Emerging Therapies in Multiple Sclerosis—New Decisions in the Formulation of Treatment Strategies

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Abstract

The therapeutic options available to neurologists treating multiple sclerosis (MS) are profoundly changing. Hitherto, disease modifying therapies (DMTs) were entirely administered by injection and were only able to retard disease progression. The frequency of site reactions and flu-like symptoms has made adherence to treatment problematic and resulted in resistance from some patients. The recent approval of the first oral DMT in MS (fingolimod) and the development of other oral agents will provide much more attractive options to both physicians and patients and may promote earlier commencement of treatment. The development of the monoclonal antibody alemtuzumab may for the first time provide a MS treatment that will, in certain patients with relapsing disease, restore some degree of lost neurologic function. Therefore these new medications will fundamentally change the decision-making process from diagnosis to choice of treatment. However, these treatments do not address progressive disease. The challenge will be which MS patients should receive the new treatments and how much benefit such treatments will provide over current strategies.

Keywords

Multiple sclerosis, disease-modifying therapies, new treatments, decision-making process

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Disease-modifying therapies (DMTs) for treating multiple sclerosis (MS) are entering a period of rapid and profound change that will greatly expand treatment options and improve quality of life for the approximately 2.5 million people worldwide who suffer from this chronic, disabling disease.[1] Five of the currently-approved DMTs are given by injection at frequent intervals and have a range of adverse effects, notably 'flu-like symptoms and injection site reactions. These effects can be a problem not only for patients who are newly prescribed the treatments, but also for some patients who experience 'injection fatigue' after years of continuous administration.[2] The probable approval within the next few years of a more effective monoclonal antibody treatment (alemtuzumab)[3] and several of the new oral DMTs (laquinimod, cladribine fingolimod, teriflumomide, and BG00012)[2,4–7] will represent a landmark change that could substantially alter approaches to MS treatment. DMTs are widely used in the treatment of patients with MS in North America and have changed the prognosis in many patients for the better.[8–10] However, in other territories they are often either not used commonly enough or not initiated early enough in the disease course to be effective. Factors including conservatism among physicians, delays in diagnosis and treatment initiation, fear of adverse events, and high cost or limited healthcare coverage can limit DMT use in these regions.

The aim of this article is to consider the way in which existing treatments have changed the outlook for MS patients and to assess the intravenous and oral treatments currently in late-stage development. Once given regulatory approval, these therapies are likely to have a dramatic effect on the choice and convenience of MS treatments. Therefore, it is timely to discuss the decision-making process neurologists go through prior to initiating treatment and during ongoing treatment and to reflect on the impact these novel therapies will have on this process.

The Impact of Current Disease-modifying Therapies on Prognosis

In 1993, the first pivotal trial of interferon beta-1β (IFNβ-1β) was published, illustrating its efficacy in relapsing–remitting MS (RRMS).[11] That same year, this drug was also made commercially available. Since then, a number of injectable DMTs have been approved for use in MS treatment, including IFNβ-1α and glatiramer acetate. These drugs all reduce relapse rates and magnetic resonance imaging (MRI) activity and appear to slow disease progression.[12,13] Unfortunately, several factors hinder researchers from assessing the true impact that current therapies have on MS disease course. First, there is a lack of natural

history data available, with only limited findings presented in older studies.[14,15] Similarly, there have been few long-term, carefully controlled or prospective studies investigating the effects of the various treatments beyond the initial two to three years.[16] Finally, patients in recent trials have experienced lower relapse rates compared with those in the earlier pivotal studies.

Trials employing the McDonald criteria for inclusion often observe an annualized relapse rate of only 0.3 (approximately one relapse every three patient-years). This makes it difficult to detect any changes due to treatment in short-term clinical trials, which typically last only two to three years. Despite these challenges in evaluation, it appears that DMTs have positively affected disease outcomes over the years. The prognosis for MS patients who receive DMTs at the time of diagnosis of clinically-isolated syndrome (CIS) or RRMS has improved significantly. The length of time between RRMS and secondary progressive MS (SPMS) has also increased, showing delayed disability progression.[8] As patients advance to SPMS, treatments lose their positive effects.[17–20] In these severe or rapidly-evolving cases, more potent treatments such as natalizumab or mitoxantrone may provide better efficacy and are often used as second-line therapy.[21]

While current treatment options have managed to reduce relapse rates to a more acceptable level, they are still by no means satisfactory. Anecdotal observations of fewer wheelchairs in MS treatment centers, however, suggest that patients today have less disability overall.[22] This may be attributable to the recent advances in therapies.

Diagnosis of Multiple Sclerosis

A definite diagnosis of at least one clinical demyelinating event, often referred to as CIS, and evidence of typical magnetic resonance imaging (MRI) abnormalities indicating areas of prior asymptomatic inflammation are required by most neurologists prior to initiating therapy. Such a diagnosis enables more accurate judgment of whether or not a patient will develop RRMS.[23] The value of treating individuals who have old lesions, as detected by MRI, but no recent clinical or MRI activity has not been demonstrated. As a result, many neurologists prefer to see dissemination in time (a second clinical attack or the appearance of new lesions on MRI) that is indicative of active disease before prescribing a DMT.[24]

The majority of MS cases can be diagnosed by clinical and imaging parameters alone. This is the case provided parameters are properly applied and other causes of CNS inflammatory white-matter disease (MS mimickers) are ruled out, usually by appropriate blood tests and occasionally by a negative cerebrospinal fluid analysis. A cerebrospinal fluid analysis that is positive for markers of abnormal intrathecal immunoglobulin synthesis (increased IgG index, synthesis rate, and/or oligoclonal bands) can also be useful in unusual presentations and in primary progressive MS, where imaging may be negative, especially early in the disease course.

Several diagnostic schemes designed to demonstrate dissemination in space and time were used prior to the advent of MRI for routine clinical use.[25,26] Traditionally, the Poser criteria[25,27] were the sole criteria used to diagnose MS in patients included in the early pivotal trials of available DMTs. These criteria required at least two documented relapses in order to make a diagnosis of clinically definite MS. An international panel chaired by W Ian McDonald reviewed pre-existing criteria for the diagnosis of MS to incorporate modern imaging techniques (i.e. MRI) into a diagnostic scheme. This scheme allowed the physician to satisfy a requirement for dissemination of lesions in time and/or space without having to wait for a second clinical manifestation of disease, as had previously been the norm.[27] These criteria were revised in 2005[28] and the resulting set are presented in *Table 1*.

Table 1: Diagnostic Criteria for Multiple Sclerosis as Specified by Polman et al. in 2005

Clinical Presentation ('Lesion' Refers to Objective Abnormality on Neurologic Exam)	Additional Data Needed for MS Diagnosis ('Lesion' Refers to Signal Abnormality on MRI Typical for Demyelination)
Two or more attacks; objective clinical evidence of two or more lesions	None
Two or more attacks; objective clinical evidence of one lesion	Dissemination in space shown on MRI or Up to two MRI-detected lesions typical of MS plus positive cerebrospinal fluid or Await a further relapse suggestive of dissemination in space (i.e. affecting another part of the CNS)
One attack; objective clinical evidence of two or more lesions	Dissemination in time shown on MRI or Second clinical attack (relapse)
One attack; objective clinical evidence of one lesion, i.e. clinically isolated syndrome	Dissemination in space demonstrated by MRI or Up to two MRI-detected lesions typical of MS plus positive cerebrospinal fluid AND dissemination in time demonstrated by MRI or Dissemination in time demonstrated by MRI (i.e. new lesion seen on MRI at least 3 months after the original scan) or Second clinical attack (relapse)
Insidious neurologic progression suggestive of MS (typical for primary progressive MS)	Positive cerebrospinal fluid AND dissemination in space, shown on MRI or Abnormal visual evoked potential plus abnormal MRI AND dissemination in time demonstrated by MRI or Continued progression for one year

CNS = central nervous system; MRI = magnetic resonance imaging; MS = multiple sclerosis. Source: Polman et al., 2005.[28]

Not long ago, a new set of criteria was put forward that relies solely on lesion location to provide evidence of dissemination in space. This has proved to be easier to use in practice without compromising specificity or accuracy.[29,30] In fact, sensitivity was higher with these new criteria than the revised McDonald criteria (72 versus 60%, respectively).[30] The new criteria simply state that dissemination in space requires one

Table 2: Summary of McDonald, Modified McDonald, and MAGNIMS Magnetic Resonance Imaging Criteria for Dissemination in Space and Time for Multiple Sclerosis

McDonald 2001[27] ≥3 of:	McDonald 2005[28] ≥3 of:	MAGNIMS[29] Lesion(s) in each of ≥2 Characteristic Locations:
Dissemination in Space (on Baseline MRI)		
≥9 T2 lesions or ≥1 Gd-enhancing lesion	≥9 T2 lesions or ≥1 Gd-enhancing lesion	≥1 periventricular
≥3 periventricular lesions	≥3 periventricular lesions	≥1 juxtacortical
≥1 juxtacortical lesion	≥1 juxtacortical lesion	≥1 posterior fossa
≥1 posterior fossa lesion	≥1 posterior fossa lesion or spinal cord lesion	≥1 spinal cord
1 cord lesion can replace 1 brain lesion	Any number of cord lesions can be included in total lesion count	All lesions in symptomatic regions excluded in brainstem and spinal cord syndromes
Dissemination in Time (on Follow-up MRI)		
1. ≥Gd-enhancing lesion at least 3 months after CIS onset (if not related to CIS)	1. ≥Gd-enhancing lesion at least 3 months after CIS onset (if not related to CIS)	1. Simultaneous presence of asymptomatic Gd-enhancing and non-enhancing lesions at any time
2. A new T2 lesion with reference to a prior scan obtained at least 3 months after CIS onset	2. A new T2 lesion with reference to a prior scan obtained at least 3 months after CIS onset	2. A new T2 and/or Gd-enhancing lesion on follow-up MRI irrespective of timing of baseline scan

CIS = clinically isolated syndrome; Gd = gadolinium; MAGNIMS = magnetic imaging in multiple sclerosis; MRI = magnetic resonance imaging.
Source: Swanton et al., 2007[30] and Montalban et al., 2010.[31]

or more T2 lesion(s) in two or more of four characteristic locations (juxtacortical, periventricular, infratentorial, and spinal cord).

Recently a workshop of the European multicenter collaborative research network that studies MRI in MS (MAGNIMS) reviewed these new criteria. The group revised the MRI-derived information that should be retained and the diagnostic criteria have now been updated further. This allows for even greater ease in diagnosis while minimizing false positives.[31] Dissemination in time requires only a new T2 lesion on any follow-up scan or the simultaneous presence of a non-enhancing asymptomatic T2 lesion and a gadolinium (Gd)-enhancing lesion on the same scan. The MAGNIMS criteria are summarized in *Table 2*.

Decision-making Process in the Treatment of Multiple Sclerosis

Results from a number of studies support early initiation of each of the injectable treatments for MS at the time of initial presentation with a CIS and at least two typical abnormalities on brain MRI. These studies include the:

- Controlled high-risk subjects Avonex MS prevention study (CHAMPS);[32]
- Early treatment Of MS (ETOMS);[33]
- Betaferon/Betaseron in newly emerging MS For initial treatment (BENEFIT);[34] and
- Early glatiramer acetate treatment in delaying conversion to clinically-definite MN in subjects Presenting with a CIS (PreCISe).[35]

While most of these placebo-controlled trials ran for only two years, prospectively-planned follow-up data from the BENEFIT study also showed that early treatment with IFNβ-1β positively affected the rate of conversion of initial CIS to clinically definite MS for up to five years of follow-up.[34] This fact is generally accepted by both prescribers and insurers in the US, with minimal obstacles to commencing therapy early in the disease course. Three of the four available injectable agents have been approved by the US Food and Drug Administration (FDA) for treatment at the time of CIS with abnormal brain MRI. Insurance companies are generally required to fund currently available MS treatments on this basis. The situation differs in other parts of the world, however, where cost and conservatism among physicians may restrict or delay access to proven effective treatments.

Currently, the decision to initiate treatment is often taken after documentation of a CIS with MRI evidence of prior and/or ongoing disease activity[29,31] and neurologists in the US now readily prescribe a DMT at this time. In fact, there are instances when neurologists may be too hasty in initiating treatment, administering it to patients without a typical CIS presentation and/or with non-specific MRI findings that do not necessarily show classic signs of demyelination.[36] As mentioned above, treatment initiation should require a definitive diagnosis of a clinical demyelinating event with at least one documented abnormality on neurologic exam. Patients without clear signs of MS who receive DMTs may question the necessity of treatment and, in fact, DMT efficacy in asymptomatic patients has never been proven. A schematic of current treatment decisions in MS is given in *Figure 1*.

The decision to start treatment at the first clinical signs of disease (CIS) must be taken by the individual neurologist in conjunction with the patient. Sometimes it is difficult to convince a patient that receiving frequent, regular injections of a preventative DMT with the potential for frequent side-effects is in their best interest, especially after initial symptoms have subsided, thus creating a barrier to optimal treatment. For such patients, physicians may opt to use steroids for symptom management and await a change on a subsequent MRI scan (dissemination in time) in order to provide further evidence that the disease is indeed likely to follow a relapsing course.

The initial DMT chosen often reflects personal preference and experience, as each neurologist will have their favored treatments. There are no head-to-head trials of DMTs for treatment at the time of CIS. The selection of high- or low-dose IFNβ versus glatiramer acetate may depend on many factors, including symptom severity, MRI activity, injection frequency, history of severe depression and other individual factors. Treatment response tends to be idiosyncratic and unpredictable. Breakthrough disease in patients taking their first-line DMT is relatively common, although all of the available DMTs are useful as first-line therapy in at least some patients. Head-to-head studies in RRMS have shown equivalence among current injectable DMTs, as well as a rapid onset of action.[35,37–39] Currently, no evidence exists to suggest that glatiramer acetate may be inferior in efficacy to the IFNβs, as was previously believed by some practitioners.

While adverse events with injectable treatments can deter patients, injection site reactions can be minimized with local measures and

frequent rotation. Perhaps counter-intuitively, the flu-like symptoms patients may experience tend to diminish over time, particularly with IFNs given at more frequent dosing intervals.

Patients with Severe or Rapidly-evolving Disease

Natalizumab and mitoxantrone infusions are generally felt to be more potent than the other DMTs. They may therefore benefit patients with severe or rapidly-evolving MS that has not responded to first-line therapy with an IFN and/or glatiramer acetate,[21] although natalizumab has never undergone clinical trial testing for this indication. While natalizumab has been shown to be effective in many patients with severe MS,[40] immunosuppressive therapy with mitoxantrone is now less commonly prescribed in the US. This is due to the increasing incidence of serious adverse events, such as cardiomyopathy and treatment-related leukemia. However, prior to employing a stronger agent, many clinicians try switching from an IFNβ to glatiramer acetate or vice versa, since a patient who does not respond to one first-line treatment may respond to a drug with a different mechanism of action. Similarly, high-dose, high-frequency IFNβs have been shown to be more effective than low-dose, once-weekly IFN in head-to-head trials, though prospective, blinded, carefully controlled switching studies are lacking. The available open-label 'breakthrough' switching studies are subject to statistical artifacts, such as regression to the mean.

A major problem with natalizumab treatment in MS patients is its association with the opportunistic viral brain disease, progressive multifocal leukoencephalopathy (PML).[41,42] Length of time on the drug and prior immunosuppressive therapy are risk factors for developing PML.[43] To address this, the Tysabri Outreach Unified Commitment to Health (TOUCH) prescribing program[44] as well as the Tysabri Global Observational Program in Safety—Rest of World (TYGRIS—ROW) started in 2006.[45] These programs have generally increased confidence in the monitoring of patients on natalizumab for early detection of PML. Furthermore, in many US centers, patients are scanned every six months for any indication of the emergence of PML.[46]

A new enzyme-linked immunosorbent assay (ELISA) for prior exposure to JC virus is currently being developed by Biogen-Idec. This promises to be far more sensitive for detecting long-standing infection than the currently available quantitative polymerase chain reaction assay, which only detects active viral replication. This new assay will presumably allow more meaningful stratification of risk for development of PML and may return natalizumab to the class of first-line therapy for JC virus-negative individuals.

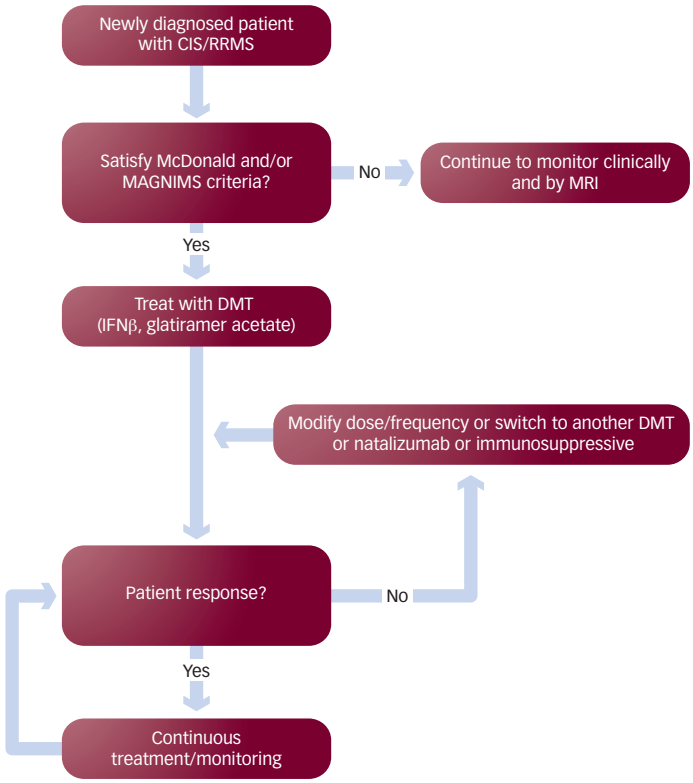
Novel Treatments Currently in Development

Parenteral Therapies

Monoclonal Antibodies

Three new monoclonal antibodies have shown encouraging results in phase II trials: alemtuzumab (anti-CD52),[47] daclizumab (anti-CD25),[48] and rituximab (anti CD-20).[49] Both daclizumab and rituximab have been used as add-on therapy to IFN and other DMTs, but they are in an early phase of development for MS treatment and data are limited. Of the new monoclonals, alemtuzumab has shown the greatest efficacy against MS and is the furthest developed in clinical trials.

Figure 1: Decision-making Process with Current Disease-modifying Therapies in Multiple Sclerosis



CIS = clinically isolated syndrome; DMT = disease-modifying therapy; IFNβ = interferon beta; MAGNIMS = magnetic imaging in multiple sclerosis; MRI = magnetic resonance imaging; RRMS = relapsing–remitting multiple sclerosis.

Alemtuzumab

Alemtuzumab is a fully humanized monoclonal antibody currently FDA-approved for use in the treatment of chronic lymphocytic leukemia, cutaneous T-cell lymphoma, and T-cell lymphoma. Alemtuzumab targets CD52, a protein present on the surface of mature lymphocytes, but not on the stem cells from which these lymphocytes are derived.[50]

In current phase III trials in MS, alemtuzumab is administered intravenously in short (five-day) courses at annual intervals,[21] making it extremely convenient for patients and giving it the potential to lower costs relative to current therapies. Previous phase II trials have shown very encouraging results, with significant reductions in disability in some patients.[47] In 334 patients with RRMS given alemtuzumab 12 or 24mg courses over 36 months or IFNβ-1α 44µg three times weekly there was a 0.39 point improvement in expanded disability status scale values for alemtuzumab compared with a 0.38 point worsening for IFNβ-1α. There were also significant reductions in annualized relapse rates, sustained accumulation of disability ($p<0.001$ for both) and MRI lesions compared with IFNβ-1α.

Alemtuzumab is undergoing several phase III trials, the results as yet unpublished. Serious adverse events have been noted, in particular acute idiopathic thrombocytopenic purpura, with one case leading to fatal intracerebral hemorrhage. Goodpasture's syndrome and autoimmune thyroid disease are also issues that will require careful

Table 3: Key Completed and Ongoing Phase III Trials in the Development of New Multiple Sclerosis Treatments

Medication (Study Name) and Design	No. Patients, Study Centers, Locations, and NCT Number	Dose/Administration Route	End-points	Duration and Completion Date
Alemtuzumab (CARE-MS I) randomized, parallel assignment, single-blind, head-to-head comparator with IFNβ-1a 44µg 3x weekly SC	581 RRMS patients at 101 study centers in US, Canada, South America, Australia, and Europe. NCT00530348	12mg/day IV, for 5 days in month 0, and 12mg/day IV for 3 days at month 12, or INFβ-1a 44µg 3x weekly SC injections	Primary: time to sustained accumulation of disability and relapse rate. Secondary: proportion relapse free at year 2, change from baseline in EDSS, acquisition of disability, % change in MRI-T2 hyperintense lesion volume	2 years; May 2011 +3-year extension completing September 2014
Alemtuzumab (CARE-MS II) randomized, parallel assignment, single-blind, head-to-head comparator with IFNβ-1a 44µg 3x weekly SC	840 RRMS patients who have relapsed on therapy at 181 study centers in US, Canada, South America, Australia, and Europe. NCT00548405	12mg/day IV, for 5 days in month 0, and 12mg/day IV for 3 days at month 12, or 24mg (same protocol), or INFβ-1a 44µg 3x weekly SC injections	Primary: time to sustained accumulation of disability, relapse rate, safety. Secondary: proportion relapse free at year 2, change from baseline in EDSS, acquisition of disability, % change in MRI-T2 hyperintense lesion volume	2 years; September 2011 +3-year extension completing September 2014
BG-12 (dimethy fumarate) (CONFIRM) monotherapy, placebo-controlled, with glatiramer acetate comparison arm	1,232 RRMS patients at 208 study centers in US, Canada, Europe, India, Mexico, and South America. NCT00451451	480mg or 720mg/day oral or placebo or glatiramer acetate	Primary: reduction in relapse rate at 2 years. Secondary: decreases in number of brain MRI lesions, delay in time to progression, safety and tolerability	108 weeks; April 2011
BG-12 (dimethy fumarate) (DEFINE) randomized, placebo-controlled, parallel assignment double-blind	1,011 RRMS patients at 169 study centers in US, Canada, Europe, India, Australia, New Zealand, South America, and South Africa. NCT00420212	480mg or 720mg/day oral or placebo	Primary: reduction of the proportion of relapsing subjects Secondary: decrease in brain lesions, delay in time to progression, safety and tolerability	2 years; December 2010
Cladribine (CLARITY)[5] randomized placebo-controlled double-blind	1,326 patients at 155 study centers in the US and Europe. NCT00213135	Low-dose 0.875mg/kg/cycle oral for 2 cycles (total dose: 1.75mg/kg) or high-dose: 0.875mg/kg/cycle oral for 4 cycles (total dose: 3.50mg/kg) or placebo	Primary: annualized relapse rate. Secondary: effect on progression of disability in subjects with RRMS	96 weeks; December 2008 + 2-year extension study completing September 2011. In extension, those previously on placebo given low-dose cladribine, those previously on cladribine randomized 2:1 to low-dose cladribine or placebo
Cladribine (ORACLE MS) randomized, parallel assignment, double-blind	600 patients with a first clinical event (CIS) at high risk of converting to MS at 34 study centers in US, Middle East, Russia, and South East Asia. NCT00725985	Low-dose 1.75mg/kg/year oral. Dosed once/week for 4 weeks at the start of a cycle or 3.5mg or placebo	Primary: time to conversion to clinically-definite MS, sustained increase in EDSS during initial treatment period	2 years; December 2012
Cladribine (PREMIERE) prospective, observational, long-term safety registry of MS patients who participated in cladribine clinical trials	1,500 patients who have been previously exposed to cladribine at study centers in the US. NCT01013350	Oral doses may vary according to the study they previously participated in	Long-term safety data on oral cladribine in MS. Measurements: will be taken when 2 years of follow-up data are available for 1,000 subjects after registry enrollment	2 years; December 2018
Fingolimod (FREEDOMS)[7] double-blind, randomized, placebo-controlled, parallel-group	1,272 patients at 115 study centers in Australia, Europe, Canada, and the US. NCT00289978	0.5mg or 1.25mg/day oral or placebo	Primary: annualized relapse rate. Secondary: time to 3-month confirmed disability progression, safety parameters, time to first relapse, % relapse-free patients; and MRI parameters	2 years; July 2009

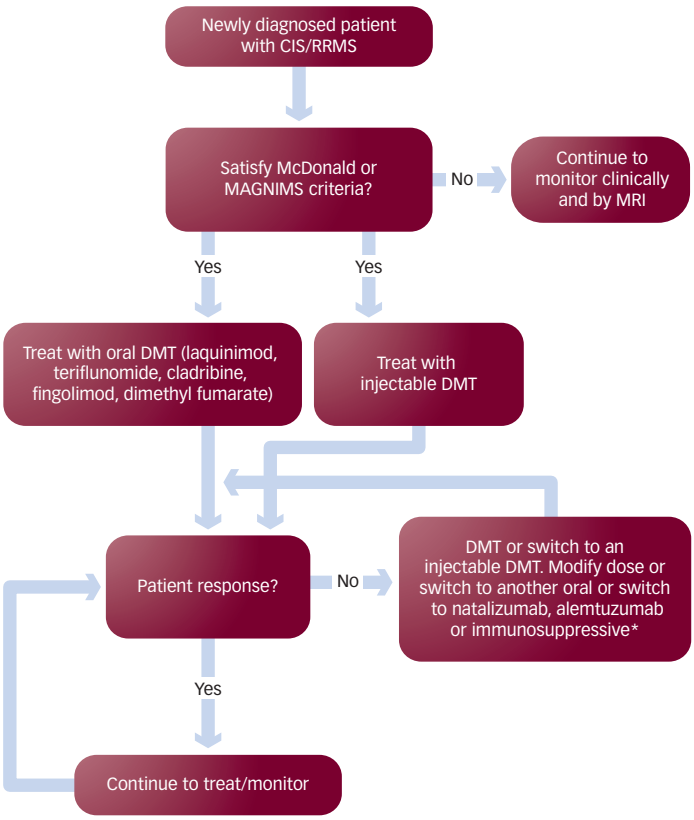
Table 3 (cont.):

Medication (Study Name) and Design	No. Patients, Study Centers, Locations, and NCT Number	Dose/Administration Route	End-points	Duration and Completion Date
Fingolimod (FREEDOMS II) randomized, placebo-controlled, parallel assignment, double-blind	1,080 RRMS patients at 107 study centers in US, Canada, Australia, and Europe. NCT00355134	0.5mg or 1.25mg/day oral or placebo	Primary: annualized relapse rate in patients treated for up to 24 months. Secondary: proportion of relapse-free patients, safety parameters	2 years; March 2011
Fingolimod (TRANSFORMS)[52] randomized, active-controlled, double blind, head-to-head with IFNβ-1a, 30µg IM weekly	1,292 patients with a recent relapse at 141 study centers in US, Canada, South America, Australia, Europe, and South East Asia. NCT00340834	0.5mg or 1.25mg/day oral or IFNβ-1a, 30µg IM weekly	Primary: annualized relapse rate. Secondary: proportion of relapse-free patients, MRI burden of disease, safety parameters	12 months; December 2008
Laquinimod (ALLEGRO) randomized placebo-controlled double-blind	1,000 RRMS patients at 167 study centers in US, Canada, and Europe. NCT00509145	0.6mg/day oral or placebo	Primary: annualized relapse rate during double-blind study period. Secondary: accumulation of physical disability, MRI outcomes	24 months; December 2010
Laquinimod (BRAVO) randomized, placebo-controlled double-blind, head-to-head with IFNβ-1a, 30µg IM weekly	1,200 RRMS patients at 190 study centers in US and Europe. NCT00605215	0.6mg/day oral for 24 months, placebo or IFNβ-1a 30µg IM once weekly for 24 months	Primary: annualized relapse rate. Secondary: accumulation of disability, MRI end-points	24 months; November 2011
Teriflunomide (TEMSO) double-blind, randomized, placebo-controlled, parallel-group	1,080 RRMS patients at 115 study centers in 20 countries including US, South America, and Europe. NCT00134563	7mg or 14mg/day oral or placebo. Patients stratified into EDSS ≤3.5 or EDSS >3.5	Primary: annualized relapse rate. Secondary: time to disability progression, % free of disability progression, MRI burden of disease, subject-reported fatigue	108 weeks; July 2010 + 4-year open-label extension
Teriflunomide (TOPIC) monotherapy in CIS. Randomized, placebo-controlled, double-blind	780 patients with CIS (first episode suggestive of MS) at 143 study centers in US and Europe. NCT00622700	7mg or 14mg/day oral or placebo	Primary: conversion to clinically-definite MS. Secondary: conversion to 'McDonald' MS, annualized relapse rate, MRI burden of disease, proportion of disability-free patients, safety parameters	2 years; April 2015
Teriflunomide (TOWER) monotherapy with IFNB-1a comparison arm	1,110 RRMS patients at 191 study centers in US, Australia, China, Canada, Europe, and Mexico. NCT00751881	7mg or 14mg/day oral or placebo	Primary: annualized relapse rate. Secondary: time to disability progression	48 weeks; September 2011
Teriflunomide (TENERE) randomized, active-controlled, parallel assignment, open label	300 RRMS patients at 58 study locations in Canada and Europe. NCT00883337	7mg or 14mg/day oral or active comparator IFNβ-1a 44µg SC 3 x weekly	Primary: time to failure, i.e. first occurrence of relapse or treatment discontinuation. Secondary: annualized relapse rate	68 weeks; October 2011

ALLEGRO = Safety and Efficacy of Orally Administered Laquinimod versus Placebo for Treatment of Relapsing Remitting Multiple Sclerosis (RRMS); BRAVO = Laquinimod Double Blind Placebo Controlled Study in RRMS Patients With a Rater Blinded Reference Arm of Interferon beta-1a (Avonex®); CARE-MS I = Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis, Study One; CARE-MS II = Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis, Study Two; CIS = clinically isolated syndrome; CLARITY = Safety and Efficacy of Oral Cladribine in Subjects With Relapsing-remitting MS; CONFIRM = Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis; DEFINE = Efficacy and Safety of Oral BG00012 in Relapsing-Remitting Multiple Sclerosis; EDSS = expanded disability status scale; FREEDOMS = Efficacy and Safety of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis; IFNβ = interferon beta; IM = intramuscular; IV = intravenous; MRI = magnetic resonance imaging; NCT = national clinical trial; PREMIERE = Prospective Observational Long-term Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Trials; ORACLE MS = Oral Cladribine in Early Multiple Sclerosis; RRMS = relapsing–remitting multiple sclerosis; SC = subcutaneous; TEMSO = Study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients With Multiple Sclerosis; TENERE = A Multicenter, Randomized, Parallel-group, Rater-blinded Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis; TOPIC = Phase III Study With Teriflunomide versus Placebo in Patients With First Clinical Symptom of Multiple Sclerosis; TOWER = An Efficacy Study of Teriflunomide in Patients With Relapsing Multiple Sclerosis; TRANSFORMS = Efficacy and Safety of Fingolimod in Patients With Relapsing–Remitting Multiple Sclerosis With Optional Extension Phase.

and frequent monitoring and may limit its use.[47] However, with alemtuzumab's apparent superior efficacy and ease of use, it is likely that alemtuzumab will have an enormous impact on future MS therapy decisions.

Figure 2: Possible Decision-making Process After the Introduction of Oral Disease-modifying Therapies and Alemtuzumab for Multiple Sclerosis Treatment



**It may not be advisable to switch from cladribine to natalizumab, alemtuzumab or other immunosuppressive agent within a short time-frame due to prolonged lymphocytopenia. CIS = clinically isolated syndrome; DMT = disease-modifying therapy; MAGNIMS = magnetic imaging in multiple sclerosis; MRI = magnetic resonance imaging; RRMS = relapsing–remitting multiple sclerosis.*

Oral Therapies

Currently, several oral agents for the treatment of MS are in late-stage development, including laquinimod, teriflunomide, and BG00012.[4–7] One agent, fingolimod, was recently approved by the FDA for use in relapsing forms of MS. Another oral agent, cladribine, is awaiting approval in the US. However, it has recently been refused marketing authorization in Europe, presumably due to increased cancer risk and insufficient benefit demonstrated at the doses used. The oral agents are generally well tolerated and obviate the need for injections. Therefore they are likely to completely change the face of MS treatment over a relatively short time period. With their relative ease of administration, oral therapies have the potential to improve adherence and quality of life[1] and could prove to be the most significant advance in MS therapy since the initial introduction of injectable DMTs. All of the oral agents in development have shown promising results using MRI outcome measures in phase II trials. Two agents—cladribine and fingolimod—have shown moderate efficacy similar to current injectable medications in phase III trials in treating MS.

Fingolimod

Fingolimod is a first-in-class oral sphingosine-1-phosphate (SIP)-receptor agonist that has recently (September 21, 2010) been approved for treatment of relapsing forms of MS. Long-term efficacy and safety data are therefore currently lacking. Binding of phosporylated fingolimod in human tissues results in faulty internalization of the SIP receptor. This renders lymphocytes incapable of detecting the SIP gradients that are needed to enable them to migrate from the secondary lymphoid organs into the peripheral circulation and into the central nervous system. Fingolimod thereby diminishes inflammation and, possibly, neurodegeneration in MS.[51]

The Efficacy and Safety of Fingolimod in Patients With Relapsing–remitting Multiple Sclerosis (FREEDOMS) trial included 1,272 patients with RRMS treated with 0.5 or 1.25mg fingolimod or placebo.[7] After two years of treatment, the annualized relapse rate was 0.18 with 0.5mg of fingolimod, 0.16 with 1.25mg of fingolimod, and 0.40 with placebo ($p<0.001$ for either dose versus placebo). Fingolimod significantly reduced the risk of disability progression ($p=0.02$) and reduced the cumulative probability of disability progression (confirmed after three months). Drug-related adverse events included bradycardia and atrioventricular conduction block, bronchiolar constriction, macular edema, and elevated liver-enzyme levels.

In the 2008 Efficacy and Safety of Fingolimod in Patients With Relapsing–Remitting Multiple Sclerosis With Optional Extension Phase (TRANSFORMS) study, 1,292 patients with one or more recent relapses were treated with 1.25 or 0.5mg fingolimod/day or an active comparator, intramuscular IFNβ-1α 30µg/week (see *Table 3*).[52] The annualized relapse rate was significantly lower with either dose of fingolimod than with IFNβ-1α (0.2, 0.16, and 0.33, respectively; $p<0.001$ for both comparisons). New and active MRI lesions were also significantly fewer in the fingolimod-treated patients. Fingolimod was associated with an increased incidence of viral infections, bradycardia, atrioventricular block, hypertension, macular edema, skin cancer, and raised liver enzyme levels. Two fatal herpes infections were seen, although these cases may not directly implicate the drug.

The FREEDOMS II trial is currently investigating the efficacy and safety of fingolimod in a further 1,080 patients with RRMS (*see Table 3*).

Cladribine

Cladribine is a nucleotide analog that, when phosphorylated, accumulates in lymphocytes leading to apoptosis. It is licensed as a parenteral treatment for hairy-cell leukemia and some long-term safety data are therefore available.[53] In previous trials, parenteral cladribine showed promising reductions in new MRI lesions in both RRMS and SPMS with good safety and tolerability.[54] After these findings, cladribine was developed as an oral treatment for MS.[54] Of the three phase III trials initiated to further evaluate oral cladribine in MS, two are still ongoing, but the CLARITY study has been completed (see *Table 3*).

In the Safety and Efficacy of Oral Cladribine in Subjects With Relapsing–Remitting MS (CLARITY) study, 1,326 RRMS patients were treated with either 3.5 or 5.25mg/kg cladribine or placebo (1:1:1 ratio) for two years. Annualized relapse rates were 0.14, 0.15, and 0.33, respectively.[5] The relative reductions in relapses compared with placebo were 57.6 and 54.5% ($p<0.001$) for the low- and high-dose treatment arms, respectively. In addition, there was a reduction of 33% with

3.5mg/kg and 31% with 5.35mg/kg clabdribine in the three-month risk of disability progression. Cladribine produced profound and lasting lymphocytopenia, as expected from its mechanism of action, and some neutropenia, but there were only marginal increases in infections.

The two ongoing trials are the Oral Cladribine in Early Multiple Sclerosis (ORACLE) study and the Prospective observational long-term safety registry of multiple sclerosis patients who have participated in cladribine clinical trials (PREMIERE). The ORACLE trial (n=600) is currently evaluating the effects of low-dose oral cladribine at 1.75mg/kg/year on conversion to clinically-definite MS and disability progression in CIS patients. The PREMIERE trial (n=1,500) is an open-label extension trial for participants who have previously received cladribine. It is designed to evaluate long-term safety (see *Table 3*). It is currently unclear where the failure to gain European marketing authorization will leave the further development of cladribine in MS.

Laquinimod

Laquinimod, a once-daily immunomodulatory compound, has shown reasonable efficacy in a phase II, multicenter, double-blind, randomized trial evaluating two different doses of the drug relative to placebo in 209 patients with relapsing MS.[55] A dose of 0.3mg was significantly superior to placebo, reducing the number of active lesions on MRI by 44%. The drug was well tolerated in this trial.

In a further phase II trial including 306 patients with RRMS, a higher dose of laquinimod (0.6mg/day) significantly reduced Gd-enhancing lesions compared with placebo over 36 weeks of treatment. There was also some improvement in relapse rate, with no new safety issue being identified.[4] Patients who were switched from placebo to laquinimod showed marked reductions in Gd-enhancing lesions.

Given the potential safety issues with several other emerging oral therapies, the risk–benefit profile of laquinimod appears to be favorable. The drug was subsequently granted fast-track status by the FDA in February 2009. Phase III trials (Safety and Efficacy of Orally Administered Laquinimod versus Placebo for Treatment of Relapsing Remitting Multiple Sclerosis [ALLEGRO] and Laquinimod Double Blind Placebo Controlled Study in RRMS Patients With a Rater Blinded Reference Arm of interferon beta-1a [Avonex®; BRAVO] totaling 2,200 patients and powered to detect a difference in clinical outcomes (relapses) are currently in progress to further evaluate laquinimod's efficacy, safety and tolerability.[56,57]

Teriflunomide

Teriflunomide inhibits immune function by decreasing DNA synthesis, thus limiting the proliferation of B- and T-cells. The active metabolite of teriflunomide, leflunomide, has been an approved treatment for rheumatoid arthritis for over 10 years and teriflunomide has shown efficacy in experimental allergic encephalitis, the animal model for studying MS.[58] In a completed phase II trial including 179 patients with RRMS, oral teriflunomide produced significantly lower increases in disability, lower relapse rates, greater proportions of relapse-free patients and lower numbers of patients needing steroid treatment compared with placebo.[59] Adverse events (nausea, increases in alanine aminotransferase, back pain, diarrhea and arthralgia) were increased, but not significantly more than placebo.

Teriflunomide is currently being assessed in the treatment of MS in one complete and three ongoing phase III randomized, controlled clinical trials that include a total planned population of 3,270 patients (see *Table 3*). Three of these trials are comparing teriflonomide with placebo and one with IFNβ-1α administered subcutaneously.

The Study of Teriflunomide in Reducing the Frequency of Relapse and Accumulation of disability in Patients with Multiple Sclerosis (TEMSO) has recently reported data for the randomized treatment period. A total of 1,088 patients with RRMS received either teriflunomide 7 or 14 mg or placebo once daily for 108 weeks. Both teriflunomide doses significantly reduced the annualized relapse rate compared with placebo (0.539, 0.370, and 0.369, for placebo, 7 and 14mg, respectively). In addition, the risk for disability progression was reduced by 23.7% (p=0.0835) and 29.8% (p=0.0279) in the 7 and 14mg groups.[60] Both teriflunomide doses also significantly reduced various MRI parameters including total lesion volume (p<0.05 for both doses), Gd-enhancing T1 lesions (p<0.001 for both doses).[61] Overall, teriflunomide was well-tolerated; similar numbers of patients in each group reported AEs and SAEs.

Dimethyl Fumarate (BG 00012)

Dimethyl fumarate has diverse modulating effects on immune function by promoting apoptosis in T-cells and changing cytokine synthesis from a Th1 to a Th2 profile. It has been shown to have both anti-inflammatory and potential neuroprotective properties in animal models.[62]

In a phase II clinical study including 257 patients with RRMS, 720mg/day dimethyl fumarate significantly reduced Gd-enhancing, new T2 and T1-hypointense lesions compared with placebo (p<0.001, p=0.006, and p=0.01, respectively). It also produced a trend towards reduction in relapses.[6] Dimethyl fumarate was generally well tolerated; adverse events included flushing, gastrointestinal symptoms, headache, fatigue, and elevation of liver enzymes in a small number of patients.

Two phase III trials are in progress comparing relapse rates and the incidence of MRI lesions in a total of 2,243 RRMS patients. These patients are being treated with 480mg/day or 720mg/day dimethyl fumarate or glatiramer acetate in one study and these same doses of dimethyl fumarate or placebo in the other study (see *Table 3*).

Likely Impact of New Medications on the Treatment of Multiple Sclerosis

A possible decision-making process in MS treatment after the introduction of alemtuzumab and oral DMTs is given in *Figure 2*. If successfully licensed for the treatment of MS, alemtuzumab may prevent many patients from progressing to more advanced MS or at least slow disease progression to a greater degree than achieved with current medications. The superior efficacy and infrequent dosing interval of alemtuzumab will make it an attractive option for both physicians and patients. Frequent laboratory monitoring will be needed between doses, however, to ensure that patients have not developed thyroid disease, idiopathic thrombocytopenic purpura or Goodpasture's syndrome.

The efficacy of the oral agents appears to be similar to or perhaps only slightly better than the current injectable treatments, with no compelling reason to alter therapy from an evidence-based approach.

However, there will likely be enormous pressure from patients to be prescribed these much more convenient oral therapies. This may cause dilemmas for neurologists whose patients are well-controlled on existing agents that are known to be safe. Convincing the newly-diagnosed patient, in particular, to start therapy with frequent injections could be very difficult when oral options become available. As such, many patients will likely take the risk of the unpredictable or unknown safety profile of a new drug in order to obviate injections when initiating or switching therapies.

Cladribine may be an attractive option to patients due to its short and infrequent dosing course. Patients with breakthrough disease on cladribine, however, will unlikely be able to switch rapidly to another immune suppressive agent such as natalizumab or alemtuzumab as a result of prolonged lymphocytopenia.[5] Fingolimod has more side effects than cladribine, necessitating a careful risk-management assessment. However, it may be a more acceptable alternative for many physicians, since its effects on lymphocyte counts are largely rapidly reversible.[63]

Some head-to-head trials comparing oral agents with intramuscular IFNβ-1α are under way or have been completed, including TRANSFORMS.[52] This study showed the superior efficacy of two doses of daily fingolimod compared to the conventional dose of weekly intramuscular IFNβ-1α on all clinical and MRI primary outcome measures over a one-year period, as described above. The BRAVO study (laquinimod versus intramuscular IFNβ-1α),[57] which is not yet complete, may show similar results. These results will provide valuable assessments of the relative efficacy and safety of new oral therapies versus an injectable DMT.

As with any new drugs, it will take time for the new oral agents to be accepted and find a place in the MS treatment algorithm. However, over time oral medications for MS are likely to make treatment more acceptable to patients and increase the proportion of MS sufferers who receive DMTs. Oral agents may not become first-line options for CIS and RRMS immediately and may instead be limited to MS specialist centers until more safety and efficacy data are available. Long-term clinical experience with alemtuzumab and the new oral DMTs will likely increase confidence in them and lead to more widespread use of these therapies, barring any unforeseen safety issues.

If oral agents become first-line treatments in the long term, the existing injectable DMTs are likely to become second-line alternatives. Alemtuzumab and natalizumab will probably remain second-line treatments for severe or refractory disease for the time being. The widespread availability of sensitive and specific JC virus antibody testing for natalizumab patients, as well as increasing confidence in risk-management for alemtuzumab patients may, however, bring these therapies to the front line for treating severe cases in particular. It is unknown whether any of the newer agents will provide benefit to patients with primary or secondary progressive MS.[17]

The Future of Multiple Sclerosis Treatment

Current knowledge of the immune process in MS and its progression remains incomplete. Greater understanding of the underlying mechanism of MS is needed to aid in the development of better treatments in the future. In terms of diagnosis, MRI remains the only available paraclinical test that is sensitive to disease activity. The current dependence on MRI as a biomarker for disease activity is costly and inconvenient and is not readily available to patients in many world regions outside the US and Europe. The development of other biomarkers for MS, such as a blood test that is indicative of active disease or is predictive of a relapse or disease progression, is sorely needed. It would simplify diagnosis, help in the monitoring of patients receiving medications and allow for more targeted treatments.

Available and new therapies are becoming ever more successful in tackling the inflammatory process in MS but do not halt progression once it is established. Although treatments may halt inflammatory disease activity for up to five years or more in some patients, many patients continue to exhibit irreversible brain atrophy and progressive disability despite the suppression of all visible markers of inflammation. Currently, no 'neuroprotective' agents are available to slow this phase of the disease course.

Medications that offer effective treatment for primary and secondary progressive MS are currently the largest unmet clinical need. The greatest challenge for the future remains to develop therapies that can provide superior neuroprotection, promote remyelination, and allow for CNS repair that would result in the restoration of neuronal function and actually reverse existing disability. ■

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