-enhancing MRI lesions (18). The BEYOND trial (Betaferon/Betaseron yielding outcomes of a new dose in MS) compared the efficacy of alternate day 250 and 500 μg subcutaneous Betaferon/Betaseron to daily subcutaneous 20 mg Copaxone in 2244 treatment-naïve patients with RRMS (19). There was no significant difference between the three treatment arms in terms of relapse risk, the proportion of relapse-free patients, time to first relapse, disability accumulation and most MRI parameters (19).

Interferon-β and glatiramer acetate are generally safe and well-tolerated, although adverse effects may be experienced, such as flu-like symptoms and lymphopenia with the interferons and skin reactions with glatiramer acetate(18,19). Furthermore, neutralising antibodies to IFN-β can develop in some patients, usually following the first year of therapy. Although the long-term consequences of these antibodies are yet to be fully ascertained, current evidence shows that they may reduce the efficacy of the drug (20–22). The antibodies tend to cross-react with different IFN-β formulations (23), therefore switching to another IFN-β drug is unlikely to be helpful in the first instance, leaving one to consider alternative DMTs.

Co-administration of corticosteroids with IFN therapy can reduce the production of neutralising antibodies and may enhance IFN therapy (24,25). In a relatively small study involving 130 patients, Sorensen et al. reported that 4-weekly pulses of 100 mg oral Methylprednisolone given in addition to subcutaneous IFN-β1a (Rebif) for 96 weeks resulted in a significant reduction in relapse rates compared with patients taking the placebo-Rebif combination (annualised relapse rate 0.22 for methylprednisolone vs. 0.59 for placebo, $p < 0.0001$)(25). Moreover, another cohort of patients using a similar combination (Methylprednisolone plus IFN-β1a, Avonex) in the multicentre MECOMBIN trial from the start of

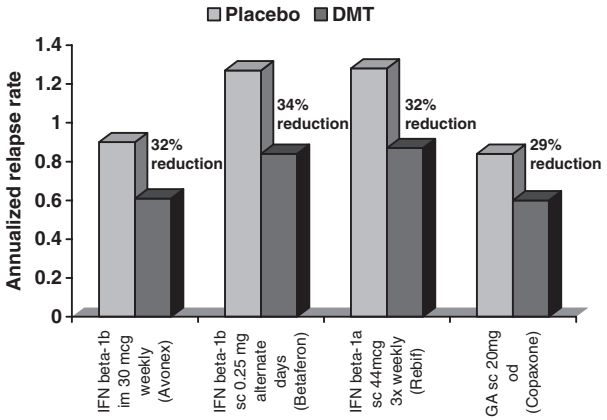

Figure 1 Comparison of annualized relapse rates in the treatment and placebo groups from four pivotal DMT trials in MS. IFN, interferon; GA, glatiramer acetate; DMT, disease-modifying therapy; sc, subcutaneous; im, intramuscular; od, once a day. Relapses were defined as the development of new neurological symptoms or worsening of pre-existing symptoms in a previously stable patient

DMT had a significant reduction in relapse rate compared with IFN-β1a and placebo, suggesting added benefit that might be of use not only in non-responders (26).

Recommendations for starting first-line disease-modifying therapy vary worldwide. In the UK, the Association of British Neurologists advocates their use in patients who have had at least two clinically disabling relapses in the last 2 years, but continue to remain ambulatory (27). However, as earlier treatment is increasingly favoured and expectations for disease control higher, a new set of criteria may emerge soon.

Patients are being involved more in choosing the appropriate first-line therapy, and may wish to consider factors such as side effects and dosage frequencies. While IFN-β treatment is seen by some to be more beneficial with higher and more frequent dosing (28,29), this is not universally shared and needs to be balanced against increased convenience of less frequent administration and lower likelihood of neutralising antibodies. Unfortunately, because of the parenteral mode of administration, problems with compliance and tolerability still remain an issue for many patients.

Natalizumab

Natalizumab (Tysabri; Biogen Idec) is a humanised monoclonal antibody to the α_4 subunit of $\alpha_4\beta_1$ integrin (VLA-4), a protein found on the surface of lymphocytes. $\alpha_4\beta_1$ Integrin interacts with the vascular-cell adhesion molecule 1 (VCAM-1) expressed on endothelial cell surface, including CNS vasculature, allowing adhesion and subsequent migration of inflammatory cells into the brain and spinal cord (30,31). Natalizumab selectively blocks this interaction, thus preventing the transmigration of inflammatory lymphocytes across the blood brain barrier into the CNS (30,31).

Natalizumab is to date, the only monoclonal antibody currently licenced for use in MS in the US and Europe and is recommended for patients with more aggressive, rapidly evolving relapsing disease and in those who have failed to respond to first-line DMTs. It is given as an intravenous infusion. There are no guidelines on the optimal duration of therapy, and patients may continue to receive the drug if perceived to be efficacious to their disease.

Phase II (32–34) and III (35,36) studies on Natalizumab provide good evidence for its use in MS. In the AFFIRM study, a randomised, double-blind, placebo-controlled phase III trial, patients on Natalizumab demonstrated a 68% reduction in annualised relapse rate ($p < 0.001$) and 42% reduction in sustained disability progression over 2 years ($p < 0.001$) compared with placebo (35). Furthermore, MRI findings from the study showed a 92% reduction in gadolinium-enhancing lesions ($p < 0.001$) (35). The SENTINEL study was a 2-year, randomised, double-blind, placebo-controlled phase III trial whose subjects had previously responded poorly to IFN-β1a therapy (Avonex). It showed a promising 53% reduction in relapse rate in patients on Natalizumab/IFN-β1a combination therapy, compared with those who remained on IFN-β1a monotherapy ($p < 0.001$) (36).

In 2005, shortly after being licenced for use, natalizumab was withdrawn from the market when two fatal cases of progressive multifocal leucoencephalopathy (PML), caused by latent JC virus infection, were reported in patients taking natalizumab in combination with IFN-β1a as part of the SENTINEL study (36). A third fatal case was subsequently reported in a Crohn's patient who received natalizumab following previous immunosuppressive treatment (37).

A subsequent safety evaluation of the drug estimated the risk of PML to be 1 in 1000 (0.1%) over an 18-month treatment period (38). Following this report, natalizumab was reapproved as monotherapy for active MS in July 2006. At the time of writing, about 56,500 patients have been treated with the drug in the postmarketing setting, with over 18,000 having received at least 18 months of therapy and 30,600 having received at least 1 year of therapy (39). Since July 2006, 11 cases of natalizumab-associated PML have so far been reported (39). This could imply that the true risk of PML associated with natalizumab monotherapy is lower than previously thought. It is usually accepted that the beneficial effects of natalizumab in active relapsing disease outweigh the risk of developing PML, as supported by a recent risk-benefit analysis (40). Risk-management programmes have been put in place to monitor and further evaluate patient safety on natalizumab, i.e. The TYSABRI Outreach: Unified Commitment to Health Prescribing Program (TOUCH) and the TYSABRI Global Observation Program in Safety (TYGRIS).

Natalizumab has also been associated with the development of neutralising antibodies, which may persist in up to 6% of patients, potentially causing hypersensitivity reactions and loss of drug efficacy over time (41). Patients who develop a reaction to the drug or show poor response to therapy may warrant being tested for antibodies. Around four cases of natalizumab-associated malignant melanoma have also been reported, which are reviewed in detail elsewhere (42).

Mitoxantrone

Whilst relapsing-remitting MS patients gain therapeutic benefit from IFN-β, glatiramer acetate and natalizumab, treatment for the progressive forms of MS is much more limited. Mitoxantrone and IFN-β1b (Betaferon, Betaseron) are licenced for use in secondary progressive MS, whereas there are no effective treatments currently licenced for primary progressive MS.

Mitoxantrone is an anthrecenedione, a cytotoxic agent with immunosuppressive properties used in various malignancies (43). In 2000, it was approved for treatment of worsening relapsing-remitting MS, progressive relapsing MS and secondary progressive MS based on evidence from a phase II (44) and a later phase III study of the drug (45). Mitoxantrone is thought to act via a wide range of mechanisms, which include inhibition of T-cell activation, suppression of T-cell, B-cell and macrophage proliferation, impaired antigen presentation, prevention of macrophage-mediated demyelination and reduction of pro-inflammatory cytokines (46–48). In the animal model of MS, experimental autoimmune encephalomyelitis (EAE), mitoxantrone was shown to effectively suppress disease activity (49,50).

In the phase III study (45), 194 patients with worsening relapsing-remitting and secondary progressive MS were randomised to either 12 mg/m^2 mitoxantrone, 5 mg/m^2 mitoxantrone or a placebo every 3 months for 2 years. The primary outcome measure was disease progression, measured using a composite score consisting of the patient's Expanded Disability Status Scale (EDSS) score, ambulation, number of treated relapses, time to first treated relapse and change in their standardised neurological status. Patients in the 12 mg/m^2 mitoxantrone treatment group showed a significant improvement ($p < 0.0001$) in their composite score, including a 69% reduction in the number of treated relapses (45). MRI outcomes from the study; however, were less robust with most MRI parameters showing no difference between the groups, except for the reduction of T2 lesions in the high-dose Mitoxantrone group over the placebo group at year 2 ($p = 0.027$) (51).

In MS patients, the recommended dose of mitoxantrone is 12 mg/m^2 every 3 months, with a maximum cumulative lifetime dose of 140 mg/m^2 (52). Although Mitoxantrone is generally reserved for patients with more active, progressive disease and those who had previously failed to improve on DMT, it may have an additional role as an induction therapy in treating early, aggressive MS. In their open label study, Ramtahal et al. demonstrated a 90% reduction in annualised relapse rate ($p < 0.001$) after Mitoxantrone induction followed by long-term Copaxone in a cohort of patients with very active early MS (53). A similar study of mitoxantrone and Rebif is currently on-going in the UK (NCT00283140).

Although rare, the most serious adverse effects of mitoxantrone treatment are cardiotoxicity and acute leukaemia. In a report by Ghalie et al., the risk of congestive heart failure was observed to be < 0.20% with a mean cumulative dose of 60.5 mg/m^2 (54). The team also noted that 2.2% of patients experienced an asymptomatic reduction in left ventricular ejection fraction to < 50%, which did not bear a significant correlation to the cumulative dose. Recently, the risk of therapy-related acute leukaemia was reported to be around 0.74% (55), significantly higher than previous estimates (56,57). It is highly important therefore to perform regular cardiac function and haematological monitoring following mitoxantrone therapy, as well as ensuring only appropriate patients are selected for treatment.

Monoclonal antibodies in development

Alemtuzumab

Alemtuzumab (Campath-1H; Genzyme, Cambridge, MA) is a humanised monoclonal antibody to CD52, a cell surface antigen present on all lymphocytes and monocytes. It was developed in Cambridge, UK and is used to treat chronic lymphocytic leukaemia. It has also been trialled as an antirejection therapy and as treatment for other autoimmune diseases. Given intravenously, the drug causes a rapid and prolonged lymphopenia (58).

An early open label Cambridge trial of alemtuzumab in 36 secondary progressive MS (SPMS) patients and 22 RRMS patients showed some promising results, in particular demonstrating more benefit if given earlier in the disease course, i.e. at the relapsing-remitting stage (59). The secondary progressive patients who received alemtuzumab also had significantly fewer relapses, but had continued to progress both clinically and radiologically. The authors suggested that this implied neurodegeneration in secondary progressive disease occurs independently of inflammation, albeit dependent on previous inflammatory activity (59). The authors further suggest that a therapeutic window of opportunity exists, whereby effective anti-inflammatory treatment early on in the disease can prevent the later-onset, irreversible degenerative processes from occurring.

In the more recent phase II trial of alemtuzumab vs. IFN-β-1a (CAMMS223), 334 patients with early RRMS were randomised to receive either 44 μg subcutaneous IFN-β1a (Rebif) three times a week or intravenous pulses of 12 or 24 mg/day Alemtuzumab for 3–5 days at months 1, 12 and 24 (60). All patients were previously untreated, and had an EDSS of 3.0 or lower, with disease duration of 3 years or less. During the trial, a total of six patients on alemtuzumab developed immune thrombocytopenic purpura (ITP), one of whom died, resulting in the suspension of therapy in the active drug arm. As a result, only about 20% of patients received the full 3-year treatment course. Nevertheless, the results showed that alemtuzumab effectively prolonged the time to sustained disability and improved clinical and MRI markers of disease activity in the short-term. Compared with IFN-β1a, alemtuzumab reduced the risk of progression to sustained accumulation of disability by 71% ($p < 0.001$) and reduced relapses by 74% ($p < 0.001$). There was no significant difference in the efficacy between the lower and higher dose regimes.

Autoimmune effects are the main concern with alemtuzumab therapy. Apart from ITP there is a risk of about 20% of developing autoimmune thyroid disease (61). Other side effects include susceptibility to infections and infusion-related reactions, the latter of which is caused by cytokine release in response to the drug and require corticosteroid pretreatment (58).

Despite the safety concerns, these studies have demonstrated a significant benefit in treating early relapsing-remitting MS patients with alemtuzumab. Further studies are needed to assess the long-term effects associated with therapy. Two phase III studies are currently underway comparing the efficacy of alemtuzumab to IFN-β1a (Rebif) in RRMS patients who have relapsed on conventional disease-modifying agents (CARE-MS II study, NCT00548405) and in those who are treatment-naïve (CARE-MS I study, NCT00530348).

Rituximab

Rituximab (Roche, Basel, Switzerland) is a chimeric (human/murine) monoclonal antibody to CD20, an antigen expressed on mature and preB-lymphocytes. It effectively depletes B-lymphocytes via complement-dependent cell lysis and antibody-dependent cellular toxicity (62,63). Rituximab is used in the treatment of certain B-cell malignancies as well as a growing number of refractory autoimmune conditions. B cells are a potential therapeutic target in MS as there is increasing evidence, both *in vivo* and in the animal model, for the involvement of the humoral immune system in the pathogenesis of MS (3). Most notably, intrathecal oligoclonal bands are found in up to 75% of MS patients (64).

In the phase II study of rituximab in relapsing-remitting MS patients, a significant reduction in both MRI and clinical markers of disease activity was shown (65).A total of 104 patients with RRMS were randomised to 2×1000 mg IV rituximab or placebo and monitored for 48 weeks. The rituximab group showed a significant reduction in the number of contrast-enhancing MRI lesions ($p < 0.001$) and volume of T2 lesions ($p = 0.04$) compared with the placebo group at weeks 24 and 36 respectively. A reduction in annualised relapse rate was further shown in the rituximab group, which was statistically significant at 24 weeks, but not at 48 weeks (65).

Rituximab was shown to be relatively safe in the study, with no significant opportunistic infections reported in the treatment group. Patients however, commonly experienced infusion-related reactions, although most of these were mild or moderate (65). There have been reports of severe viral infections associated with rituximab therapy, including reactivation of JC virus, in patients with lymphoproliferative and other autoimmune disorders (66). The true risk of rituximab-associated PML is difficult to ascertain and this topic has been comprehensively reviewed by Carson et al. (67).

The role of B-lymphocytes in progressive MS is less certain. Immunohistochemical studies at postmortem have identified B-cell follicles in the meninges of a proportion of patients with secondary progressive MS, but not in primary progressive disease (68,69). An early study of rituximab in primary progressive MS patients showed that B-lymphocytes were not as effectively depleted in the cerebrospinal fluid compared with the periphery (70). A subsequent phase II/III trial of rituximab in primary progressive patients failed to provide evidence for a significant impact on disease progression (71).

Rituximab has also been trialled in neuromyelitis optica (NMO), a subtype of MS predominantly affecting the eye (optic neuritis) and spinal cord (transverse myelitis), which is mediated by autoimmune B cells. In a small open label study, eight patients with NMO refractory to immunosuppressive therapy experienced a significant improvement in relapse rate and relapse recovery following treatment with rituximab (72). A further retrospective study of 25 patients confirms these beneficial effects (73), making rituximab a favourable option in those with more severe illness.

Daclizumab

Daclizumab is a humanised monoclonal antibody against the α subunit of interleukin-2 receptor (CD25), which is present on activated T-cells. Blockage of this receptor subunit prevents the binding of interleukin-2, limiting T-cell expansion (74). Daclizumab is mainly used in the treatment of graft rejection in renal transplant patients and has also shown efficacy in trials of non-infectious uveitis and MS (75,76). The exact mechanism of action of daclizumab in treating autoimmunity has not been fully elucidated. In a study on MS patients, it was shown that daclizumab treatment mainly causes an expansion of CD56 (bright) natural killer cells, which in turn inhibits the survival of peripheral T-cells and corresponds with a reduction in CNS inflammation (77). Three different formulations have been used in trials, which are discussed below.

In open label studies (78–82), it was observed that MS patients with relapsing disease despite conventional therapy responded favourably to intravenous daclizumab (Zenapax; Roche). Daclizumab was given either mainly as monotherapy (78) or combined with IFN-β (79–82). The vast majority of subjects showed either a significant improvement in disease activity or disease stabilisation, as measured by standardised disability scores and MRI parameters. It was also noted that some patients who worsened on daclizumab monotherapy or in combination with IFN-β, subsequently responded to a higher dose of the drug (80,81).

A recently completed phase II, double-blinded, placebo-controlled trial (CHOICE) looked at the efficacy and safety of 1 and 2 mg/kg of subcutaneous daclizumab (DAC-Penzberg) as an add-on therapy to IFN-β in 230 relapsing-remitting patients with active disease (83). Subjects had an EDSS score of 5.0 or less, and had continued to relapse whilst on IFN-β therapy. Preliminary results based on 24 weeks of trial data showed that patients on biweekly 2 mg/kg of daclizumab had a significant reduction of 72% in the total number of new or enlarged contrast-enhancing lesions on brain MRI compared with the placebo group ($p = 0.04$) (83). The study was not powered to compare relapse rates; although a non-significant reduction in annualised relapse rate by about 35% was noted in the daclizumab group. Monitoring is planned for up to 72 weeks, following which further results of the outcome measures should be available.

An on-going phase II study is investigating the safety and efficacy of daclizumab HYP (DAC HYP) monotherapy in relapsing-remitting patients with active disease (NCT00390221). Patients are being trialled on 4-weekly subcutaneous daclizumab 150 mg, 300 mg or a placebo. The primary outcome measure is the annualised relapse rate. Secondary outcomes include MRI markers, proportion of relapsing subjects and quality of life. The trial is currently in the extension phase.

Safety data collected so far from the above-mentioned studies showed that daclizumab was generally well-tolerated. Although overall rates of infection between treatment and placebo groups were comparable in the CHOICE study, there was an increased risk of severe infections (5.2% of infections were grade 3 vs. 0% in placebo group) and cutaneous events in the daclizumab group (83).

Oral therapies in development

Fingolimod (FTY720)

Fingolimod (FTY720; Novartis, Basel, Switzerland) is a sphingosine-1-phosphate receptor (S1P1) modulator, which binds to S1P1 receptors on T-cells, affecting the receptor's signalling pathways. The result is an inhibition of T-cell migration from lymphoid tissue into the peripheral circulation and target organs, including the CNS, thus attenuating inflammation without affecting their function (84,85). In the animal model of MS, fingolimod treatment has shown to protect against disease development and cause a rapid and sustained improvement in neurological deficits (86,87). In *in vitro* studies, fingolimod induced a functional effect on oligodengrocyte progenitor cells, suggesting an additional role in CNS remyelination (88).

In a 6-month, phase II controlled trial in RRMS, fingolimod significantly lowered annualised relapse rates by over 50% ($p = 0.009$ for 1.25 mg/day and $p = 0.01$ for 5 mg/day) and reduced the cumulative number of contrast-enhancing MRI lesions ($p < 0.001$ for 1.25 mg/day and $p = 0.006$ for 5 mg/day) compared with placebo (89). These findings were corroborated in the recently completed 12-month, phase III controlled trial (TRANSFORMS) (90).A total of 1292 patients with active relapsing-remitting disease with a mean EDSS score of 2.2 were randomised to 0.5 mg or 1.25 mg daily oral Fingolimod or 30 μg once-weekly intramuscular IFN-β1a (Avonex). Fingolimod significantly reduced annualised relapse rates (52% for 0.5 mg and 38% for 1.25 mg, both $p < 0.0001$) and MRI measures of inflammation compared with Avonex. Safety data showed that the drug was generally well-tolerated, although there was an increased rate of localised skin malignancies and two fatalities from severe herpes infection.

A further multicentre, phase III, 24-month controlled study is currently comparing the efficacy and safety of 0.5 and 1.25 mg daily oral fingolimod to a placebo in relapsing-remitting MS patients (FREEDOMS I and II; NCT00289978 and NCT00355134 respectively). End-points include relapse-related outcome measures, MRI markers of inflammatory change and drug safety profile. As of yet, an interim analysis is not available, although one a case of haemorrhagic focal encephalitis in a FREEDOMS II trial patient was recently reported (91). The efficacy of fingolimod in primary progressive MS is currently being investigated in a double-blinded, controlled trial (INFORMS; NCT00731692). The main outcome measure is the time to sustained disability progression.

Cladribine

Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analogue with lymphotoxic effects. It is resistant to adenosine deaminase, mimicking the immune-deficient state of hereditary adenosine deaminase deficiency (92). It causes an accumulation of deoxyneuclotides in selected T-lymphocytes, which is detrimental to the cell's function and proliferation, resulting in their sustained depletion (92). It is approved for the treatment of hairy cell leukaemia and lymphoma.

Encouraged by the results of early controlled studies (93–95), cladribine has recently re-emerged as an effective oral therapy for relapsing-remitting MS. In the recent randomised, double-blind, placebo-controlled phase III study (CLARITY), 1326 patients with relapsing-remitting MS were randomised to 1.75 or 3.5 mg/kg cumulative dose of cladribine tablets or a placebo (in 2–4 courses) in the first year (96). A second year of re-treatment followed where patients were given either the lower dose of cladribine or a placebo in two courses. Both cladribine groups showed a rapid, sustained and statistically significant reduction in relapse rates. Specifically, patients in the 1.75 and 3.5 mg/kg treatment groups showed a significant reduction in annualised relapse rates of 58% ($p < 0.001$) and 55% ($p < 0.001$) respectively, compared with the placebo (96). MRI evaluations were also significantly improved in both Cladribine groups. As with the earlier studies, lymphopenia was seen as an expected dose-dependent effect of cladribine, although good tolerability was reported overall.

At present there are on-going studies investigating the safety and efficacy of oral cladribine as an add-on therapy in MS patients who have continued to relapse on IFN-β (ONWARD study; NCT00436826) and as monotherapy in clinically isolated syndrome (ORACLE MS study; NCT00725985).

The sustained immunosuppressive effects of cladribine make it ideal for intermittent dosing, which should improve patient adherence and tolerability especially as it can be taken in tablet form. It is not yet licenced for use in MS; however, given the positive results of the trials so far this is likely to change in the near future.

Teriflunomide

Teriflunomide is the active metabolite of leflunomide, a novel immunosuppressant effective in the treatment of autoimmune disorders, especially rheumatoid arthritis. Leflunomide is rapidly converted to its active metabolite *in vivo* (97). Although the exact mechanism of action of teriflunomide has not yet been fully elucidated, its main immunomodulatory effect is thought to be the inhibition of dihydro-orotate dehydrogenase, an enzyme involved in the biosynthesis of pyramidine, a metabolic component crucial to the expansion and differentiation of lymphocytes (97). Further effects on inflammatory cell recruitment and other *in vivo* immunomodulatory processes have been postulated (98). In the animal model of MS (EAE), leflunomide/teriflunomide was shown to be effective in mitigating the disease course and symptoms (99,100).

The first phase II study of oral teriflunomide in MS reported a reduction in both MRI and clinical disease parameters (101). A total of 179 patients with relapsing MS were randomised to 7 or 14 mg daily terflunomide or a placebo. As a primary end-point, the study group assessed the number of combined unique (CU) active lesions, which consisted of new and persisting contrast-enhancing and T2 lesions on MRI. Both teriflunomide treatment groups showed a

significant reduction of over 61% in the number of CU active lesions compared with the placebo group ($p < 0.03$ and $p < 0.01$ for 7 and 14 mg respectively). The study was not powered to measure clinical end-points of the disease; however, the group did observe a trend towards lower annualised relapse rates and fewer numbers suffering an increase in disability amongst the teriflunomide-treated patients. The overall safety profile of the drug was good, in keeping with previously observed data from leflunomide trials in rheumatoid arthritis (102,103). Notably, no opportunistic infections were reported.

Teriflunomide is currently being trialled in a number of phase III clinical studies. The phase III TEMSO (NCT00134563) and TOWER (NCT00751881) studies are investigating the safety and efficacy of 7 and 14 mg daily teriflunomide compared with a placebo in patients with relapsing MS. Primary outcome measures are EDSS and annualised relapse rate respectively. A third phase III trial will include an IFN-β1a – control arm (TENERE study, NCT00883337) to compare the effectiveness and safety of 7 and 14 mg teriflunomide to IFN-β1a in relapsing MS patients.

It remains to be seen if clinical end-point measures, especially relapse rate and disability progression, are met in the phase III studies of teriflunomide. If so, teriflunomide will offer an effective and convenient alternative to current DMT.

Laquinimod

Laquinimod (ABR-215062) is a linomide-related synthetic compound developed to provide effective immunomodulation without significant adverse immunosuppressive effects. Taken orally, laquinimod prevents the migration of peripheral lymphocytes into the CNS, although its exact mode of action has not been fully elucidated (104). Successful studies in the animal model (EAE) of acute and chronic relapsing disease demonstrate its therapeutic potential in MS (104).

In the first phase II clinical study of the drug (105), patients with active relapsing MS taking 0.3 mg/day laquinimod demonstrated a significant reduction of 44% in active MRI lesions compared with a placebo ($p = 0.0498$). A larger phase II study (106) also demonstrated a reduction of about 40% in active MRI lesions in relapsing-remitting patients taking a slightly higher dose of laquinimod (0.6 mg daily), compared with the placebo ($p = 0.0048$). Neither of these studies was powered to provide efficacy data based on clinical outcome measures such as EDSS score and rate of relapses.

Two multicentre phase III studies of laquinimod in active relapsing-remitting MS are currently taking place. In the first study, the efficacy and safety of laquinimod 0.6 mg/day will be compared with a placebo (NCT00509145). The second study is a parallel-group comparing the safety and efficacy of laquinimod 0.6 mg/day to intramuscular IFN-β and a placebo (NCT00605215). Outcome measures in both studies include relapse rate (primary), disability progression and MRI parameters. It is estimated that both studies will run until 2011.

Dimethyl fumarate (BG00012)

BG00012 is an oral formulation of dimethyl fumarate, an antipsoriatic agent with anti-inflammatory and neuroprotective properties. An early clinical study of Fumaderm, another fumaric acid ester, demonstrated the therapeutic potential of fumarate in MS (107). BG0002 is a potent activator of nuclear factor E2-related factor 2 (Nrf2), a transcription factor, which plays a crucial role in neuronal protection during oxidative stress and chemical insults (108,109) and in the maintenance of CNS myelin (110). Further *in vitro* studies have also shown that it inhibits expression of pro-inflammatory cytokines and cell adhesion molecules, providing an anti-inflammatory effect (111,112).

A double-blind, placebo-controlled, dose-ranging phase II study of BG00012 in RRMS showed that it was effective in reducing MRI measures of disease activity (113).A total of 257 patients with relapsing-remitting disease were randomised to receive oral BG00012 120 mg once daily, 120 or 240 mg three times a day or a placebo for 24 weeks. The study found that treatment with 240 mg three times a day significantly reduced the number of contrast-enhancing MRI lesions by 69% compared with placebo ($p < 0.0001$), alongside other MRI parameters. The study was not powered to compare clinical outcomes; although a reduction of about 32% in annualised relapse rate was observed in the high-dose active treatment group. BG00012 was shown to be safe and generally well-tolerated, although gastrointestinal effects were commonly reported in the earlier stages of treatment.

Two on-going, phase III, dose-ranging, placebo-controlled studies, DEFINE (NCT00420212) and CONFIRM (NCT00451451) are evaluating the safety and efficacy of oral BG00012 in patients with relapsing-remitting MS. Patients in both studies will be randomised to BG00012 240 mg twice daily or three times a day or a placebo. The CONFIRM study will have an added glatiramer acetate treatment arm, given as a 20 mg daily subcutaneous injection, for further comparison.

Firategrast

Firategrast (SB-683699) is, like natalizumab, a α4-integrin antagonist which interferes with the binding

of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins to its ligand, VCAM-1, preventing the migration of immune cells to the site of inflammation (114). Unlike natalizumab; however, it is a small molecule in the form of an oral preparation, which has the benefit of a more convenient mode of delivery and reduced drug costs.

A multicentre, phase II trial (NCT00395317) is currently investigating the MRI efficacy and safety of Firategrast in relapsing-remitting patients. Around 350 patients have been enrolled in the study, with preliminary result still pending.

DMT in CIS

Clinically isolated syndrome (CIS) may represent the first demyelinating attack of MS in a large proportion of patients. For many, there is already radiological evidence of MS at this stage (115–117). Using defined MRI criteria, we are able to gauge the risk of a patient developing a second clinical attack diagnostic of MS (118–120). However, irrespective of the patient's MRI findings, the current trend is such that the vast majority of CIS patients with little or no disability are given the 'wait and see' approach to therapy.

There is growing evidence that early treatment in MS may significantly alter the course of the disease. Axonal degeneration, which is responsible for the permanent disability in MS, is seen to occur early on in the disease process (121–123). Studies have suggested a causal link between acute inflammation and axonal loss (123) along with the accepted role of chronic demyelination. Furthermore, highly active disease early on correlates to increased disability at a later stage and increased likelihood of secondary progression (124). Thus, early anti-inflammatory treatment could potentially delay or prevent the onset of permanent disability.

Evidence from a number of phase III clinical trials supports this. The CHAMPS study group reported on the outcome of a randomised, double-blind, placebo-controlled trial of 30 μg intramuscular IFN-β1a (Avonex) weekly in patients presenting with CIS (125). They showed that early treatment significantly lowered the probability of developing clinically definite MS (CDMS) at 3 years compared with placebo (hazard ratio 0.56, $p = 0.002$). In their 10-year follow-up study, the group continued to show a reduced conversion rate to CDMS in patients who had early treatment compared with those who delayed therapy (hazard ratio 0.64, $p = 0.03$) (126).

The ETOMS study investigated the efficacy of 22 μg subcutaneous IFN-β1a (Rebif) weekly in a similar trial (127). They also demonstrated significantly lower numbers of patients who converted to MS after 2 years of treatment (34% of Rebif group vs. 45% of placebo, $p = 0.047$). The BENEFIT study group followed suit with positive result from their study of alternate day 250 μg subcutaneous IFN-β1b (Betaferon/Betaseron) in CIS (128). In particular, treatment with IFN-β1b for 2 years significantly delayed the conversion to CDMS, and McDonald-criteria defined MS (hazard ratio 0.50, $p < 0.0001$ and 0.54, $p < 0.00001$ respectively) compared with placebo-treated patients. A recent Cochrane meta analysis of the above CIS studies concluded that IFN-β treatment in CIS significantly lowered the proportion of patients who converted to CDMS at year 1 (pooled odds ratio 0.53, $p < 0.0001$) and year 2 of therapy (pooled odds ratio 0.52, $p < 0.0001$) compared with those on a placebo (129).

The study group for the PreCISe trial of glatiramer acetate (Copaxone) in CIS recently revealed the results of their interim analysis on data accumulated from approximately 80% of the three-year study exposure (130). Compared with placebo, the risk of conversion to CDMS in patients who received 20 mg daily subcutaneous Copaxone was reduced by 45% ($p < 0.0001$). Moreover, the time for 25% of patients to develop CDMS was prolonged by 115% in the Copaxone group ($p = 0.0005$).

A prospective, double-blind, placebo-control phase III trial is currently underway, investigating the effectiveness of subcutaneous 44 μg IFN-β1a (Rebif) in delaying the conversion of CIS to CDMS. Two other similar phase III trials are also investigating oral cladribine (NCT00725985) and teriflunomide (NCT00622700) in CIS patients, with time to conversion to CDMS as the primary outcome measures.

Although the logical conclusion from the above studies is that DMT should be initiated at the onset of the first clinically demyelinating event, this may not be an advantage for all patients. Many may have a favourable or mild disease course (131), making lifelong treatment unnecessary. Moreover, the inconvenience of parenteral therapy and possible side effects may make it difficult for many patients to comply with long-term treatment. Ultimately, the decision on when to commence disease-modifying therapy should be jointly made by the neurologist and patient after considering all the available evidence.

DMT in progressive MS

Irreversible progression is attributed to neurodegeneration, implying that standard anti-inflammatory disease-modifying agents may not have an impact on disease progression, as shown to be the case in many of the above-mentioned studies. Primary progressive MS also differs from secondary progressive and relapsing-remitting disease in their pathological features, whereby in primary disease, more diffuse

inflammation affecting the so-called normal-appearing white and grey matter is seen.

Far fewer therapeutic agents are currently being trialled in progressive MS in comparison to relapsing-remitting MS, although a small number have been completed in the last few years. The European and North American Study Groups of Interferon-β1b in secondary progressive MS showed positive results with regards to relapse rate and MRI evidence of disease activity (132,133). In the European study, IFN-β1b significantly delayed the time to confirmed disability progression, i.e. increase in EDSS of 1.0 point, by 9–12 months (odds ratio 0.65, $p = 0.0008$). The North American group however, did not achieve this (133). Nonetheless the results of the European study subsequently led to the approval of IFN-β1b therapy for secondary progressive MS.

Rebif was trialled in SPMS in the SPECTRIMS study, a multicentre, placebo-controlled trial using two doses of the drug, 22 and 44 μg. The study drug failed to show a significant effect on disability progression, although it improved relapse rates ($p < 0.001$ for both doses) (134). Similarly, Avonex failed to show a significant impact on EDSS progression in a SPMS trial (IMPACT study), although it benefited Multiple Sclerosis Functional Composite scores ($p = 0.033$), relapse rates ($p = 0.008$) and MRI measures of disease activity ($p < 0.001$) (135).

In two small, separate primary progressive MS trials, neither Avonex ($n = 50$) nor Betaferon ($n = 73$) showed a significant impact on disease progression and brain and spinal cord atrophy (136,137). The efficacy of glatiramer acetate in primary progressive MS (PPMS) was evaluated in a large placebo-controlled, double-blinded trial involving 943 patients. Results showed a non-significant delay in the progression of disability in the active treatment group, although there was a significant improvement in MRI markers of disease activity ($p = 0.0193$) (138). Other agents that have recently failed to show a significant impact on disability progression in PPMS include mitoxantrone (139) and rituximab (as detailed elsewhere in the text)(71).

In trials involving both primary and secondary progressive patients, cladribine failed to show any significant impact on disease progression although it improved some MRI-defined outcome measures (94). On the other hand, a relatively small study of monthly intravenous immunoglobulin (IVIg) therapy showed a positive reduction in the proportion of patients with sustained disability progression compared with a placebo, which was significant in PPMS, but not in SPMS patients (140). Previous findings in SPMS also failed to show any significant benefit of IVIg (141). This could indicate that IVIg has a potentially favourable effect in PPMS, but not in SPMS, although further study is warranted.

Other forms of therapy currently being assessed for the treatment of progressive MS include the aforementioned oral disease-modifying agent fingolimod and haematopoietic stem cell transplantation (HSCT). The efficacy of HSCT in progressive MS has been controversial, especially regarding MRI evaluation of disease progression and the high mortality risk faced by more severely disabled patients. This subject matter has been comprehensively reviewed by Saccardi et al. (142).

A trial of cannabinoids as disease-modifying treatments in progressive MS is underway.

Conclusion

Increasing knowledge of the pathological process of MS has allowed us to continue developing highly selective immunomodulatory therapies. The main aim of treatment thus far has been to reduce the frequency and severity of relapses, likely delaying the onset of irreversible disability. We have only partially achieved this with current DMT. Encouragingly, the emergence of several agents showing early promise in clinical trials may soon help realise this and offer patients a wider repertoire to choose from. Alemtuzumab appears to be a promising monoclonal antibody treatment for MS; however, the results of larger phase III studies are still awaited. Rituximab may benefit patients with MS and other autoimmune conditions, although further risk/benefit analysis would be required given the reported cases of PML so far. Of the oral agents, Fingolimod and cladribine have shown positive results as disease-modifying agents in large phase III studies, although their long-term safety and efficacy in MS have yet to be established. Many more experimental therapies beyond the scope of this review are currently being explored at various stages, including autologous haematopoietic stem cell transplantation for more aggressive forms of MS, Ataticept (a recombinant fusion protein, which inhibits B-cell stimulation and proliferation, currently in phase II RRMS trials; NCT00642902 and NCT00853762) and other drugs that may offer neuroprotection. Trials that re-evaluate 'traditional' immunosuppressive agents such as azathioprine and cyclophosphamide may also provide fresh evidence for treating refractory cases of MS. The choice of disease-modifying treatment is increasingly individualised depending on the disease characteristics, patient lifestyle and drug risks/benefits. Within the established first-line therapies, the risk of flu-like symptoms need to be weighed against the inconvenience of daily injections. As for newer and

novel therapies, their immunosuppressive properties and our less than abundant experience with them need to be balanced against the safety and relative predictability of established treatments.

References

1 Weinshenker BG, Bass B, Rice GP et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989; **112**(Pt 1): 133–46.

2 Kebir H, Kreymborg K, Ifergan I et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med* 2007; **13**: 1173–5.

3 Cross AH, Trotter JL, Lyons J. B cells and antibodies in CNS demyelinating disease. *J Neuroimmunol* 2001; **112**: 1–14.

4 Double-masked trial of azathioprine in multiple sclerosis. British and Dutch multiple sclerosis azathioprine trial group. *Lancet* 1988; **2**: 179–83.

5 Yudkin PL, Ellison GW, Ghezzi A et al. Overview of azathioprine treatment in multiple sclerosis. *Lancet* 1991; **338**: 1051–5.

6 La Mantia L, Milanese C, Mascoli N et al. Cyclophosphamide for multiple sclerosis. *Cochrane Database Syst Rev.* 2007, Issue 1: CD002819.

7 Alam J, Goelz S, Rioux P et al. Comparative pharmacokinetics and pharmacodynamics of two recombinant human interferon beta-1a (IFN beta-1a) products administered intramuscularly in healthy male and female volunteers. *Pharm Res* 1997; **14**: 546–9.

8 Dhib-Jalbut S. Mechanisms of interferon beta action in multiple sclerosis. *Mult Scler* 1997; **3**: 397–401.

9 Bornstein MB, Miller A, Slagle S et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. *N Engl J Med* 1987; **7**: 408–14.

10 Dhib-Jalbut S. Glatiramer acetate (copaxone) therapy for multiple sclerosis. *Pharmacol Ther* 2003; **98**: 245–55.

11 Gran B, Tranquill LR, Chen M et al. Mechanisms of immunomodulation by glatiramer acetate. *Neurology* 2000; **55**: 1704–14.

12 The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; **43**: 655–61.

13 PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; **352**: 1498–504.

14 Jacobs LD, Cookfair DL, Rudick RA et al., The Multiple Sclerosis Collaborative Research Group (MSCRG) Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996; **39**: 285–94.

15 Johnson KP, Brooks BR, Cohen JA et al., The Copolymer 1 Multiple Sclerosis Study Group Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. *Neurology* 1995; **45**: 1268–76.

16 Freedman MS, Hughes B, Mikol DD et al. Efficacy of disease-modifying therapies in relapsing remitting multiple sclerosis: a systematic comparison. *Eur Neurol* 2008; **60**: 1–11.

17 Galetta SL, Markowitz C, Lee AG. Immunomodulatory agents for the treatment of relapsing multiple sclerosis: a systematic review. *Arch Intern Med* 2002; **162**: 2161–9.

18 Mikol DD, Barkhof F, Chang P et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol* 2008; **7**: 903–14.

19 O'Connor P, Arnason B, Comi G et al. *Interferon Beta-1b 500 mcg, Interferon Beta-1b 250 mcg and Glatiramer Acetate: Primary Outcomes of the Betaferon®/Betaseron® Efficacy Yielding Outcomes of a New Dose Study*. Abstract from the American Academy of Neurology (AAN) 60th Annual Meeting. Chicago, IL, 2008. Abstract No: LBS.004.

20 The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Neutralizing antibodies during treatment of multiple sclerosis with interferon beta-1b: experience during the first three years. *Neurology* 1996; **47**: 889–94.

21 Rudick RA, Simonian NA, Alam JA et al., Multiple Sclerosis Collaborative Research Group (MSCRG). Incidence and significance of neutralizing antibodies to interferon beta-1a in multiple sclerosis. *Neurology* 1998; **50**: 1266–72.

22 Sorensen PS, Koch-Henriksen N, Ross C et al. Appearance and disappearance of neutralizing antibodies during interferon-beta therapy. *Neurology* 2005; **65**: 33–9.

23 Khan OA, Dhib-Jalbut SS. Neutralizing antibodies to interferon beta-1a and interferon beta-1b in MS patients are cross-reactive. *Neurology* 1998; **51**: 1698–702.

24 Pozzilli C, Antonini G, Bagnato F et al. Monthly corticosteroids decrease neutralizing antibodies to IFNbeta1 b: a randomized trial in multiple sclerosis. *J Neurol* 2002; **249**: 50–6.

25 Sorensen PS, Mellgren SI, Svenningsson A et al. NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. *Lancet Neurol* 2009; **8**: 519–29.

26 Ravnborg M. *A Multi-Centre, Double Blind, Randomized, Placebo Controlled, Parallel Group Trial Investigating Methylprednisolone (MP) in Combination with Interferon-b-1a for the Treatment of Relapsing-Remitting Multiple Sclerosis (RRMS)*. Abstract from the 61st Annual Meeting of the American Academy of Neurologists (AAN). Seattle, WA, 2009. Abstract No: LB3.002.

27 Compston A, Dick J, Leigh N et al. ABN Guidelines for Treatment of Multiple Sclerosis with Beta-Interferon and Glatiramer acetate. London, UK: Association of British Neurologists, 2007.

28 The Once Weekly Interferon for MS Study Group. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. *Neurology* 1999; **53**: 679–86.

29 Blumhardt LD. Once weekly interferon beta for multiple sclerosis is superseded by higher and more frequent dosing. *Int J Clin Pract Suppl* 2002: 9–16.

30 Leger OJ, Yednock TA, Tanner L et al. Humanization of a mouse antibody against human alpha-4 integrin: a potential therapeutic for the treatment of multiple sclerosis. *Hum Antibodies* 1997; **8**: 3–16.

31 Steinman L. Blocking adhesion molecules as therapy for multiple sclerosis: natalizumab. *Nat Rev Drug Discov* 2005; **4**: 510–8.

32 Tubridy N, Behan PO, Capildeo R et al., The UK Antegren Study Group The effect of anti-alpha4 integrin antibody on brain lesion activity in MS. *Neurology* 1999; **53**: 466–72.

33 Miller DH, Khan OA, Sheremata WA et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003; **348**: 15–23.

34 O'Connor PW, Goodman A, Willmer-Hulme AJ et al. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. *Neurology* 2004; **62**: 2038–43.

35 Polman CH, O'Connor PW, Havrdova E et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354**: 899–910.

36 Rudick RA, Stuart WH, Calabresi PA et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; **354**: 911–23.

37 Van Assche G, Van Ranst M, Sciot R et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; **353**: 362–8.

38 Yousry TA, Major EO, Ryschkewitsch C et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006; **354**: 924–33.

39 Biogen Idec Inc. TYSABRI update; 2009 24th July. http://www.biogenidec.com/site/tysabri-information-center.html (accessed August 2009).

40 Thompson JP, Noyes K, Dorsey ER et al. Quantitative risk-benefit analysis of natalizumab. *Neurology* 2008; **71**: 357–64.

41 Calabresi PA, Giovannoni G, Confavreux C et al. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology* 2007; **69**: 1391–403.

42 Ismail A, Kemp J, Sharrack B. Melanoma complicating treatment with natalizumab (Tysabri) for multiple sclerosis. *J Neurol* 2009; **256**: 1771–2.

43 Shenkenberg TD, Von Hoff DD. Mitoxantrone: a new anticancer drug with significant clinical activity. *Ann Intern Med* 1986; **105**: 67–81.

44 Edan G, Miller D, Clanet M et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997; **62**: 112–8.

45 Hartung HP, Gonsette R, Konig N et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002; **360**: 2018–25.

46 Fidler JM, DeJoy SQ, Gibbons JJ Jr. Selective immunomodulation by the antineoplastic agent mitoxantrone. I. Suppression of B lymphocyte function. *J Immunol* 1986; **137**: 727–32.

47 Fidler JM, DeJoy SQ, Smith FR 3rd, Gibbons JJ Jr. Selective immunomodulation by the antineoplastic agent mitoxantrone. II. Nonspecific adherent suppressor cells derived from mitoxantrone-treated mice. *J Immunol* 1986; **136**: 2747–54.

48 Fox EJ. Mechanism of action of mitoxantrone. *Neurology* 2004;**63** (12 Suppl 6): S15–8.

49 Watson CM, Davison AN, Baker D et al. Suppression of demyelination by mitoxantrone. *Int J Immunopharmacol* 1991; **13**: 923–30.

50 Lublin FD, Lavasa M, Viti C, Knobler RL. Suppression of acute and relapsing experimental allergic encephalomyelitis with mitoxantrone. *Clin Immunol Immunopathol* 1987; **45**: 122–8.

51 Krapf H, Morrissey SP, Zenker O et al. Effect of mitoxantrone on MRI in progressive MS: results of the MIMS trial. *Neurology* 2005; **65**: 690–5.

52 Rizvi SA, Zwibel H, Fox EJ. Mitoxantrone for multiple sclerosis in clinical practice. *Neurology*. 2004;**63** (12 Suppl 6): S25–7.

53 Ramtahal J, Jacob A, Das K, Boggild M. Sequential maintenance treatment with glatiramer acetate after mitoxantrone is safe and can limit exposure to immunosuppression in very active, relapsing remitting multiple sclerosis. *J Neurol* 2006; **253**: 1160–4.

54 Ghalie RG, Edan G, Laurent M et al. Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. *Neurology* 2002; **59**: 909–13.

55 Martinelli V. *Incidence of Acute Leukaemia in Multiple Sclerosis Patients Treated with Mitoxandrone: A Multicentre Retrospective Italian Study*. Abstract from the 61st Annual Meeting of the American Academy of Neurology (AAN). Seattle, WA, 2009.

56 Ghalie RG, Mauch E, Edan G et al. A study of therapy-related acute leukaemia after mitoxantrone therapy for multiple sclerosis. *Mult Scler* 2002; **8**: 441–5.

57 Voltz R, Starck M, Zingler V et al. Mitoxantrone therapy in multiple sclerosis and acute leukaemia: a case report out of 644 treated patients. *Mult Scler* 2004; **10**: 472–4.

58 Moreau T, Coles A, Wing M et al. CAMPATH-IH in multiple sclerosis. *Mult Scler* 1996; **1**: 357–65.

59 Coles A, Deans J, Compston A. Campath-1H treatment of multiple sclerosis: lessons from the bedside for the bench. *Clin Neurol Neurosurg* 2004; **106**: 270–4.

60 Coles AJ, Compston DA, Selmaj KW et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008; **359**: 1786–801.

61 Coles AJ, Wing M, Smith S et al. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. *Lancet* 1999; **354**: 1691–5.

62 Reff ME, Carner K, Chambers KS et al. Depletion of B cells *in vivo* by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994; **83**: 435–45.

63 Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate *in vivo* cytoxicity against tumor targets. *Nat Med* 2000; **6**: 443–6.

64 Tintore M, Rovira A, Rio J et al. Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? *Neurology* 2008; **70**(13 Pt 2): 1079–83.

65 Hauser SL, Waubant E, Arnold DL et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008; **358**: 676–88.

66 Aksoy S, Harputluoglu H, Kilickap S et al. Rituximab-related viral infections in lymphoma patients. *Leuk Lymphoma* 2007; **48**: 1307–12.

67 Carson KR, Evens AM, Richey EA et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the research on adverse drug events and reports project. *Blood* 2009; **113**: 4834–40.

68 Serafini B, Rosicarelli B, Magliozzi R et al. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. *Brain Pathol* 2004; **14**: 164–74.

69 Magliozzi R, Howell O, Vora A et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. *Brain* 2007; **130** (Pt 4): 1089–104.

70 Monson NL, Cravens PD, Frohman EM et al. Effect of rituximab on the peripheral blood and cerebrospinal fluid B cells in patients with primary progressive multiple sclerosis. *Arch Neurol* 2005; **62**: 258–64.

71 Hawker KS, O'Connor P, Freedman MS et al. *Efficacy and Safety of Rituximab in Patients with Primary Progressive Multiple Sclerosis: Results of A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial*. Presented at the World Congress on Treatment and Research in Multiple Sclerosis: 2008 Joint Meeting of the American, European, and Latin America Committees on Treatment and Research in Multiple Sclerosis. Montreal, Quebec, 2008.

72 Cree BA, Lamb S, Morgan K et al. An open label study of the effects of rituximab in neuromyelitis optica. *Neurology* 2005; **64**: 1270–2.

73 Jacob A, Weinshenker BG, Violich I et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Arch Neurol* 2008; **65**: 1443–8.

74 Waldmann TA. Anti-Tac (daclizumab, Zenapax) in the treatment of leukemia, autoimmune diseases, and in the prevention of allograft rejection: a 25-year personal odyssey. *J Clin Immunol* 2007; **27**: 1–18.

75 Nussenblatt RB, Fortin E, Schiffman R et al. Treatment of noninfectious intermediate and posterior uveitis with the humanized anti-Tac mAb: a phase I/II clinical trial. *Proc Natl Acad Sci U S A* 1999; **96**: 7462–6.

76 Waldmann TA, O'Shea J. The use of antibodies against the IL-2 receptor in transplantation. *Curr Opin Immunol* 1998; **10**: 507–12.

77 Bielekova B, Catalfamo M, Reichert-Scrivner S et al. Regulatory CD56 (bright) natural killer cells mediate immunomodulatory effects of IL-2Ralpha-targeted therapy (daclizumab) in multiple sclerosis. *Proc Natl Acad Sci U S A* 2006; **103**: 5941–6.

78 Rose JW, Watt HE, White AT, Carlson NG. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Ann Neurol* 2004; **56**: 864–7.

79 Bielekova B, Richert N, Howard T et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. *Proc Natl Acad Sci U S A* 2004; **101**: 8705–8.

80 Bielekova B, Howard T, Packer AN et al. Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. *Arch Neurol* 2009; **66**: 483–9.

81 Rose JW, Burns JB, Bjorklund J et al. Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. *Neurology* 2007; **69**: 785–9.

82 Ali EN, Stazzone LA, Brown BA et al. *Daclizumab in the Treatment of Patients with Multiple Sclerosis*. Presented at the 59th Annual Meeting of the American Academy of Neurology. Boston, MA, 2007.

83 Montalban X, Wynn D, Kaufman M et al. Preliminary CHOICE results: a Phase 2, randomised, double-blind, placebo-controlled multicentre study of subcutaneous daclixumab in patients with active, relapsing forms of multiple sclerosis on interferon B. Presented at the 23rd Congress of the European Committee for the Treatment and Research in Multiple Sclerosis. Prague, Czech Republic, 2007.

84 Brinkmann V, Cyster JG, Hla T. FTY720: sphingosine 1-phosphate receptor-1 in the control of lymphocyte egress and endothelial barrier function. *Am J Transplant* 2004; **4**: 1019–25.

85 Mehling M, Brinkmann V, Antel J et al. FTY720 therapy exerts differential effects on T cell subsets in multiple sclerosis. *Neurology* 2008; **71**: 1261–7.

86 Fujino M, Funeshima N, Kitazawa Y et al. Amelioration of experimental autoimmune encephalomyelitis in Lewis rats by FTY720 treatment. *J Pharmacol Exp Ther* 2003; **305**: 70–7.

87 Webb M, Tham CS, Lin FF et al. Sphingosine 1-phosphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice. *J Neuroimmunol* 2004; **153**: 108–21.

88 Miron VE, Jung CG, Kim HJ et al. FTY720 modulates human oligodendrocyte progenitor process extension and survival. *Ann Neurol* 2008; **63**: 61–71.

89 Kappos L, Antel J, Comi G et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med* 2006; **355**: 1124–40.

90 Cohen J, Pelletier J, Kappos L et al. *Oral Fingolimod (FTY720) Versus Interferon Beta-1a in Relapsing Remitting Multiple Sclerosis: Results from a Phase III Study (TRANSFORMS)*. Presented at the 61st Annual Meeting of the American Academy of Neurology (AAN). Seattle, WA, 2009.

91 Leypoldt F, Munchau A, Moeller F et al. Hemorrhaging focal encephalitis under fingolimod (FTY720) treatment: a case report. *Neurology* 2009; **72**: 1022–4.

92 Carson DA, Wasson DB, Taetle R, Yu A. Specific toxicity of 2-chlorodeoxyadenosine toward resting and proliferating human lymphocytes. *Blood* 1983; **62**: 737–43.

93 Sipe JC, Romine JS, Koziol JA et al. Cladribine in treatment of chronic progressive multiple sclerosis. *Lancet* 1994; **344**: 9–13.

94 Rice GP, Filippi M, Comi G, Cladribine MRI Study Group. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. *Neurology* 2000; **54**: 1145–55.

95 Romine JS, Sipe JC, Koziol JA et al. A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. *Proc Assoc Am Physicians* 1999; **111**: 35–44.

96 Giovannoni G. *Clinical Efficacy of Cladribine Tablet Therapy in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the CLARITY Study, a 96-week, Phase III, Double-Blind, Placebo-Controlled Trial*. Presented at the 61st Annual Meeting of the American Academy of Neurology (AAN). Seattle, WA, 2009.

97 Tallantyre E, Evangelou N, Constantinescu CS. Spotlight on teriflunomide. *Int MS J* 2008; **15**: 62–8.

98 Herrmann ML, Schleyerbach R, Kirschbaum BJ. Leflunomide: an immunomodulatory drug for the treatment of rheumatoid arthritis and other autoimmune diseases. *Immunopharmacology* 2000; **47**: 273–89.

99 Merrill JE, Hanak S, Pu SF et al. Teriflunomide reduces behavioral, electrophysiological, and histopathological deficits in the Dark Agouti rat model of experimental autoimmune encephalomyelitis. *J Neurol* 2009; **256**: 89–103.

100 Korn T, Magnus T, Toyka K, Jung S. Modulation of effector cell functions in experimental autoimmune encephalomyelitis by leflunomide – mechanisms independent of pyrimidine depletion. *J Leukoc Biol* 2004; **76**: 950–60.

101 O'Connor PW, Li D, Freedman MS et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology* 2006; **66**: 894–900.

102 Kalden JR, Schattenkirchner M, Sorensen H et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study. *Arthritis Rheum* 2003; **48**: 1513–20.

103 Emery P, Breedveld FC, Lemmel EM et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000; **39**: 655–65.

104 Brunmark C, Runstrom A, Ohlsson L et al. The new orally active immunoregulator laquinimod (ABR-215062) effectively inhibits development and relapses of experimental autoimmune encephalomyelitis. *J Neuroimmunol* 2002; **130**: 163–72.

105 Polman C, Barkhof F, Sandberg-Wollheim M et al. Treatment with laquinimod reduces development of active MRI lesions in relapsing MS. *Neurology* 2005; **64**: 987–91.

106 Comi G, Pulizzi A, Rovaris M et al. Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet* 2008; **371**: 2085–92.

107 Schimrigk S, Brune N, Hellwig K et al. Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label, baseline-controlled pilot study. *Eur J Neurol* 2006; **13**: 604–10.

108 Calabrese V, Ravagna A, Colombrita C et al. Acetylcarnitine induces heme oxygenase in rat astrocytes and protects against oxidative stress: involvement of the transcription factor Nrf2. *J Neurosci Res* 2005; **79**: 509–21.

109 Li J, Johnson D, Calkins M et al. Stabilization of Nrf2 by tBHQ confers protection against oxidative stress-induced cell death in human neural stem cells. *Toxicol Sci* 2005; **83**: 313–28.

110 Hubbs AF, Benkovic SA, Miller DB et al. Vacuolar leukoencephalopathy with widespread astrogliosis in mice lacking transcription factor Nrf2. *Am J Pathol* 2007; **170**: 2068–76.

111 de Jong R, Bezemer AC, Zomerdijk TP et al. Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate. *Eur J Immunol* 1996; **26**: 2067–74.

112 Vandermeeren M, Janssens S, Borgers M, Geysen J. Dimethylfumarate is an inhibitor of cytokine-induced E-selectin, VCAM-1, and ICAM-1 expression in human endothelial cells. *Biochem Biophys Res Commun* 1997; **234**: 19–23.

113 Kappos L, Gold R, Miller DH et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet* 2008; **372**: 1463–72.

114 Jackson DY. Alpha 4 integrin antagonists. *Curr Pharm Des* 2002; **8**: 1229–53.

115 Ormerod IE, McDonald WI, du Boulay GH et al. Disseminated lesions at presentation in patients with optic neuritis. *J Neurol Neurosurg Psychiatry* 1986; **49**: 124–7.

116 Martinelli V, Comi G, Filippi M et al. Paraclinical tests in acute-onset optic neuritis: basal data and results of a short follow-up. *Acta Neurol Scand* 1991; **84**: 231–6.

117 Ford B, Tampieri D, Francis G. Long-term follow-up of acute partial transverse myelopathy. *Neurology* 1992; **42**: 250–2.

118 Barkhof F, Filippi M, Miller DH et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997; **120** (Pt 11): 2059–69.

119 Swanton JK, Fernando K, Dalton CM et al. Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. *J Neurol Neurosurg Psychiatry* 2006; **77**: 830–3.

120 Tintore M, Rovira A, Rio J et al. Baseline MRI predicts future attacks and disability in clinically isolated syndromes. *Neurology* 2006; **67**: 968–72.

121 Trapp BD, Ransohoff R, Rudick R. Axonal pathology in multiple sclerosis: relationship to neurologic disability. *Curr Opin Neurol* 1999; **12**: 295–302.

122 Zivadinov R, Sepcic J, Nasuelli D et al. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2001; **70**: 773–80.

123 Kuhlmann T, Lingfeld G, Bitsch A et al. Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. *Brain*. 2002; **125** (Pt 10): 2202–12.
124 Fisniku LK, Brex PA, Altmann DR et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* 2008; **131** (Pt 3): 808–17.
125 Jacobs LD, Beck RW, Simon JH et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med* 2000; **343**: 898–904.
126 Kinkel R, Dontchev M, Tanner J et al. *CHAMPIONS EXTENSION Study: 10-Year Follow-up After a Clinically Isolated Syndrome (CIS) Involving High-Risk Patients*. Abstract from the 61st Annual Meeting of the American Academy of Neurology (AAN). Seattle, WA, 2009. Abstract No: P06.137.
127 Comi G, Filippi M, Barkhof F et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet* 2001; **357**: 1576–82.
128 Kappos L, Polman CH, Freedman MS et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006; **67**: 1242–9.
129 Clerico M, Faggiano F, Palace J et al. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. *Cochrane Database Syst Rev* 2008, Issue 2: CD005278.
130 Comi G, Filippi M. *Treatment with Glatiramer Acetate Delays Conversion to Clinically Definite Multiple Sclerosis (CDMS) in Patients with Clinically Isolated Syndromes (CIS)*. Presented at the American Academy of Neurology (AAN) 60th Annual Meeting. Chicago, IL, 2008.
131 Pittock SJ, Mayr WT, McClelland RL et al. Change in MS-related disability in a population-based cohort: a 10-year follow-up study. *Neurology* 2004; **62**: 51–9.
132 European Study Group on interferon beta-1b in secondary progressive MS. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. *Lancet* 1998; **352**: 1491–7.
133 Panitch H, Miller A, Paty D, Weinshenker B. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology* 2004; **63**: 1788–95.
134 SPECTRIMS Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. *Neurology* 2001; **56**: 1496–504.
135 Cohen JA, Cutter GR, Fischer JS et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* 2002; **59**: 679–87.
136 Leary SM, Miller DH, Stevenson VL et al. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. *Neurology* 2003; **60**: 44–51.
137 Montalban X. Overview of European pilot study of interferon beta-Ib in primary progressive multiple sclerosis. *Mult Scler* 2004;**10** (Suppl. 1): S62; discussion-4.
138 Wolinsky JS, Narayana PA, O'Connor P et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol* 2007; **61**: 14–24.
139 Kita M, Cohen J, Fox R. A phase II trial of mitoxantrone in patients with primary progressive multiple sclerosis (abstract). *Neurology* 2004; **000**: A99.
140 Pohlau D, Przuntek H, Sailer M et al. Intravenous immunoglobulin in primary and secondary chronic progressive multiple sclerosis: a randomized placebo controlled multicentre study. *Mult Scler* 2007; **13**: 1107–17.
141 Hommes OR, Sorensen PS, Fazekas F et al. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* 2004; **364**: 1149–56.
142 Saccardi R, Kozak T, Bocelli-Tyndall C et al. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for blood and marrow transplantation autoimmune diseases working party database. *Mult Scler* 2006; **12**: 814–23.

Paper received August 2009, accepted September 2009