Established, new and future disease modifying therapies for MS

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Over recent years the pace of therapeutic development in multiple sclerosis has increased, and there are now 10 disease-modifying therapies available. In this review the authors discuss the evidence supporting the use of these drugs and consider which new treatments may be available in the future.

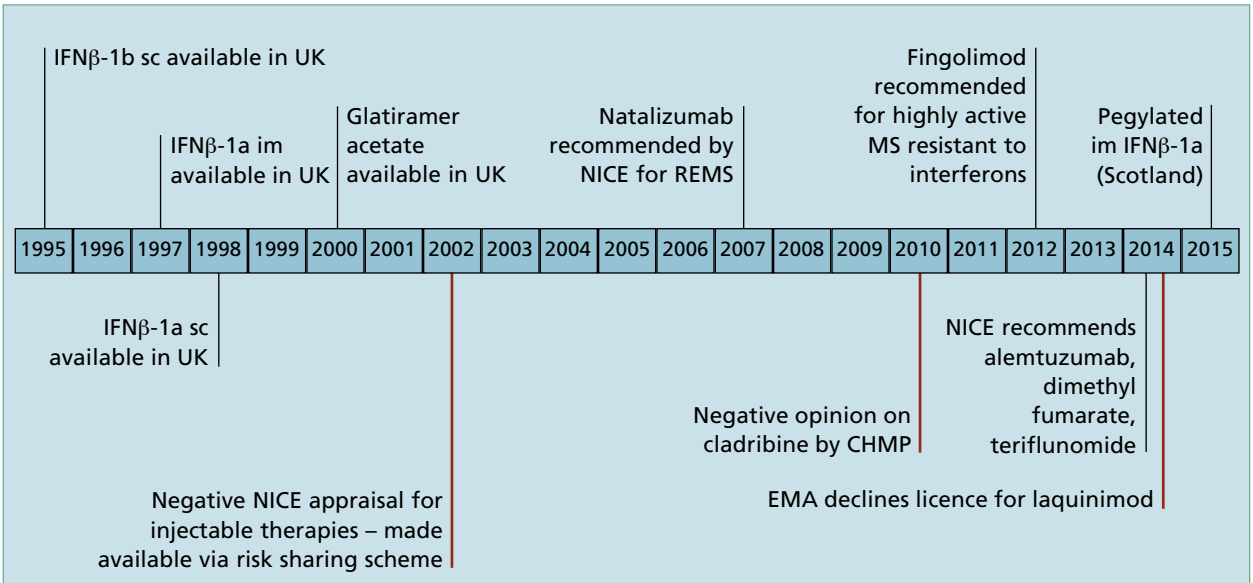
Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), experienced by patients as discrete episodes of neurological dysfunction (relapses). The initial inflammatory events are thought to trigger a second, neurodegenerative phase with irreversible axonal loss; clinically evident as progressive neurological disability.[1] Immunomodulation with disease modifying therapy (DMT) aims to suppress relapses, attenuating or even preventing accrual of disability in the longer term.

Over recent years the pace of therapeutic development has quickened (Figure 1); in the UK there are now 10 DMT options including oral and infusion therapies with a range of efficacies and side effects. Thus, the focus is on achieving an individualised approach incorporating patient preference and balancing disease activity against risk-benefit ratio of licensed agents. Early disease suppression is important: lesion load acquisition within the first five years correlates with accumulation of disability at 14 years, and to disability and conversion to secondary progressive MS at 20 years.[2,3]

In this article, we review both current DMTs and those in development. Most are indicated in relapsing forms of MS (Figure 2) with evidence for reduction of relapse rate and short-term development of disability. Data for effect on long-term progression of disease are less established, and there remains an unmet need for therapies with impact in progressive MS.[1,4]

Prescribing guidelines

Guidelines for use of DMTs in MS have been issued by the Association of British Neurologists (ABN) (2009, recently updated in 2015).[5,6] These therapies are also



CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; NICE: National Institute for Health and Care Excellence; REMS: Rapidly Evolving Severe MS

Figure 1. Milestones in DMT development and availability in the UK

subject to assessment by NICE prior to acceptance into routine practice.[7] Due to debate over long-term efficacy and cost-effectiveness, many are available only under a risk sharing or patient access discount scheme.[7]

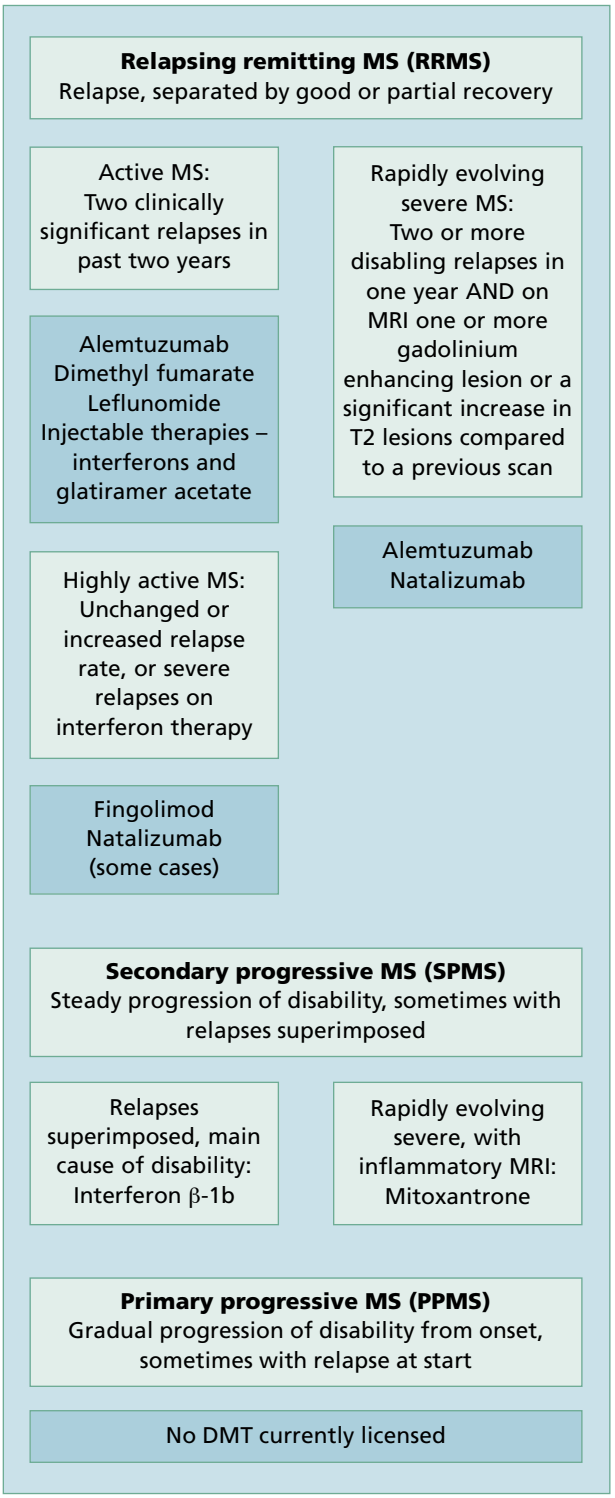


Figure 2. Indications of available DMTs

First-line injectable therapies

Four injectable therapies (three types of interferon-beta and glatiramer acetate) were launched from 1995–2000 and represent the first DMTs to enter clinical practice. They are recommended by the ABN for active relapsing-remitting (RRMS) MS, but not deemed cost-effective by NICE.[5,8] The 2009 ABN guidelines advise interferon β-1b may be used in secondary progressive (SPMS) MS with relapses, if relapses are judged primarily responsible for disability accumulation.[5]

Interferon β-1b given subcutaneously on alternate days (Betaferon, Extavia) is complemented by two formulations of interferon β-1a: Rebif is given subcutaneously three times a week in low (22μg) or high (44μg) dose, and Avonex by the intramuscular route once weekly. Interferons achieve a reduction in relapse rate of 27% to 34% (subcutaneous) and 18% (intramuscular, intention to treat population).[9-12] Neutralising antibodies may develop in some individuals, which may adversely affect clinical efficacy.[5,12] Key side-effects include injection site reactions, flu-like symptoms, elevated liver enzymes and suicidal ideation, hence interferons should be avoided in severely depressed patients.[12] A very rare but potentially fatal complication of high-dose subcutaneous interferon β-1a is thrombotic microangiopathy, presenting with acute kidney injury with an identifiable prodrome of hypertension and impaired renal function.[13] As well as a full blood count, renal and liver function, protein electrophoresis should be performed prior to initiating therapy; the presence of an undiagnosed monoclonal gammopathy is associated with systemic capillary leak syndrome.[5] However, serious and life-threatening adverse effects are rare, and one of the advantages of the injectables is a predictable and lengthy safety record.[4,6,14] Glatiramer acetate (Copaxone), given as a daily subcutaneous injection, is an alternative to interferons, achieving a comparable (29%) reduction in relapse rate.[15] The precise mechanism of action remains unknown.[16] Patients can experience an unpleasant post-administration phenomenon mimicking cardiac ischaemia, however, depressive, injection site and flu-like reactions are less common than with interferons.[12]

Biosimilars to both interferon and glatiramer are in development, but careful inspection of trial data will be required to verify equivalent safety and biological activity.[17] Other innovations include long-lasting formulations, such as pegylated intramuscular interferon, which can be given every two weeks.[18] These steps, aimed at improving cost-efficacy and patient convenience, may extend clinical utility of these first-line injectables.

First-line oral therapies

Teriflunomide (Aubagio) is a metabolite of leflunomide, a long-established DMT in rheumatoid arthritis. It is thought to inhibit dihydro-orotate-dehydrogenase, an enzyme necessary for pyrimidine synthesis in actively dividing cells.[19] Phase III trials confirmed a relative reduction in annualised relapse rate (ARR) of 31.5–36.3%, and of progression of disability of 29.8–31.5% compared with placebo.[20-21] At the UK licensed dose of 14mg once daily, teriflunomide has an acceptable side-effect profile which, with its efficacy, places it alongside the injectable therapies. Teriflunomide is approved by NICE for active, but not highly active or rapidly evolving severe MS.[22] Common side-effects include hair thinning, which is usually transient, and elevated liver enzymes.[19-21,23] Liver function tests, as well as a full blood count and blood pressure, should be monitored during treatment.[19] Teriflunomide is strictly contraindicated in pregnancy and a negative pregnancy test should be confirmed prior to commencement of therapy.[19,24] Due to teriflunomide's long half-life of 15-18 days, activated charcoal or cholestyramine is required to eliminate the drug in a reasonable time frame.[24]

Dimethyl fumarate The active ingredient of dimethyl fumarate (DMF, Tecfidera) has previously been used in treatments for psoriasis.[25] Two phase III trials, DEFINE and CONFIRM, demonstrated a relative reduction of ARR of 44–53% with twice-daily DMF 240mg compared with placebo, and so DMF is also approved by NICE for active relapsing MS.[26-28]

DMF is speculated to cross the blood / brain barrier and exert neuroprotective effects, potentially on myelin.[25,29] However, while the two pivotal trials (DEFINE and CONFIRM) demonstrated significantly fewer gadolinium-enhancing lesions, T2 lesions and T1 hypointense lesions in DMF twice daily compared with placebo, DMF does not significantly reduce brain atrophy,[30] and the 38% relative reduction in sustained disability in the DEFINE trial was not replicated by CONFIRM.[26-27]

A troublesome side-effect is gastrointestinal disturbance and flushing. This usually abates, and can be eased by taking with food and gradual up-titration of dose.[25,29] Monitoring requirements include a full blood count six–eight weekly, as cases of progressive multifocal leucoencephalopathy (PML) have been linked to prolonged lymphopaenia.[25,31-32] Nevertheless, PML, a potentially fatal demyelinating brain disease caused by reactivation and replication in oligodendrocytes of the JC virus, remains most recognised secondary to natalizumab (Tysabri) treatment.[33]

Second-line oral therapy

Fingolimod When approved by NICE in 2012, fingolimod (Gilenya) was the first oral MS therapy. It is approved in the UK for highly active relapsing-remitting disease which has not responded to interferons and is taken once daily at a dose of 0.5mg.[34] Fingolimod is an inactive prodrug but is phosphorylated and causes internalisation of S1P receptors, which are required for lymphocyte trafficking.[35-36] Lymphocytes remain in nodes and are restrained from sites of central nervous system (CNS) inflammation.[35] As fingolimod crosses the blood / brain barrier, a neuroprotective effect was hoped for via interaction with S1P receptors on glial cells and oligodendrocytes, but negative results from a study in primary progressive MS were recently announced.[36-38]

In phase III testing, fingolimod achieved 48-54% relative reduction in ARR in two placebo-controlled trials, and a 52% relative reduction in ARR compared with an active comparator, intramuscular interferon.[39-41] Two of the phase III trials did not show a significant impact on disability measures,[40-41] whereas in the FREEDOMS I placebo-controlled study, there was a 30% reduction in confirmed disability at 24 months and a 30% slowing in brain atrophy among fingolimod patients.[39] Set against these results is an active side-effect profile, which, as well as first dose bradycardia, includes first and second degree atrioventricular block, macular oedema, lymphophenia and infections.[39-41] Therefore ECG pre- and post-first dose is indicated.[14] Ophthalmologic monitoring is required during treatment and patients should have varicella immunity,[14] although a case of varicella encephalitis was recently reported in an immunised fingolimod patient.[42] To date, 3 cases of PML have been reported in patients using fingolimod; however a precise risk of this rare complication remains to be determined and clinicians should remain vigilant.[43]

Infusion therapies

Natalizumab was approved by NICE in 2007 for REMS (rapidly evolving severe RRMS) and is given as an IV infusion at 300mg every 28 days.[44] It is a monoclonal antibody to the $\alpha 4\beta 1$ integrin molecule on lymphocyte membranes. Through the interaction of this molecule with vascular cell adhesion molecule 1 (VCAM1), lymphocytes are able to attach to and penetrate the blood/brain barrier.[45] It follows that blocking this interaction reduces CNS inflammation.

Accordingly, the phase III AFFIRM trial found that, compared to placebo patients, those on Natalizumab had a relative reduction of 68% in relapse rate at one year and of 42% in the risk of

acquiring a permanent increase in disability at two years.[46] These clinical findings were supported by MRI data which at two years revealed the natalizumab group to benefit from a relative reduction of 92% in gadolinium-enhancing lesions and 83% in T2 lesions.[46] No head-to-head trial against a direct comparator was performed prior to licensing, but in 2012 a retrospective cohort study comparing natalizumab to IFNβ-1a 44μg concluded natalizumab was more effective on measures of ARR, disability progression and enhancing lesions.[47]

Efficacy of Natalizumab must be balanced alongside the risk of natalizumab-associated PML. More than 500 cases of natalizumab-associated PML,

DMT / UK launch year	Pivotal trials / study groups	Effect on relapse	Effect on disability	Key MRI findings
First-line injectables				
Interferon β-1b s/c (1995)	The IFNβ multiple sclerosis study group[9,83]	34% RR in relapse rate vs placebo at two years	No significant effect in pivotal trial	80% RR in patients with 'active scans' and 23% RR in 'disease burden' vs placebo
Interferon β-1a IM (1997)	The multiple sclerosis collaborative research group[11]	18% RR in relapse rate vs placebo (all patients)	37% RR in 104-week SAD vs placebo	52% RR gadolinium lesions vs placebo (borderline p=0.05); 40% RR total T2 lesion load, but intra-individual % change T2 lesions non-significant
Interferon β-1a s/c (1998)	PRISMS[10]	27% RR in relapse rate vs placebo (22μg), 33% RR for 44μg dose	Both doses reduced risk of disability as measured by time to sustained progression of disease	Reduces T2 lesion load vs. placebo; 67% RR (22μg) and 78% RR (44μg) in active T2 lesions vs. placebo
Glatiramer acetate (2000)	The copolymer 1 multiple sclerosis study group[15]	29% RR in relapse rate vs placebo	No difference in 90-day SAD	Not described in pivotal trial
First-line oral therapies				
Teriflunomide (2014) (at 14mg once daily)	TEMSO[20] TOWER[21] TOPIC (CIS patients)[23] TENERE (vs comparator)[84]	31.5% – 36.3% RR in relapse rate vs placebo Non-inferior in effect on relapse rate to IFN β-1a s/c 44μg	29.8% - 31.5% RR in 12-week SAD vs placebo	67.4% RR in total lesion load vs placebo in RRMS (TEMSO) No effect on brain atrophy in RRMS or CIS
Dimethyl fumarate (2014)	DEFINE[26] CONFIRM[27,30]	44%-53% RR in relapse rate vs placebo	38% RR in 12-week SAD vs placebo in DEFINE	71-85% RR in new / enlarging T2 lesions vs placebo No effect on brain atrophy
First-line infusion therapies				
Alemtuzumab (2014)	CARE-MS I[54] CARE-MS II[55]	49.4% (previously treated) – 54.9% (treatment naïve) RR in relapse rate compared to IFN β-1a s/c 44μg	42% RR in risk of 6-month SAD vs IFN β-1a s/c 44 μg in previously treated patients; also net benefit of 0.41 EDSS points in alemtuzumab group	Reduces new and enlarging T2 and gadolinium lesions vs IFN β-1a s/c 44μg 40% slowing of brain atrophy vs IFN β-1a s/c 44μg (naïve patients)

Abbreviations: CIS = clinically isolated syndrome; EDSS = Expanded disability status scale; IM = intramuscular; SAD = sustained accumulation of disability; s/c = subcutaneous; RR = relative reduction

Table 1: First-line DMTs at a glance

including 119 deaths,[48] have been reported. However, it is now known that risk can be stratified by three factors: prior immunosuppressant use, serological status for JC virus and duration of natalizumab use above 24 months.[33] Risk of PML is low (0.09 per 1000) if patients are negative for all three. A tool and patient app defining risk is available from: http://multiple-sclerosis-research.blogspot.com.[49] It is worth noting that most of the immunosuppressants implicated in PML development (methotrexate, azathioprine, cyclophosphamide and mycophenolate) are infrequently used in MS in the UK. Disease activity is known to recur relatively rapidly post-cessation of natalizumab, and fingolimod may be initiated after a suitable washout period if therapy switch is required due to increased PML risk (*eg* JC virus seroconversion).[50]

Alemtuzumab In May 2014 Alemtuzumab (Lemtrada) was granted a wide scope of use by NICE, which recommended it for use in active RRMS.[51] A humanised anti-CD52 monoclonal antibody, it works through pan-lymphocyte depletion and immune reconstitution with re-skewing of the immune repertoire.[52] It is given annually as an infusion of 12mg/day for five days in year one and three days in year two, with methylprednisolone given concurrently to alemtuzumab infusion.[52] Most patients require only two cycles for stabilisation of disease activity.[52]

Notably, phase II and phase III trials have all been performed against an active comparator, subcutaneous IFN β-1a 44μg. In the phase II CAMS223 trial, alemtuzumab 12mg at 36 months produced a 75% reduction in the risk of sustained disability and a 69% reduction in relapse compared with IFN β-1a 44μg.[53] Additionally, alemtuzumab patients demonstrated a 0.39 points improvement on the Expanded Disability Status Scale (EDSS) and increased brain volume.[53] Countering these results, enhanced pharmacovigilance was implemented after one patient died of a brain haemorrhage secondary to immune thrombocytopaenic purpura (ITP).[53]

Phase III trials confirmed a 49.4 (previously treated patients)-54.9% (treatment naïve individuals) reduction in ARR compared with IFNβ -1a 44μg.[54-55] In previously treated patients, there was also a 42% reduction in the risk of acquiring fixed disability.[55] Both trials found significant differences in favour of alemtuzumab in the number of new or enlarging T2 lesions, gadolinium enhancing lesions and the rate of brain atrophy.[54-55] Emerging four-year data from these trials have demonstrated 79.3% of treatment naïve and 67% of previously treated patients with stable or improved EDSS at four years.[56-57]

Alemtuzumab is associated with an infusion reaction, which can be managed by concurrent administration of steroid, antihistamine and antipyretic.[58] However, the principal side-effects are secondary

DMT / UK launch year	Pivotal trials / investigators	Effect on relapse	Effect on disability	Key MRI findings
Oral therapies				
Fingolimod	FREEDOMS[39] FREEDOMS II[40] TRANSFORMS[41]	48-54% RR in relapse rate vs. placebo; 52% RR in relapse rate vs Interferon β-1a IM	30% RR of confirmed disability over 24 months vs placebo (FREEDOMS trial)	Effective against inflammatory MRI changes; also 30% RR of brain atrophy vs placebo (FREEDOMS trial)
Infusion therapies				
Mitoxantrone	Edan 1997 (vs methylpred)[60] Millefiorini 1997[61] Hartung 2002[62] (Both vs placebo)	Mean difference of -0.85 in in annualised relapse rate with mitoxantrone (Cochrane meta-analysis)[59]	Odds ratio of 0.30 for 2-year confirmed progression of disease with mitoxantrone (Cochrane meta-analysis)	Odds ratio of 0.24 of active MRI lesions at 6 months or 1 year (Cochrane meta-analysis)
Natalizumab (2007)	AFFIRM[46]	68% RR in relapse at one year vs placebo	42% RR in risk of acquiring disability at two years vs placebo	92% RR in gadolinium enhancing lesions and 83% RR in new and enlarging T2 lesions vs. placebo
Abbreviations: methylpred = methylprednisolone; RR = relative reduction				

Table 2: DMTs for highly active or rapidly evolving MS or used second line at a glance

autoimmunity, reaching nearly 50% in a seven-year open-label follow-up.[52,58] This is principally thyroid related, but ITP and Goodpasture syndrome remain key safety concerns.[52,58] Therefore, patients must be able to comply with a strict monitoring programme of regular blood tests.[58] As conception can be attempted four months post infusion, alemtuzumab may represent a useful option for individuals planning a family.[58]

Mitoxantrone has not been assessed by NICE but is indicated in the 2009 ABN guidelines for rapidly evolving MS; in clinical practice its principal role is in worsening secondary progressive disease with evidence of inflammatory activity on MRI.[5] A Cochrane review concluded the drug was efficacious in reducing ARR, progression of disability and radiological evidence of disease in worsening RRMS and SPMS.[59] A cytotoxic drug borrowed from the oncology setting, mitoxantrone interferes with DNA replication in rapidly dividing cells.[59] It is prescribed as an induction therapy, with two protocols developed; in the UK, the Edan protocol, with monthly infusions for six months, followed by an alternate immunomodulatory drug, is preferred.[60]

Mitoxantrone carries a significant side-effect profile. Due to risk of cardiotoxicity, there is a strict weight-based dosing limit with an absolute ceiling of 140mg/m^2.[59] However, outside of oncological practice a lower ceiling dose – in France, where it holds a licence in MS, of around 70mg/m^2 – is applied.[60] This is relevant as cardiotoxicity is dose-related; baseline ECG and echocardiogram should be obtained, and mitoxantrone is contraindicated where left ventricular ejection fraction is less than 50%.[61,62] Another important consideration is treatment-related acute myeloid leukaemia, which was recently found to affect as many as 27% and carry a 37% mortality rate in an Italian cohort.[63] Mitoxantrone can cause infertility and amenorrhoea and is contra-indicated in pregnancy.[60-62]

Future therapies

Daclizumab is a humanised CD25 monoclonal antibody currently in phase III development. As the first MS immunotherapy whose prinicipal mechanism may be through the innate, not the adaptive, immune system, daclizumab is an interesting addition to the debate on the biology of MS.[64] It is given as a subcutaneous injection with a dose of 150mg once monthly currently under evaluation.[65] Phase III results are awaited, but recently released imaging results suggested a positive impact on brain atrophy as well as on gadolinium-enhancing, T2 and T1 hypointense lesions compared to intramuscular interferon β-1a.[66] In phase II testing, compared with placebo, daclizumab had achieved a 54% relative reduction of ARR and a 57% relative reduction in risk of sustained disability at one year.[65] Skin reactions and rashes are a common side-effect, and one patient died in the phase II trial while recovering from a severe rash.[64,65] Surveillance has been stepped up, and enhanced skin care, including use of sunscreen and emollients, is recommended.[64]

Humoral therapies The success of clinical trials of B-cell directed therapies argues for a contribution of humoral immunity in MS. Rituximab, an anti-CD20 monoclonal antibody targeting B-cells, was shown to reduce the number of gadolinium enhancing lesions by 91% compared with placebo in the phase II HERMES trial in RRMS, and reduced the number of patients with relapse by 50%.[67] Despite these beneficial results, rituximab, which is coming off patent, is not currently being carried forward into phase Ill trials.

However, manufacturer Roche is developing a successor molecule. Ocrelizumab is an anti-CD20 monoclonal antibody, but fully humanised and predicted to increase therapeutic efficacy and reduce immunogenicity.[68] In a phase II trial, ocrelizumab in two different infusion regimes achieved 89-96% reduction in gadolinium enhancing lesions and 80-73% reduction in relapse rate.[68]

Laquinimod Marketing authorisation for laquinimod was recently declined by the European Medicines Agency,[69] despite one phase III trial showing a 33% reduction in ARR compared with placebo, and results from this and a second phase III study demonstrating impact on disability progression and brain atrophy.[70-71] Manufacturer Teva is pursuing a new phase III trial which will focus on disability and brain atrophy measures and it is hoped the drug may have a future role as a neuroprotective agent.[72]

Old drugs, new tricks?

The discovery that excess CNS sodium is implicated in MS disease progression has led to interest in sodium channel blockers.[73] Recruitment is ongoing for a trial (NCT01451593) which will examine whether phenytoin has a neuroprotective effect in patients presenting with optic neuritis.[74] Another sodium-channel blocker already in clinical use, amiloride, is one of three 'repurposed' drugs to be evaluated in the MS-SMART trial in SPMS (NCT01910259).[75] Riluzole, an antiglutamatergic drug currently licensed in motor neuron disease, and

Fluoxetine, an antidepressant in the selective seratonin reuptake inhibitor (SSRI) class, are the other two to be studied.[75] Statins are well known from the cardiovascular setting and a placebo-controlled phase II trial of high-dose simvastatin (80mg) in SPMS recently reported a positive effect on brain atrophy and disability progression.[76]

While the idea of introducing known therapies with predictable safety records into MS clinical practice is attractive, practicalities around funding of large-scale phase III trials and management of the licensing process remain to be addressed.[77] This was recently illustrated by the withdrawal of the marketing licence application for oral cladribine by its manufacturer Merck Serono,[78] despite a phase III trial showing a 54.5–57.6% reduction in relapse rate.[79]

Conclusions

The MS DMT armamentarium has greatly expanded in recent years and a number of therapies are in the pipeline. This expansion has provided both patient benefit and insights into the aetiology of MS. With DMTs recommended in active and highly active relapsing disease, future phase III trials should employ an active comparator. The relatively short (two to three year) timespan of most pivotal trials is a hurdle to examining the long-term effect on disease progression in a lifelong condition. Although there are data over as long as 16 years from the first DMTs,[80] this is an unlikely area of expansion for commercial clinical trials. Inclusion of additional disability outcomes alongside the traditional EDSS, such as cognitive and upper limb function, may be more sensitive to detect impact on disease progression in future trial cohorts.[81] A pragmatic approach using data registries, for example the MSBase registry project, can also address areas of research need such as head-to-head comparisons and long-term follow up.[82]

The emergence of PML after the adoption of natalizumab into clinical practice remains a salutary lesson on patient safety, further emphasised by cases in DMF and fingolimod patients. Individual risk and benefit should be carefully weighed up as part of the decision-making process to match DMT to level of clinical MS activity. For individuals with aggressive disease, careful vigilance and stratification can minimise but not eliminate the risks accompanying potent immunotherapies. Future directions include molecules with new mechanisms of action, those with putative neuroprotective effects and combination therapy.

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Declaration of interests

From 2004-2007 Dr Binks was a paid employee of Schering Health Care Ltd. Dr Binks is involved in ongoing analyses from the MS-STAT trial.
Dr Dobson had no conflicts of interest to declare.

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POEMs

ESSENTIAL EVIDENCE PLUS

Citalopram plus methylphenidate better than either alone for geriatric depression

Clinical question

What is the comparative efficacy of citalopram, methylphenidate, or both for the treatment of depression among geriatric patients?

Reference

Lavretsky H, Reinleib M, St Cyr N, Siddarth P, Ercoli LM, Senturk D. Citalopram, methylphenidate, or their combination in geriatric depression: A randomized, double-blind, placebo controlled trial. Am J Psychiatry 2015;172(6):561-569.

Synopsis

This randomized controlled trial of geriatric patients with depression compared citalopram plus placebo (n = 48), methylphenidate plus placebo (n = 47), and both active treatments (n = 47). Inclusion criteria were unipolar depression by DSM-IV-TR criteria, a score of at least 16 on the Hamilton Depression Rating Scale (HAM-D), and a score of at least 22 on the Mini-Mental State Examination. Methylphenidate (or placebo) was titrated during the first 4 weeks, as tolerated, starting at 2.5 mg twice daily and increasing to a maximum 20 mg twice daily. If response was insufficient at 4 weeks citalopram (or placebo) was also increased from 20 mg to 40 mg or, in some cases, 60 mg daily. Remission rates were 30% among patients who received placebo instead of citalopram, 42% with 20 mg citalopram, 56% with 40 mg, and 69% with 60 mg. There was no dose-response gradient with methylphenidate. Change in HAM-D score was greater and faster with combined therapy. Remission was defined as a HAM-D score of 6 or less and was more likely with combined therapy (62%) at 16 weeks, compared with citalopram alone (42%) or methylphenidate alone (29%) (chi-squared = 9.2; P = .001). There were no significant differences between groups in cognitive change, which improved across all groups.