Disease modification in multiple sclerosis: an update

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▶ For details of other drugs in development please see the online supplementary files. To view please visit the journal online (http://dx.doi.org/10.1136/practneurol-2013-000601)

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Published Online First
8 October 2013

To cite: Rice CM. *Pract Neurol* 2014;**14**:6–13.

ABSTRACT

Although there has been unequivocal progress in the development of treatments for multiple sclerosis over the last 20 years, currently licensed treatments have demonstrated convincing effects on disease course only with reference to relapse frequency. This review summarises the progress made, highlights the indications for, and limitations of, current disease-modifying therapies and discusses some interventions currently in development.

INTRODUCTION

Over the last 20 years, there has been a sea change in the range of options for consideration as disease-modifying treatments for multiple sclerosis (MS). While falling far short of the long-awaited cure, the first disease modifying drugs (interferons (IFNs) and glatiramer acetate (GA)), together with fingolimod (the first tablet licensed for MS), are important 'firsts'. However, with choice comes the need for discrimination: we must weigh the relative safety of IFNs and GA against the practical advantages of an oral agent (fingolimod), and the higher risk but greater clinical effectiveness of newer 'biological' agents, such as natalizumab and alemtuzumab. The clinical dilemma is compounded by our inability to predict accurately which patients stand to gain the most from aggressive treatment early in the disease course while appreciating that, if effective treatment is not started before there is significant axonal loss, the prospect of recovery—or even disease stability—is poor. This concern is reinforced by the failure of any currently licensed therapy to alter convincingly the course of established progressive disease, be that primary or secondary progressive MS.

The treatment strategies for relapsing–remitting disease that have significantly reduced relapse frequency are mostly immunomodulatory. While not denying the importance of inflammation to MS pathophysiology, the greater appreciation of the importance of axonal loss and reduced emphasis on the contribution of relapses to the accrual of disability[1 2] has shifted attention to the development of neuroreparative and neuroprotective therapies. It remains controversial whether immunomodulatory approaches alone can prevent axonal loss.[3–5] Given that many potential modes of action may be exploited, cellular therapy may have particular advantages, although the challenges of clinical translation are acknowledged.[6–8]

This article reviews disease modifying therapies for MS that are either licensed or in the later stages of development, with a particular focus on the rationale behind their use, the evidence basis for their efficacy and the practicalities of clinical application (tables 1 and 2). Therapeutic interventions in the earlier stages of development[9] and symptomatic therapies[10] have been recently reviewed elsewhere.

DISEASE-MODIFYING THERAPIES FOR MS WITH A POSITIVE OPINION FOR MARKETING APPROVAL FROM UK AND/OR US REGULATORY AUTHORITIES

Several drugs now have favourable marketing authorisation from the European Marketing Agency (EMA), although some of these await formal approval by the European Commission (EU) at the time of writing (July 2013). Mitoxantrone does not have EMA approval but has been approved by the US Food and Drug Administration (FDA).

IFNs and glatiramer acetate

IFN-β and GA were the first disease modifying therapies to be licensed for MS. The widespread uptake of these drugs over the last 15–20 years, combined with monitoring schemes designed

Table 1 Disease modifying therapies for MS with a positive opinion regarding marketing authorisation from the European Marketing Agency (EMA)

Drug	Registered trade name	Date of current EU marketing licence	Approved indication	NICE approval	Administration	Most common or serious side effects
Interferon-β 1a	Rebif	4 May 1998	Relapsing–remitting MS	No	sc x3 per week	Hypersensitity reactions, mood disturbance, liver toxicity, blood disorders, thyroid disease, 'flu-like symptoms and injection site reactions including lipodystrophy. Neutralising antibodies may develop in up to one-third patients
Interferon-β 1a	Avonex	13 March 1997	Relapsing–remitting MS or a single demyelinating event with an active inflammatory process (severe enough to warrant iv corticosteroid and patient is at high risk of developing MS)	No	im weekly	
Interferon-β 1b	Extavia	20 May 2008	Relapsing–remitting MS or progressive MS with active disease or for a single demyelinating event with an active inflammatory process (if severe enough to require iv corticosteroid and patient at high risk for developing MS)	No	sc alternate days	
Interferon-β 1b	Betaferon/ Betaseron	30 November 1995	Relapsing–remitting MS or progressive MS with active disease or for a single demyelinating event with an active inflammatory process (if severe enough to require iv corticosteroid and patient at high risk for developing MS)	No	sc alternate days	
Glatiramer acetate	Copaxone	23 December 1996	UK Initial symptoms in patients at high risk of developing MS and reducing the frequency of relapses in ambulatory patients with relapsing–remitting MS with at least 2 clinical relapses in the past 2 years	No	sc daily	Hypersensitity reactions, mood disturbance, flu-like symptoms, injection site reactions including lipodystrophy
Natalizumab	Tysabri	27 June 2006	UK Highly active relapsing–remitting MS despite treatment with interferon β or rapidly evolving severe relapsing–remitting MS	Yes	iv every 4 weeks	Risk of PML increases after 2 years of therapy. Hypersensitivity reactions and liver toxicity
Fingolimod	Gilenya	17 March 2011	UK Highly active relapsing–remitting MS despite treatment with interferon β or in those with rapidly evolving severe relapsing–remitting MS	Yes	po x1/day	AV block, mood disturbance, headache, nasopharyngitis, fatigue, lymphopenia, liver abnormalities, dyspnoea and macular oedema. Herpes viral infections. Possible increased risk of lymphoma and other malignancies
Dimethyl fumarate	Tecfidera	Awaited following recommendation for approval from EMA 21 March 2013	Adults with relapsing–remitting MS	Not yet known	po x2–3/day	Flushing, gastrointestinal upset, lymphopenia, elevated liver enzymes
Teriflunomide	Aubagio	Awaited following recommendation for approval from EMA 21 March 2013	Adults with relapsing–remitting MS	Not yet known	po x1/day	Upper respiratory tract infections, urinary tract infections, diarrhoea, nausea, paraesthesia, alopecia and increase in the liver enzyme alanine aminotransferase. Possible teratogenetic effect with the potential for on-going effects postcessation of therapy
Alemtuzuamab	Lemtrada	Awaited following recommendation for approval from EMA 27 June 2013	Adults with relapsing–remitting MS, with active disease defined by clinical or imaging features	Not yet known	iv 12 mg daily for 5 days with further 3-day course >1 year later	Infusion reactions, lymphopenia, autoimmune disease including ITP and thyroid disease, infection

Definition of relapsing–remitting MS for the purposes of drug licensing in the UK: patient has demyelinating disease with at least two attacks over the previous 2–3 years and who is able to walk unaided.
AV, atrioventricular; im, intramuscularly; ITP, idiopathic thrombocytopenic purpura; iv, intravenously; MS, multiple sclerosis; NICE, National Institute for Health and Care Excellence; PML, progressive multifocal leucoencephalopathy; po, oral; sc, subcutaneously.

Table 2 Mechanism of action and evidence basis for currently available disease modifying therapies and those undergoing regulatory review

Drug	Summary of clinical effect	Selected clinical trials	Proposed mechanism of action	Selected on-going clinical trials
IFNs and glatiramer	Reduce relapse frequency by approximately one-third	Comparison of IFN-B and GA REGARD[11] BEYOND[12]	Unknown but biological effects include altered expression of numerous IFN-induced gene products and markers eg, MHC Class I, Mx protein, 2′/5′-oligoadenylate synthetase, β2-microglobulin, and neopterin	Efficacy and safety of PEGylated IFN-B1a (NCT01337427, NCT01332019, NCT00906399)
Natalizumab	Reduced relapse frequency by 68%	AFFIRM[13] SENTINEL[14] (Risk of PML with β-IFN cotreatment)	α4-integrin blocker; blocks migration of leucocytes into the CNS	INFORMS—phase 3 trial in PPMS (NCT00731692)
Fingolimod	Up to 60% reduction in ARR	FREEDOMS[15] Comparison with IFN-B TRANSFORMS[16 17]	Sphingosine-1-phosphate (S1P) receptor blocker; retains T and B cells in secondary lymphoid tissue	Longer-term safety and efficacy study in RRMS (NCT00670449) INFORMS efficacy in PPMS (NCT00731692)
Dimethyl fumarate	Reduction in ARR against placebo (44–53%)	DEFINE placebo-controlled phase 3 CONFIRM Phase 3 study vs placebo and including GA as reference comparator	Activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway	Longer-term safety and efficacy study in RRMS (NCT00835770)
Teriflunomide	Approximately 30% reduction in ARR	TEMSO[18] Safety study of cotreatment with IFN-B1a[19]	Metabolite inhibits mitochondrial dihydroorate dehydrogenase with subsequent inhibition of proliferation and effector functions of B and T cells	TOWER—phase 3 vs placebo (NCT00751881) Comparison with IFN-B1a (NCT00883337) Efficacy of cotreatment with IFNB1a (NCT01252355) TOPIC—phase 3, efficacy in clinically isolated syndrome (NCT00622700) TENERE—phase 3, comparison with IFN-B1a (NCT00883337) TERACLES—phase 3 cotreatment with IFN-B vs IFN-B and placebo (NCT01252355)
Alemtuzumab	55% improvement in number of patients relapsing over a 2-year period when compared against IFN-1Ba	CAMMS223[20] Phase 2 study vs IFN-B1a CARE-MS I phase 3 study as 1st line vs IFN-1Ba[21] CARE-MS II phase 3 study following 1st-line failure[22]	Lymphocyte depletion with possible neurotrophic effects	Longer term extension studies in progress

ARR, annualised relapse rate; GA, glatiramer acetate; IFN, Interferon; PML, progressive multifocal leucoencephalopathy; PPMS, primary progressive MS; RRMS, relapsing-remitting MS.

to assess their efficacy in clinical practice (such as the UK risk-sharing scheme[23]) confirmed that they reduce relapse rates by approximately one-third and are safe when administered appropriately.[24–26] Many of the actions of these drugs are known and include altered expression of numerous IFN-induced gene products and markers, such as MHC Class I, Mx protein, 2′/5′-oligoadenylate synthetase, β2-microglobulin and neopterin, but the mechanism(s) underlying their clinical effects have not been definitively established.

The delivery of IFNs and glatiramer is either by intramuscular or subcutaneous injection and all can be associated with injection-site reactions and, in the longer term, by lipodystrophy. On-going clinical trials of PEG-ylated IFN-β1a are examining whether this longer-acting formulation is safe and effective (NCT01337427, NCT01332019, NCT00906399). Systemic 'flu-like symptoms are common but are frequently managed conservatively and, although they may impact negatively upon compliance, do not always necessitate drug withdrawal. Less frequent but more significant adverse reactions include drug hypersensitivity, blood and marrow abnormalities and thyroid and liver dysfunction. Mood disorders, particularly depression, may be a limiting adverse effect. One-third of patients may develop neutralising antibodies to IFNβ; they predict a poor therapeutic effect.[27] Regular follow-up and monitoring blood tests are essential between 1 and 3 months after starting treatment, then three-monthly for the first year and six-monthly thereafter.

Despite initial optimism, the longer-term impact of IFNs or GA on progressive disability is disappointing.[28–30] Combination therapy (IFN and GA, or IFN with azathioprine and corticosteroids) does not benefit clinical disability over 2–3 years' follow-up.[31 32]

Most neurologists recommend stopping IFN or GA when pregnancy is considered or confirmed, due to inadequate and sometimes conflicting data. Overall however, there is little evidence for significantly increased risk to mother or fetus from early exposure to GA. IFN-β therapy is associated with lower birth weight, shorter mean length and preterm (<37 weeks) delivery, but preclinical data suggesting increased fetal death rates have not been confirmed.

Fingolimod

Fingolimod (FTY720; Gilenya) was the first oral agent licensed in the USA and Europe for monotherapy treatment of relapsing–remitting MS (RRMS). Subsequently, English clinical guidelines recommended it only as a second-line therapy following IFN failure,[33] and it is currently not recommended in Scotland.[34] Fingolimod is phosphorylated by sphingosine kinase 2 and mimics sphingosine 1-phosphate binding to lymphocytes, preventing migration of CD4 and CD8 T cells and B cells from secondary lymphoid tissue.[35 36] Furthermore, it may have neuroprotective or reparative effects.[37] There is a trial in progress examining its effect in primary progressive MS (PPMS) (INFORMS; NCT00731692).

Fingolimod use is evolving, but there are significant safety concerns, including sudden unexpected death.[38 39] Guidance has recently been updated regarding the associated cardiovascular risks; in the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has increased the recommended level of cardiovascular monitoring following the first dose of fingolimod, given the risk of transient heart block and bradycardia, and advise avoiding it in patients with cardiovascular risk factors.[40] There may also be adverse effects following its reintroduction after previously stopping treatment. All patients must have a baseline ECG before starting treatment and have subsequent cardiovascular monitoring (box). Other practical issues include checking the full blood count and liver function tests, possibly with on-going monitoring. Patients with no definite history of chicken pox should have their varicella zoster serology checked. An ophthalmological review or optical coherence tomography (to exclude macular oedema) should be performed before starting treatment and every 3–4 months while on treatment. Furthermore, there is a possibility of 'rebound' disease activity after

Box 1 Updated advice (January 2013) from the MHRA regarding cardiovascular monitoring when starting fingolimod (Gilenya™)

- All patients should be monitored before, during, and immediately after the first 6 hours of treatment.
- If the patient's heart rate decreases to its lowest point at the end of the 6-hour treatment period, monitoring should be extended until heart rate increases.
- Monitoring should also be extended at least overnight if there is significant atrio–ventricular block, bradycardia, or QTc prolongation.

Treatment interruption:

The same first-dose monitoring as for treatment initiation* should be repeated if treatment is interrupted as follows:

- 1 day or more during the first 2 weeks of treatment.
- more than 7 days during weeks 3 and 4 of treatment.
- more than 2 weeks after one month of treatment.

Following pharmacological intervention to treat bradyarrhythmia-related symptoms after first dose:

*As per current recommendations, patients requiring pharmacological intervention during the first dose monitoring should be monitored overnight in a medical facility.

In these patients, it is now recommended to repeat the first-dose monitoring* after the second dose of fingolimod.

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stopping fingolimod; this requires on-going vigilance.[41]

There is little information on its use in pregnancy but animal studies suggest potential teratogenicity and embryo death. The EMA and the FDA have issued warnings regarding the need for effective contraception while taking fingolimod; current advice is to avoid conception while taking the drug, and for 2 months after stopping it.

Natalizumab

Natalizumab (Tysabri) is a humanised monoclonal antibody (IgG4κ) targeting α4β1-integrin. It inhibits the leucocytes migration across the blood–brain barrier by blocking the interaction between α4-integrin on leucocytes and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells; other CNS ligands, such as fibronectin and osteopontin, may also be important.[42–44]

The AFFRIM trial (NCT00027300) reported a reduced relapse rate of 68% with 42% less progression of disability at 2 years.[13] The effect on long-term disability remains unclear; a large study examining the effect of natalizumab in secondary progressive disease is in progress (NCT01416181).

Natalizumab was initially approved as an intravenous infusion once every 4 weeks for treating RRMS in the USA in 2004. However, it was subsequently voluntarily withdrawn in 2005, after recognising the association between combination therapy with IFN-β and natalizumab, and the development of progressive multifocal leucoencephalopathy (PML).[14] PML is a life-threatening condition most often seen in immunosuppressed patients as a consequence of JC virus infection; there is no effective treatment other than immune reconstitution. The development of a surveillance programme enabled the reintroduction of Tysabri in 2006, and safety has been further improved via the development of treatment protocols employing plasma exchange to reduce natalizumab saturation of α4-integrin receptors and corticosteroids to reduce the risk of immune reconstitution inflammatory syndrome, together with refinement of risk stratification algorithms and the availability of screening for JC virus antibodies using a two-step ELISA test. However, it has become apparent that, while cotreatment with IFNs remains a contraindication, there is a significant risk of PML with natalizumab monotherapy in people who are JC virus positive. The risk rises with increasing duration of therapy (0.6 per 1000 <2 years; 5 per 1000 2–4 years), particularly if there is a prior history of immunosuppression (1.6 per 1000 <2 years; 11 per 1000 at 2–4 years).[45] In the light of this, clinicians must carefully discuss the potential risks and benefits with the patient, with regular re-evaluation, particularly with treatment duration approaching or beyond 2 years.

There are concerns regarding 'rebound' increases in disease activity after stopping natalizumab, though this was not observed in the large cohort of patients who stopped therapy when the drug was withdrawn in 2005.[46] It is currently unknown which, if any, treatment should replace natalizumab if it is stopped; although the RESTORE study (NCT01071083) attempts to address this, it does not include oral agents.

The development of neutralising antibodies to natalizumab is a potential problem and may occur in ~6% patients. Their presence has been associated with reduced drug efficacy and persistent infusion reactions.[47]

The limited data on natalizumab safety in pregnancy do not suggest an increased risk of adverse outcome.[48–51]

Dimethyl fumarate

Dimethyl fumarate (BG-12; Tecfidera) is a fumaric acid ester which was first licensed in Germany for treating psoriasis in 1990 (Fumaderm), although its use dates back to the 1950s.[52] There have been over 150 000 patient years of treatment and this has increased confidence in its relative safety. A cautionary note is sounded, however, given the recent publication of a few case reports detailing the occurrence of PML associated with dimethyl fumarate treatment (although none have been reported in those treated for MS).[53–55] Risk factors appear to be prolonged lymphopenia and recent or co-treatment with other immunomodulatory agents.

The mechanism of action of BG-12 in MS has not been definitively established, but it is thought likely to have anti-inflammatory, antioxidant and neuroprotective actions. It can activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway which alters the expression of multiple genes with the downstream effect of reducing oxidative stress.[56–59] It also suppresses nuclear factor κB-dependent transcription with consequent preferential expression of chemokines and cytokines in an anti-inflammatory profile.[60 61]

The EMA and the FDA approved Tecfidera for marketing in March 2013. This followed two phase 3 trials in 2012 comparing dimethyl fumarate with placebo in treating RRMS,[62 63] one of which included GA as a reference comparator.[63] The trials reported a relative reduction in annualised relapse rate of 44–53% against placebo and, although not designed to assess superiority or non-inferiority against GA, posthoc analysis showed a lower annualised relapse rate and fewer changes on MRI as secondary outcome measures. Adverse effects included flushing (with the potential to adversely affect blinding), gastrointestinal upset, lymphopenia and elevated liver enzymes.

Although there are no data on its teratogenicity in MS, its use in treating psoriasis has not pointed towards a toxic effect.

The EU is likely to approve dimethyl fumarate, following the favourable EMA recommendations, and a review by the UK National Institute for Health and Care Excellence (NICE) is already underway. Its oral availability and relatively favourable risk-benefit profile mean that dimethyl fumarate may be a realistic first-line treatment option for RRMS.

Teriflunomide

Teriflunomide (L04AA31, Aubagio) is a selective immunosuppressant with anti-inflammatory properties. It is the active ring malononitrile metabolite of leflunomide, a prodrug used for rheumatoid arthritis (Arava).[64] The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but it reduces lymphocytes proliferation by blocking the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH). This enzyme is the rate-limiting step in de novo synthesis of pyrimidine, and is necessary for the proliferation and effector functions of activated T and B cells.[65 66] Alternative modes of action may include reduced IFN-γ and interleukin-10 production by T cells, interference in the interaction between T cells and antigen-presenting cells, and changes in integrin signalling during T cell activation,[67] as well as possible antioxidant effects.[68]

The phase 3 TEMSO trial examined whether 7 mg/day and 14 mg/day teriflunomide were effective compared with placebo, and showed reduced annualised relapse rate with both doses of 31%.[18] Over the 2-year study period, there was reduced progression with the 14 mg dose only. Initial results from the on-going TENERE study, comparing teriflunomide with IFB-β1a, suggest relatively little additional advantage from teriflunomide over the original disease-modifying therapies, beyond the convenience of oral availability (data from ClinicalTrials.gov). Phase II studies of teriflunomide adjunctive therapy with IFB-β (NCT00489489) and GA (NCT00475865) have shown fewer enhancing lesions on MRI scans although this was significant only when compared against IFN-β alone (data from ClinicalTrials.gov). The phase 3 TERACLES study is currently comparing relapse frequency in patients on cotreatment with IFN-β and teriflunomide against that in patients treated with IFN-β and placebo (NCT01252355).

The EMA approved teriflunomide for marketing in Europe in March 2013 and it already has FDA approval (September 2012), although the latter includes a 'boxed warning' regarding possible hepatotoxicity. Other potential side effects include nausea, diarrhoea, alopecia, neutropenia, skin rashes, weight loss and hypertension.[18] Notably however, leflunomide (a teriflunomide pro-drug used for rheumatoid arthritis), in addition to hepatotoxicity, increases the risk of interstitial lung disease in patients with rheumatoid arthritis and coexistent pulmonary disease, or those who have previously received methotrexate.[69]

Leflunomide is a known teratogen and the effects may persist for many months after stopping treatment, due to its long half-life in the enterohepatic circulation. Cholestyramine may help reduce this. Although a retrospective analysis of a trial database (n=43) showed no increased risk in pregnancy with teriflunomide,[70] it carries the highest-risk FDA warning (category X) after animal studies showed an association with fetal death and malformation. A negative pregnancy test is therefore required before starting the drug and effective contraception must be advised. Terifluonamide is also excreted in semen, and men who wish to father a child should stop the drug with an accelerated washout procedure.

Mitoxantrone

Mitoxantrone (Novantrone) is a chemotherapeutic agent which has been given FDA approval for use in aggressive RRMS, secondary progressive multiple sclerosis (SPMS) and relapsing progressive MS. Its mechanism of action is probably multifactorial, including inhibition of B cell, T cell and macrophage proliferation.[71] It is given as an intravenous infusion, four times per year (12 mg/m^2) with a maximum cumulative lifetime dose of 100–140 mg/m^2. Several highly significant issues have emerged, mostly pertaining to cardiac toxicity (number needed to harm (NNH)=8) and leukaemia (NNH=123), which in postmarketing use appeared to occur at higher rates and with lower (<100 mg/m^2) cumulative doses.[72] A 'black box' warning regarding these safety issues was issued in 2005. It is mandatory to measure left ventricular ejection fraction (LVEF) at baseline and before each infusion. Mitoxantrone should not be used if the LVEF is <50% or if there is a clinically significant drop in LVEF during treatment. The recommendation by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology that the original phase 3 trial[73] should be replicated has not been fulfilled[72] and, in view of the adverse safety profile of the drug and availability of alternative agents, it is unlikely to be widely used for the treatment of RRMS, and its use in SPMS restricted to those with unusually rapid rates of progression.[74]

Alemtuzumab

Alemtuzumab was the first humanised monoclonal antibody to be produced (CAMPATH-1H). It targets the surface antigen CD52 expressed on lymphocytes and monocytes and causes rapid and profound lymphopenia. Lymphocyte numbers do recover, although the time course over which this occurs varies and is subset dependent; CD4-positive T cells are particularly slow and it may be many years before their circulating levels approach those seen before a single 5-day course of intravenous alemtuzumab treatment.[75–77]

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Early recovery of CD4-positive cells may be a marker of relapse.[78] Additionally, alemtuzumab may have neuroprotective effects secondary to increased delivery of trophic factors.[79] Its current European marketing license is for treating chronic lymphocytic leukaemia, but an application for marketing approval for alemtuzumab (Lemtrada) in the treatment of MS was accepted for review by EMA in July 2012 and by FDA in January 2013. A favourable opinion regarding marketing authorisation for the treatment of active RRMS was issued by EMA in June 2013 and EC approval is expected imminently.

A phase 2 clinical trial examined the effect of alemtuzumab when compared with IFN-β1a in patients with early, relapsing–remitting disease (CAMMS223).[20] This randomised and blinded trial reported a reduced risk of relapse and sustained accumulation of disability of >70% when compared with IFN-β1a. However, widespread uptake of the drug was limited by its propensity to induce other autoimmune diseases—including idiopathic thrombocytopenic purpura (ITP) (1–2%) and Graves' disease (20–30%).[21 22 80 81] If there is appropriate monitoring and prompt treatment, alemtuzumab-induced autoimmunity is relatively amenable to treatment, and strategies are being developed to identify those most at risk and to minimise the impact of alemtuzumab-induced autoimmune disease.[80 82 83] An example is an on-going trial of coadministration of keratinocyte growth factor which promotes thymic T cell regeneration (CAM-THY, NCT01712945). Although infections occur more frequently in patients treated with alemtuzumab, serious infections are relatively rare.

In the most recent phase 3 trials, alemtuzumab was administered as a daily intravenous infusion (12 mg) for 5 days, with a second 3-day cycle 1 year later. Although infusion reactions do occur, these can be managed with corticosteroids, antipyretics and antihistamines. The role of additional cycles of alemtuzumab therapy is currently unclear, but there is an imperative for frequent and regular blood monitoring for the emergence of autoimmune disease (particularly ITP and thyroid dysfunction) for a minimum of several years after treatment.

There have been two recent phase 3 trials of alemtuzumab in treating RRMS. One directly compared alemtuzumab with IFN-1βa as first-line therapy for RRMS (CARE-MS I)[21], and the second examined the effect of alemtuzumab in those who had already failed first-line treatment with IFN-1β or GA (CARE-MS II).[22] These studies confirmed that alemtuzumab reduces relapse frequency, although the previously reported effect on sustained disability accumulation was not observed in CARE-MS I.[21] However, the IFN-1βa-treated patients in this trial showed an unexpectedly low rate of disability progression, causing the trial to be underpowered. Longer-term outcome data from the phase 2 study[84] and early analysis of the longer-term follow-up data in the CARE-MS studies suggest that the beneficial effects of alemtuzumab infusion persist.[85]

Alemtuzumab is not recommended for those wishing to conceive, and carries an EMA category 1 warning based on reported cases where alemtuzumab was suspected to contribute to congenital malformation. The duration of this effect is unclear and there are reported successful pregnancies after alemtuzumab treatment.

▶ **For details of other drugs in development please see online supplementary files.**

SELECTED AGENTS NO LONGER IN DEVELOPMENT

Lamotrigine

The use of the sodium-channel blocker, lamotrigine, as a treatment for secondary progressive MS was examined in a trial employing reduction in rates of brain atrophy as the primary outcome measure.[129] However, despite its neuroprotective properties in models of disease, lamotrigine was associated with enhanced rates of volume loss, and was rather poorly tolerated.

Cladribine

Cladribine (2 chloro-2′ deoxyadenosine) is an analogue of adenosine, and intravenous infusion is licensed for the treatment of some leukaemias and lymphomas. It is a known teratogen and is a pro-drug which is activated by deoxycytidine kinase, degraded by deoxynucleotidase and is resistant to adenosine deaminase. Cladribine is preferentially activated in lymphocytes due to their relatively high levels of deoxycytidine kinase and low levels of deoxynucleotidase.[130] Activated cladribine disrupts DNA synthesis and repair in dividing lymphocytes with consequent depletion of lymphocytes.

A phase 3, 96-week clinical trial of cladribine administered as two short oral courses repeated after 1 year (CLARITY) showed a reduction of annualised relapse rate of ~55% with a more moderate effect on sustained progression. However, in addition to the expected side effects of lymphopenia, there was also suppression of neutrophils and myeloid lineage cells along with an increased frequency of herpes zoster infection and malignancies. On the basis of safety concerns, the oral preparation of cladribine was rejected for marketing approval for the treatment of MS in the USA and the EU and, although it did receive a license in Australia and Russia it has been withdrawn from the market by the manufacturer. A prospective, observational, long-term safety registry for those who were treated has been established (PREMIERE; NCT01013350).

Antitumour necrosis factor agents

Early trials of antitumour necrosis factor (TNF) agents were associated with an increase in disease activity and subsequent reports of demyelinating disease emerging on anti-TNF treatment have emerged.[131–134] This finding has been linked to genome-wide association studies which have identified a single nucleotide polymorphism in the TNF receptor 1 (TNFR1) which is associated with MS and results in expression of a novel form of soluble TNF receptor which, in turn, causes downstream blockade of TNF signalling.[135]

Ustekinumab

Based on preclinical data supporting a role for IL-12/23 in EAE, ustekinumab, the human monoclonal antibody directed against IL-12/23 p40, was predicted to be effective in MS. Such an effect was not demonstrated in a phase 2 clinical trial versus placebo in RRMS,[136] and the drug is no longer in development as a treatment for MS.

Atacicept

Atacicept is a human recombinant fusion protein which inactivates B-cell activating factor (BAFF, CD257) and A PRoliferation-Inducing Ligand (APRIL, CD256) which regulate B-cell function. A phase 2 study of atacicept in RRMS (ATAMS; NCT00642902) and in optic neuritis as a CIS (ATON; NCT00624468) were both terminated early due to an increase in disease activity in the treatment groups.

CONCLUSIONS

For those with progressive disease there is, at present, on-going reliance on symptomatic therapy, but there is cause for optimism given the renewed focus on research in progressive MS, and the development of multimodal disease-modifying strategies.

While the novelty of having a selection of MS disease-modifying agents to choose from for those with RRMS undoubtedly represents progress, it is likely that logistical and practical issues, as well as safety concerns, will continue to make the choice a highly individualised one, necessitating a high degree of involvement of the patients themselves. In particular, method of drug delivery, comorbidity, fertility and family planning issues, susceptibility to other autoimmune diseases and compliance with long-term drug monitoring, as well as an understanding of the balance of risks and benefits involved will be of particular importance.

As the risks of treatment are more clearly delineated and strategies evolve to minimise them, it would seem inevitable that there will be a drive to institute therapy early in the disease course with the aim of reducing the likelihood of progressive disease. While this may be true for some agents, it may not apply to all, and risks of treatment, particularly with new biological agents, must be carefully evaluated. Trials which demonstrate unexpected, detrimental effects despite a well-justified treatment rationale based on preclinical data are particularly important. Caution must also be exercised given the known caveats of clinical trial data in general and with specific regard to MS, particularly the relatively short duration of follow-up, insensitivities of clinical rating scales and use of surrogate, paraclinical markers of disease activity. Improved mechanisms of detecting those most at risk of future progressive disease and biomarkers to predict response to therapies are eagerly awaited and would be of great value in guiding appropriate patient selection for aggressive treatments so as to maximise benefit while protecting those with benign disease who stand to gain little.

Acknowledgements CMR thanks Professor Neil Scolding for his comments on the manuscript. CMR gratefully acknowledges the support of the National Institute for Health Research and the Burden Neurological Institute.

Competing interests CMR was the beneficiary of an Ipsen Clinical Research Fellowship (2003/4) but has otherwise received no funding, honoraria or grant support from pharmaceutical companies.

Provenance and peer review Commissioned; externally peer reviewed. This paper was reviewed by Chris Allen, Cambridge, UK.

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