TARGET AUDIENCE
This activity has been designed for physicians, nurses, and other clinical practitioners involved in the treatment of patients with multiple sclerosis.

ACTIVITY OVERVIEW
Neurologists and multiple sclerosis (MS) nurses provide the foundation of care for patients with MS. Together, they determine the best course of action and management plans for each patient. However, the most recent evidence-based guidelines on disease-modifying therapies (DMTs) were published in 2002. Since then, data regarding new approaches to therapy have been published, and there are orally administered therapies being evaluated in phase II/III clinical trials, which are not discussed in the guidelines. In order to maximize patient outcomes, neurologists and other specialists who care for patients with MS need to be informed of the latest developments regarding MS and any emerging data on DMTs that could impact their practice. This journal supplement focuses on magnetic resonance imaging findings and their role in treating patients with a CIS, the risks/benefits of oral agents in the pipeline, and how to incorporate these topics into clinical practice.

EDUCATIONAL OBJECTIVES
Upon completion of this activity, participants should be able to:

• Describe current approaches to the clinical management of patients with MS and the evidence base for these practices
• Discuss the rationale for making changes to treatment protocols in patients with MS
• Evaluate emerging treatments for MS and the potential impact they may have with first-line use in newly diagnosed patients
• Explain how magnetic resonance imaging supports treatment decision making in patients with a clinically isolated syndrome

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<tr>
<td>Suhayl Dhib-Jalbut, MD</td>
<td>Grants/research support from Teva Neuroscience, Serono, and Bayer.</td>
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<td></td>
<td>Consultant with Teva Neuroscience, Serono, Bayer, and Biogen.</td>
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<td>Peter Calabresi, MD</td>
<td>Grants/research support from Teva Neuroscience, Serono, Bayer, Biogen-IDEC, and Vertex.</td>
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**MEDIA**

Journal supplement

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There is no fee for this educational activity.
Today’s Practice, Tomorrow’s Potential: Evidence-Based Debates in MS Management

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INTRODUCTION

These are the proceedings of a symposium that occurred at the Consortium of Multiple Sclerosis Centers annual meeting on June 4, 2010. Since then, the oral agent, fingolimod, has been approved by the United States Food and Drug Administration (FDA) for first-line use (September 22, 2010).

Multiple sclerosis (MS) is an immune-mediated, chronic, and debilitating disease of the central nervous system (CNS) currently affecting approximately 400,000 individuals in the United States, mostly women. The disease is characterized by discrete lesions or plaques in the CNS with demyelination of axonal sheaths and axonal loss. This occurs early, is persistent, and leads to the progressive neurologic disability seen in most patients over the long term. Relapsing-remitting MS (RRMS) is a form of MS seen in approximately 85% of patients. Typically, patients with RRMS have clearly defined acute attacks/exacerbations (relapses) of neurologic symptoms followed by remissions. These relapses have a measurable and sustained effect on accrued disability.

The first attack of RRMS is a clinically isolated syndrome (CIS), commonly presenting as optic neuritis, a brainstem syndrome, or partial myelitis. Most patients with untreated RRMS ultimately will transition to secondary progressive MS (SPMS), a progressive phase of irreversible neurologic deterioration, with or without relapses; approximately 50% will develop SPMS within 10 years of diagnosis.

Reducing the occurrence of relapses and slowing neurologic progression are central goals in treating MS. Currently available disease-modifying therapies (DMTs), which include 3 interferon (IFN) beta preparations (intramuscular [IM] IFN beta-1a, subcutaneous [SC] IFN beta-1a, SC IFN beta-1b), glatiramer acetate (GA), natalizumab, mitoxantrone, and fingolimod, have demonstrated meaningful benefits in patients with RRMS in randomized clinical trials. Extension trials for IFN beta and GA have demonstrated fewer relapses and lesions on conventional magnetic resonance imaging (cMRI) and slowing of disease progression. More recent randomized trials have found that the SC IFN beta agents and GA are equally effective in achieving these outcomes. However, all of these agents are only partially effective, with many patients not achieving significant benefit. In addition, DMTs’ ability to prevent long-term disability remains unproven.

Currently, research is moving at a rapid pace toward developing new therapies and treatment protocols that can more effectively prevent disease progression and limit disability in patients with MS. To optimize patient outcomes, clinicians who care for MS patients need to be informed of the latest developments and new ways to maximize clinical benefits in their practice. Four particular areas of interest to clinicians routinely managing MS patients include:

1. the role of MRI in determining when to initiate DMT following a CIS;
2. the risk/benefit of investigational oral agents that are and may soon be available, which will present clinicians and patients with an alternative to injectable therapy;
3. the practical implications of treating CIS patients with DMTs, emphasizing patient concerns and treatment adherence; and
4. the potential clinical and patient-related issues surrounding the implementation of oral MS therapy in daily practice.

CAN MRI FINDINGS DETERMINE WHEN TO INITIATE A DMT IN PATIENTS WITH A CIS?

Rationale

Histological studies have demonstrated that while MS is characterized by demyelination of axonal sheaths and axonal damage and loss, the key underlying pathological changes likely are related to oligodendrocyte damage or loss in the course of chronic inflammation of CNS tissue. The progressive phase of MS, activated microglia appear to promote axonal damage and loss; multiple studies in patients with MS indicate that early tissue damage leads to cumulative disability in the future. Treatment with a DMT has been shown to be more effective in treating RRMS compared with progressive MS.

Baseline cMRI studies have shown that 50%-80% of patients with a CIS have ≥1 asymptomatic gadolinium (Gd)-enhancing or T2 lesion, confirming early onset of disease activity predating the initial clinical event. Spinal cord T2 lesions, brain and spinal cord atrophy, and chronic T1 hypointensities (black holes) also are seen on MRI in CIS patients at presentation. Studies using advanced and quantitative MRI techniques reveal reduced levels of neuronal metabolites, such as N acetyl aspartate (NAA) or whole brain NAA (WBNA) in patients with a CIS. Nonconventional MRI studies have shown that tissue damage occurs in normal-appearing white matter (NAWM) and normal-appearing gray matter (NAGM) outside of T2 lesions. Studies indicate that widespread axonal damage occurs at the earliest stages of MS, even before presentation. Further studies show that changes in metabolite levels also correlate with functional disability as measured by the Kurtzke Expanded Disability Status Scale (EDSS) and that
early axonal damage and transection within the CNS contributes to the development of functional disability from the earliest stages of the disease. \textsuperscript{12,34,35} These data strongly support the institution of early therapy with a DMT in patients presenting with a CIS to slow or prevent early axonal damage and disability and reduce the risk of developing MS in the future.

However, not all CIS patients with brain lesions on MRI suggestive of MS will develop MS. Once other conditions that can mimick MS have been ruled out, specific diagnostic criteria for MS must be met, such as clinical/lesion dissemination in time (DIT) and dissemination in space (DIS) on MRI. Furthermore, patients with a CIS who do not have initial brain lesions on MRI can develop MS. The initial challenge to the clinician is to identify which patients with a CIS are at highest risk for progression to MS and subsequent disability, as this can help determine a prompt and appropriate therapeutic strategy. Many studies have demonstrated the value of cMRI findings in guiding this decision.

Evidence

The following studies indicate that baseline brain lesions on cMRI in patients with a CIS are predictive of developing MS and future disability.

**Summary of CIS Follow-up Studies**

In an early and seminal study, O’Riordan and colleagues conducted a follow-up study of 81 patients with a CIS who had serial cMRI at baseline, 1.3 years, 5.3 years, and 10 years. \textsuperscript{30} Initial brain MRI was abnormal in 54 of the patients (67%). In patients without baseline lesions, the chance of developing MS at 10 years was only 11%. However, patients with 1 baseline lesion had a 33% chance of developing MS, those with 2-3 baseline lesions had an 87% chance, those with 4-10 baseline lesions had an 87% chance, and those with > 10 baseline lesions had an 85% chance of developing MS.

In patients without baseline lesions on MRI, a score of 5.5 on the EDSS (usually needing a cane to walk at 5.5-6.0) during the 10-year follow-up period was reached in 4%, 13% reached an EDSS of 5.5 with 2-3 baseline lesions, 20% reached an EDSS of 5.5 with 4-10 baseline lesions, and 35% reached an EDSS of 5.5 with > 10 baseline lesions.

In this study, the clinical subtype of disease at 10 years of follow-up also was associated with the number of lesions on baseline brain MRI. Of the 27 patients (33%) with no initial MRI lesions, 82% had no second relapse at 10 years. Of the patients with baseline brain MRI lesions, the 10-year follow-up found that 39% had benign MS, 20% had RRMS, and 24% had SPMS. In total, 83% of patients had progressed to MS.

In another study by Brex et al, a cohort of patients with a CIS (N = 71) were followed for a mean of 14 years with cMRI performed at baseline, 5 years, and 10 years. \textsuperscript{39} Outcomes were similar to those of the O’Riordan et al study. Most patients with no initial MRI lesions (76%) had not experienced further relapses nor had developed MS at 14 years. Patients with a CIS and baseline lesions on MRI had a higher risk both of developing MS and more subsequent disability.

### Table 1. Abnormalities on MRI and Disability From MS\textsuperscript{28}

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Number of Asymptomatic Lesions at Baseline</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0 (N = 21)</td>
</tr>
<tr>
<td>Isolated syndrome – no. (%)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Clinically probable MS – no. (%)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Clinically definite MS – no. (%)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>EDSS score – no.</td>
<td></td>
</tr>
<tr>
<td>&gt; 3</td>
<td>0</td>
</tr>
<tr>
<td>≥ 6</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Median EDSS score</td>
<td>1.75</td>
</tr>
<tr>
<td>Range of EDSS score</td>
<td>1-2</td>
</tr>
</tbody>
</table>

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The study of Fisniku et al\textsuperscript{36} carried out the longest follow-up of patients with a CIS to date (N = 107; 20 years) and included the same cohort of patients from the Brex et al study. In the Fisniku trial, nearly 80% of patients with no baseline MRI lesions still had not progressed to RRMS at 20 years. The risk of developing MS over 20 years varied based on initial MRI lesions: 21% for those patients with no initial lesions; > 80% for those with ≥ 1 lesion; and 82%, 85%, and 81% for those with 1-3, 4-9, and > 10 baseline lesions, respectively. The risk of long-term disability on the EDSS also increased significantly with a greater number of baseline lesions on cMRI. An EDSS of ≥ 6.0 at 20 years was exhibited in 6% of those with no baseline lesions, 18% in those with 1-3 baseline lesions, 35% in those with 4-9 lesions, and 45% in those with ≥ 10 lesions.

Gauthier et al compared annualized rates of brain atrophy in patients with benign MS (disease duration 10-14 years from initial diagnosis and EDSS score of ≤ 1.5 or disease duration ≥ 15 years and EDSS score ≤ 2.0) with that of typical patients with early RRMS (disease duration ≤ 5 years). \textsuperscript{37} In both groups, MRI was performed at baseline and at a mean of 2 years; the rate of brain atrophy progression was significantly faster in patients with early RRMS vs those with benign MS (P = 0.02). This difference remained significant despite treatment with a DMT in either group (P = 0.01). Although benign MS can be diagnosed only in retrospect, these data suggest that...
patients with a low rate of brain atrophy might have a benign course. However, further evaluation is needed to determine if brain atrophy rates can accurately and reliably predict the disease course in MS.

**Summary of CIS Study Outcomes**

These studies demonstrate that there is a 50%-98% chance of a subsequent diagnosis of MS in patients with a CIS presenting with lesions on a baseline cMRI compared with a < 25% chance in those with no detectable baseline lesions.10,12,28-30,36,38-41 The risk of long-term disability correlated with the number and volume of baseline lesions in these studies. Baseline spinal cord T2 lesions also are predictive, and the frequency of subsequent MS has been higher with combined brain and spinal cord lesions at baseline compared with brain lesions alone.10,43,45 Spinal cord lesions also have been significant predictors of disability in patients presenting with optic neuritis who progressed to MS.46 The abnormalities seen in normal-appearing brain tissue (mentioned earlier) can indicate progression to MS.12

**MRI Criteria for MS in Patients With a CIS**

The early diagnosis of MS in patients with a CIS facilitates prompt treatment with DMTs, alleviates patient and physician uncertainty, and enables clinicians to provide patients with prognostic counseling.11 A recent position paper from the MAGNIMS (Magnetic Imaging in MS) group proposed a new diagnostic algorithm based on T2 lesions for patients with a CIS.11 A potentially useful algorithm proposed to neurologists and other clinicians who manage MS patients suggests that a single cMRI at any time showing multiple lesions in different places in the brain and 1 or more asymptomatic Gd-enhancing lesion is sufficient to diagnose MS, since both DIT and DIS criteria are satisfied in one MRI.

**Evidence for Benefits of Early Treatment in a CIS**

Conventional MRI is used to determine when or if a DMT is indicated in patients with a CIS, with a goal of starting treatment as early as possible to slow underlying disease processes. In pivotal, placebo-controlled trials of first-line agents in MS, treatment with all of the IFN beta preparations or GA (all are considered first line for a CIS) were shown to slow disease progression between these groups, 3-year BENEFIT performance in the early treatment group.

Furthermore, the 1- and 3-year extension phases of BENEFIT53,54 and the 2-year extension of CHAMPS55 demonstrated that outcomes were significantly worse with delayed treatment (patients given placebo first and then started on a DMT 2-3 years later) compared to treatment with DMT from the outset. In the 3-year (total) follow-up of BENEFIT, the risk for progression of disability also was reduced significantly with early vs delayed treatment.53 Although the 5- and 10-year total follow-up of CHAMPS55,56 and the 5-year total follow-up of BENEFIT54 found no significant difference in risk for disease progression between these groups, 3-year BENEFIT data indicated that early treatment at the time of a CIS (as opposed to starting treatment 2 years after a CIS diagnosis) can slow disability for at least 3 years.53 In addition, the 5-year follow-up of BENEFIT indicated better cognitive performance in the early treatment group.53

In the BENEFIT trial, Moraal and colleagues57 studied 468 patients with a CIS who received either early or delayed treatment with IFN beta-1b. They analyzed the prognostic value of baseline cMRI for risk of conversion to MS over 3 years (original trial plus 1-year extension) and assessed whether this was affected by treatment intervention. This study also examined increased risk for conversion to MS posed by DMT on follow-up MRI; at baseline, 64% of patients had fulfilled DIS criteria on cMRI. After 3 years, the overall conversion rate to MS was 42% (37% in the early treatment group and 51% in the delayed treatment group). In this study, the Barkhof diagnostic criteria with the strongest prognostic value for predicting a high risk of developing MS were ≥ 9 T2 lesions (P = 0.006) or ≥ 3 periventricular lesions (P = 0.009) at baseline. The time to MS was related to the number of Barkhof criteria on baseline cMRI and was unaffected by treatment intervention. Onset of CDMS was fastest in patients who received delayed treatment and fulfilled 4 Barkhof criteria at baseline.

**Table 2. Pivotal Clinical Trials in CIS Patients**

<table>
<thead>
<tr>
<th>Trial and Duration</th>
<th>N</th>
<th>Treatment</th>
<th>Progression to MS†</th>
<th>Time to MS (days)</th>
</tr>
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<tbody>
<tr>
<td>CHAMPS58,59</td>
<td>383</td>
<td>IM IFN beta-1a</td>
<td>IFN beta: 35%</td>
<td>IFN beta: 809</td>
</tr>
<tr>
<td>3 yrs</td>
<td>30 mcg weekly or PL</td>
<td>PL: 50%</td>
<td>PL: 397†</td>
<td></td>
</tr>
<tr>
<td>ETOMS60</td>
<td>309</td>
<td>SC IFN beta-1a</td>
<td>IFN beta: 34%</td>
<td>IFN beta: 569</td>
</tr>
<tr>
<td>2 yrs</td>
<td>22 mcg once weekly or PL</td>
<td>PL: 45%</td>
<td>PL: 252‡</td>
<td></td>
</tr>
<tr>
<td>BENEFIT61,62</td>
<td>468</td>
<td>SC IFN beta-1b</td>
<td>IFN beta: 28%</td>
<td>IFN beta: 618</td>
</tr>
<tr>
<td>2 yrs</td>
<td>250 mcg every other day or PL</td>
<td>PL: 45%</td>
<td>PL: 255†</td>
<td></td>
</tr>
<tr>
<td>PreCIS63</td>
<td>481</td>
<td>SC GA 20 mg daily or PL</td>
<td>GA: 25%</td>
<td>GA: 722</td>
</tr>
<tr>
<td>2.3 yrs mean</td>
<td></td>
<td>PL: 43%</td>
<td>PL: 336†</td>
<td></td>
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</table>

†Gd-enhancing and/or T2 lesions were significantly reduced by IFN beta or GA in all trials; T1-hypointense lesions were significantly lower with GA than PL in ETOMS.‡25th percentile

*The current recommended dose is 22 or 44 mcg 3 times weekly

†30th percentile

CHAMPS=Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study; BENEFIT=Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment trial; ETOMS=Early Treatment of Multiple Sclerosis Study; IFN=interferon; IM=intramuscular; GA=glatiramer acetate; PL=placebo; PreCIS=Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis in Subjects Presenting with a Clinically Isolated Syndrome study; SC=subcutaneous

Supplement to the International Journal of MS Care
ing those with baseline cMRI abnormalities, some degree Since not all patients with a CIS progress to MS, includ emphasizes that effective treatment at an early stage of MS long-term proven efficacy and safety of using IFN beta or GA accumulation of functional disability. Freedman highlights the key consideration in stroke management for years, indicating that early implementation of treatment may prevent loss of normal brain tissue and function.64 Similarly, early initiation of therapy in MS may prevent irreversible CNS damage related to axonal damage and loss of brain volume, as well as the accumulation of functional disability. Freedman highlights the long-term proven efficacy and safety of using IFN beta or GA in patients with a CIS to reduce the chances of future clinical/radiological relapses and disease progression; this article emphasizes that effective treatment at an early stage of MS may not be as effective later in the disease course.

Conversely, some MS specialists have voiced concerns about early treatment with DMTs in patients with a CIS.60,61 Since not all patients with a CIS progress to MS, including those with baseline cMRI abnormalities, some degree of caution is indicated to avoid months of unnecessary treatment and emotional distress for the patient.60,61 However, the majority of MS experts strongly advocate early treatment with DMTs if clinical and MRI evidence favors progression to MS. Some clinical parameters/features predictive of conversion to MS are younger age (although this is somewhat controversial),52,62 smoking,63 poly-symptomatic vs unifocal onset,47 and presence of cerebrospinal fluid (CSF) oligoclonal bands (OCBs).64,65 Studies show that a severe initial demyelinating event, a short time period between first and second neurological events, poor recovery from a first event, and a higher number of relapses in early years all are moderately predictive of increased future disability.12,66 Whether to treat a patient with a CIS often is a physician’s decision based on analysis of all available clinical, imaging, and laboratory information. For some patients with a CIS, the presence of brain atrophy or black holes on MRI (which can be seen in a CIS and reflect chronic and severe tissue damage) or OCBs may favor early and more aggressive treatment with DMTs.

In most patients with a CIS and > 90% of those with MS, OCBs are present in the CSF. OCBs typically are detected using isoelectric focusing/immunoblotting; although they are not specific for MS, they can be used together with brain MRI to strengthen predictive accuracy. One recent study has shown that the presence of OCBs in patients with a CIS increased the risk of MS independent of baseline cMRI characteristics (using Barkhof criteria).64 Analysis of CSF for OCBs may be helpful most in patients with a normal brain MRI or those with nonspecific neurological symptoms and MRI findings. OCBs add little predictive value if the MRI shows CNS damage in tissues that appear normal on imaging, and laboratory information. For some patients with a CIS, advanced MRI techniques, such as magnetization transfer imaging (MTI), magnetic resonance spectroscopy (MRS), and diffusion-tensor imaging (DTI), have shown CNS damage in tissues that appear normal on Advanced MRI

In patients with a CIS, advanced MRI techniques, such as magnetization transfer imaging (MTI), magnetic resonance spectroscopy (MRS), and diffusion-tensor imaging (DTI), have shown CNS damage in tissues that appear normal on

![Figure 1](http://meridian.allenpress.com/doi/pdf/10.7224/1537-2073-12.S3.1)
cMRI. Although there is some evidence in small studies that advanced imaging techniques may help in predicting progression to MS, additional studies are needed. These MRI techniques also have limited availability in daily clinical practice. At present, cMRI is the best available tool to predict subsequent development of MS and future disability.

**Patient Preferences**

Patient concerns and preferences always should be considered in the treatment decision making process whenever possible. Some patients with a CIS may not be ready for or want early treatment. Patients must be willing to adhere to a DMT regimen, even if they are feeling well. Some patients may prefer to wait until a diagnosis of MS is confirmed before they make a commitment to a treatment regimen. Physician-patient interactions (discussed below) and detailed patient education on treatment risks and benefits are of great importance in the therapeutic decision making process, patient adherence to therapy, and clinical outcomes.

**WILL ADVERSE EFFECT PROFILES OF ORAL AGENTS LIMIT THEIR FIRST-LINE USE IN THE TREATMENT OF RRMS?**

**Rationale**

New oral drugs currently under investigation for the treatment of MS are becoming available and present a long-awaited opportunity for clinicians to decrease the burden of painful DMT injections. An effective and safe oral agent could reduce restrictions on patients’ lifestyle and improve patient adherence to therapy, which has been a significant problem with current long-term DMTs. Studies of traditional DMT use in MS have reported patient adherence rates as low as 28%. Poor adherence to therapy decreases optimal clinical benefit of any medication, including DMTs for MS. The World Health Organization (WHO) recently concluded that improving adherence would have an even greater effect on health outcomes than improving the efficacy of specific treatments.

IFN beta preparations or GA are first-line agents for the treatment of RRMS. Oral MS agents will be attractive for first-line therapy if they are proven to be at least as effective and safe as these DMTs. The differing mechanisms of action of new oral agents also may facilitate improved treatment of suboptimal responders to initial DMTs by offering more options for switching agents and/or combination regimens.

However, some significant adverse effects (AEs) of investigational oral agents have been observed, and the risk/benefit profiles for these agents and their long-term safety still are under investigation. AEs of oral drugs may outweigh benefits in certain individuals with MS, and whether they replace existing first-line agents is a matter of debate among clinicians. Recent literature suggests that as AEs have accounted for much of the lack of patient adherence to injectable DMTs, including AEs unrelated to direct injection-site reactions, administering therapeutic agents through an alternative route, such as orally, may not eliminate poor patient adherence to treatment. It remains to be seen if AEs of new investigational oral agents also will result in poor adherence or if giving treatment orally will improve adherence significantly.

**Evidence**

Five investigational oral agents for the treatment of MS have reached the most advanced stages of clinical testing: fingolimod (approved by the FDA on September 22, 2010 as a first-line treatment for relapsing forms of MS); cladribine (completed phase III trials; in July 2010, cladribine was approved for use in Russia and received priority review status by US drug regulators); laquinimod (in phase III trials); teriflunomide (in phase III trials); and oral fumarate (BG00012; in phase III trials). Characteristics and putative mechanisms of action of these agents in MS are shown in Table 3. Knowledge of the efficacy vs toxicity of these oral agents in major trials and comparison with current DMTs (in head-to-head trials or indirectly) are required to accurately assess risks/benefits and to determine whether these new oral drugs might be considered first-line therapy for MS. Head-to-head trials would provide the best evidence for comparative efficacy between new oral agents and established DMTs. Selected AEs of these 5 oral drugs that likely are drug related are shown in Tables 4 and 5.

**Fingolimod (FTY720)**

The recently completed 1 year, phase III TRANSFORMS (Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis) study included 1292 RRMS patients and found that oral fingolimod 0.5 or 1.25 mg daily was significantly more effective than IM IFN beta-1a 30 mcg/week in reducing annualized relapse rates (52% with 0.5 mg and 38% with 1.25 mg, P < 0.001 for both) and MRI outcomes (reduction in brain volume and number of new or enlarged lesions) (Figure 2). For annualized rate of relapse, the relative risk reduction for fingolimod was 54% for 0.5 mg

![Figure 2. Fingolimod Phase III TRANSFORMS Trial](image-url)
Oral formulation of dimethyl fumarate

Synthetic purine analog

Analogue of sphingosine and acts as a sphingosine-1-phosphate (S1P) receptor modulator

Not appear serious. Continued administration of fingolimod and usually resolved within 24 hours; they did not appear serious. Effects were seen approximately 1 hour after the first dose of fingolimod.

Leading to study withdrawal included bradycardia, sinus bradycardia, and antioventricular (AV) block. These symptoms seen in the fingolimod treatment groups were related to myocar- dia, and atrioventricular (AV) block. These symptoms seen in the fingolimod treatment groups were related to myocar-

Effects were dose related and generally differed from the AEs in the IFN beta group. The most common side effects were headache, upper respiratory infection (URI), and fatigue. AEs leading to study withdrawal included bradycardia, sinus brady-

T-cell interactions with antigen-presenting cells, and decreased microglial activity

Immuno-suppressant with a main effect of preferential lymphocyte depletion in both proliferating and quies-

dose and 60% for the 1.25 mg dose compared with placebo. Significantly less brain atrophy was evident in the fingolimod treatment groups compared with placebo.

Disability progression was similar (and infrequent) in both treatment groups.

In the fingolimod treatment group resulted in 2 fatalities (dissemi-

Patients starting cladribine should be informed that the dose regimen will cause immunosuppression for a year or longer, which includes a long duration of any AEs related to immunosuppression, and that it may be carcino-

Table 3. Putative Mechanisms of Action of New Oral MS Drugs

BG00012

Oral formulation of dimethyl fumarate

Mechanism of benefit in MS patients unclear

Preclinical data suggest activation of the nuclear factor-E2-related factor 2 (Nrf2) transcriptional pathway,

Other suggested mechanisms of action include inhibitory effects on transcription of RNF alpha-induced genes

Fingolimod

Analogue of sphingosine and acts as a sphingosine-1-phosphate (S1P) receptor modulator

Binding of fingolimod to S1P receptors of lymphocytes and thymocytes causes receptor internalization, result-

Binding of fingolimod to S1P receptors in the CNS may elicit a neuroprotective effect

Comparison of fingolimod vs placebo alone over 2 years in patients with RRMS.

Flu-like symptoms and depression occurred more often with fingolimod than IFN beta.

Table 4, and 2 other deaths occurred post-study. However, the role of fingolimod in these was uncertain. Macular edema occurred in the fingolimod groups, but the mechanism was unclear. Malignancies, including basal-cell carcinoma, melanoma, and breast cancer also occurred, but the number of cases was too low to assess causality (1.9% of the 0.5 mg group, 1% of the 1.25 mg group, and 0.2% of the IFN beta-1a group).

Fingolimod was significantly superior to placebo

Flu-like symptoms and depression occurred more often with IFN beta than fingolimod.

A second large, phase III trial of fingolimod called FREE-

DOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis) (N = 1272) confirmed benefits of fingolimod vs placebo alone over 2 years in patients with RRMS. 85 Fingolimod was significantly superior to placebo.
### Table 4. Adverse Effects of Cladribine and Fingolimod (FTY720) in Phase III Trials*

<table>
<thead>
<tr>
<th>Study and Adverse Effects†</th>
<th>Incidence in Treatment Groups (% or n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFN beta-1a</td>
</tr>
<tr>
<td>TRANSFORMS (N = 1280)</td>
<td></td>
</tr>
<tr>
<td>ALT elevation</td>
<td>2</td>
</tr>
<tr>
<td>Bradycardia, serious</td>
<td>0</td>
</tr>
<tr>
<td>AV block, 1st or 2nd degree</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.6</td>
</tr>
<tr>
<td>Neoplasm¶</td>
<td></td>
</tr>
<tr>
<td>Herpes virus infection</td>
<td>3</td>
</tr>
<tr>
<td>Serious</td>
<td>0.2</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>0</td>
</tr>
<tr>
<td>Macular edema</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>n = 0</td>
</tr>
<tr>
<td>Fatal infection</td>
<td>n = 0</td>
</tr>
<tr>
<td>Leading to study withdrawal</td>
<td>4</td>
</tr>
<tr>
<td>FREEDOMS (N = 1272)</td>
<td></td>
</tr>
<tr>
<td>LRI or lung infection</td>
<td>6</td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>5</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.2</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.8</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>n = 4</td>
</tr>
<tr>
<td>Serious</td>
<td>n = 0</td>
</tr>
<tr>
<td>Bradycardia or bradyarrhythmia</td>
<td>0.7</td>
</tr>
<tr>
<td>Serious bradyarrhythmia</td>
<td>0.2</td>
</tr>
<tr>
<td>AV block, first degree§</td>
<td>0.5</td>
</tr>
<tr>
<td>Neoplasm▲</td>
<td>n = 10</td>
</tr>
<tr>
<td>Macular edema</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE leading to study withdrawal</td>
<td>8</td>
</tr>
<tr>
<td>CLARITY (N = 1319)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia, severe</td>
<td>n = 0</td>
</tr>
<tr>
<td>Infections, all</td>
<td>43</td>
</tr>
<tr>
<td>Serious</td>
<td>2</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>n = 0</td>
</tr>
<tr>
<td>Serious</td>
<td>n = 0</td>
</tr>
<tr>
<td>Neoplasm (see text)</td>
<td>0</td>
</tr>
<tr>
<td>Leading to study withdrawal</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocytopenia or leukopenia</td>
<td>0</td>
</tr>
</tbody>
</table>

*Table only includes AEs that occur more than with placebo and likely are drug related.  
†N = number of patients in studies available for adverse-event reporting (less than baseline N)  
§Much higher incidence of first- and second-degree AV block observed on electrocardiography performed on day 1 (see text).  
▲Basal-cell carcinoma (BCC), breast cancer, melanoma, Bowen’s disease, and endometrial cancer, which overall occurred more often with placebo; however, BCC was more frequent with fingolimod (5 cases) than placebo (3 cases).  
¶BCC (5 patients), melanomas (3 patients), and breast cancer (4 patients) in fingolimod groups, and 1 case of squamous-cell carcinoma in the IFN beta group; fingolimod-associated cases did not appear dose related.  
‡One caused by disseminated primary varicella zoster infection (in an already immunocompromised patient), and one caused by herpes simplex encephalitis.  
ALT=alanine aminotransferase; LRI=lower respiratory tract infection; URI=upper respiratory tract infection
with respect to reductions in annualized relapse rates (55% with 0.5 mg and 60% with 1.25 mg, \( P < 0.001 \) for both) and kept 75%-79% of patients from both treatment groups relapse-free over the 24-month period, compared to 46% with placebo (Figure 3).85 Both fingolimod doses (0.5 mg and 1.25 mg) also significantly reduced the risk of disability progression and MRI disease measures, including brain volume loss. Similar to TRANSFORMS, the most common AEs were headache, URI, fatigue, and abnormal liver function tests. AEs resulting in study withdrawal included bradycardia and AV block, most often after the first dose. AV block was reported infrequently as an adverse event (Table 4), with electrocardiography on day 1 revealing first-degree AV block in 9% of patients in the 1.25 mg group and 5% of the 0.5 mg group compared with 1% of the placebo group. Second-degree AV block after the first dose was seen on electrocardiography in 0.2% of the 0.5 mg group and 0.9% of the 1.25 mg group. Cancers (basal-cell carcinoma, breast cancer, melanoma, and Bowen's disease) were reported (Table 4). Other serious AEs included macular edema and lymphopenia. Three deaths occurred (2 in placebo group, 1 from suicide in fingolimod group).

Cladribine (2-chlorodeoxyadenosine)

CLARITY (Cladribine Tablets Treating Multiple Sclerosis Orally) is a recently completed placebo-controlled, phase III trial of cladribine in RRMS patients (N = 1326). Cladribine was given in cumulative doses of either 3.5 mg/kg or 5.25 mg/kg over 96 weeks. The drug was administered in 2-4 short courses in the first 48 weeks and 2 short courses during a second 48-week period, with courses constituting one or two 10 mg tablets once daily for the first 4-5 days of a 28-day period. As seen in Figure 4,84 the relapse rate at 96 weeks (primary endpoint) was reduced by over 50% with either dose of cladribine vs placebo (\( P < 0.01 \)), and a high proportion of patients in the treatment groups were relapse-free (80% of the 3.5 mg/kg group and 79% of the 5.25 mg/kg group). There also was a significant reduction in the risk of 3-month sustained disability progression and measures of MRI disease activity in both cladribine treatment groups.

Adverse effects of cladribine included headache, lymphocytopenia, nasopharyngitis, URI, nausea, and 20 cases of herpes zoster (occurring more often in the higher-dose treatment group, see Table 4). Neoplasms were benign, malignant, or unspecified and included cervical carcinoma in situ, benign uterine leiomyoma, melanoma, pancreatic or ovarian cancer, and myelodysplastic syndrome. There were 3 cases of cancer in the 3.5 mg/kg cladribine treatment group—a melanoma and carcinomas of the pancreas and ovary. The role of cladribine in these malignancies is uncertain due to the small number of cases. Study withdrawal occurred in 2% of the placebo group, 3.5% of the 3.5 mg/kg group, and 8% of the 5.25 mg/kg group. Six deaths occurred, equally distributed across study groups; the role of cladribine is uncertain.

Laquinimod

A proof-of-concept study in patients with relapsing MS, primarily RRMS (N = 209)87 was published by Polman et al. In this multicenter, double-blind, randomized, controlled trial, patients with RRMS (n = 177) or SPMS (n = 32) were randomized to either laquinimod 0.1 mg, laquinimod 0.3 mg, or placebo and followed for a total of 32 weeks. Laquinimod 0.3 mg/day was significantly more effective than placebo in reducing active lesions on brain MRI after 24 weeks (lesion reduction of 44%, \( P = 0.0498 \)), whereas 0.1 mg/day was not. A greater reduction in active lesions (52%) was seen in patients with \( \geq 1 \) active lesion at baseline (\( P = 0.005 \)). There was no significant difference between the treatment groups and placebo with regard to clinical parameters, including relapses and disability. Treatment AEs included urinary tract infection (UTI), brain contusion, iritis, and burning sensation; follow-up AEs included tonsillitis and breast cancer. Twenty-

**Figure 3.** Fingolimod Phase III FREEDOMS Trial85

**Figure 4.** Cladribine Phase III CLARITY Trial84
five percent of patients had an exacerbation of MS during the treatment period, with no significant difference between treatment groups.

In a placebo-controlled, 36-week, phase IIb trial in RRMS patients (N = 306), brain MRI scans were performed at baseline and monthly from weeks 12 to 36. In patients in the laquinimod 0.6 mg/day treatment group achieved a 40% reduction in the mean cumulative number of Gd-enhancing lesions per scan on the last 4 MRI scans compared with placebo (P = 0.0048). The 0.3 mg/day dose in this trial had no significant effect on enhancing lesions vs placebo. The incidence of AEs was similar in all groups (5.1% of the 0.3 mg group, 2.8% of the 0.6 mg group, 4.9% of the placebo group), and no deaths were reported. Chest pain occurred in 2 patients in the 0.3 mg group and in 4 patients in the 0.6 mg group. Other AEs included arthralgias, elevated C-reactive protein (CRP), elevated fibrinogen, and dose-dependent increases in liver function tests (LFTs). Infection rates did not differ in the treatment groups compared with placebo, except for herpes virus infections.81

Adverse effects likely related to laquinimod in both the Comi et al and Polman et al trials are shown in Table 5. Elevations in CRP were not determined to be drug related in either study.88

### Teriflunomide

In a 36-week, placebo-controlled, phase II trial involving patients with RRMS (n = 157) or SPMS with relapses (n = 22),86 teriflunomide at doses of 7 or 14 mg/day significantly reduced the median number of active lesions per MRI scan (enhancing, new, or enlarging T2) compared with placebo (P < 0.01). In the 14 mg/day treatment group, teriflunomide significantly reduced the T2 disease burden and decreased disability.

Some AEs occurred more with teriflunomide than placebo (Table 5). Treatment-emergent AEs were reported in all patients, but the majority of these were considered unrelated to the study drug. Common AEs included nasopharyngitis, alopecia, nausea, limb pain, arthralgia, and diarrhea. Serious AEs included hepatic dysfunction, neutropenia, rhabdomyolysis, and trigeminal neuralgia. Reasons for study withdrawal

### Table 5. Adverse Effects of Laquinimod, Teriflunomide, and BG00012 in Phase II Studies*

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Adverse Effects in Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laquinimod</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1 or 0.3 mg/day</td>
<td>209</td>
<td>• LFT elevations: PL 34%, 0.1 mg 34%, 0.3 mg 47%</td>
</tr>
<tr>
<td>Polman et al, 200587</td>
<td></td>
<td>• ESR elevation: PL 6%, 0.1 mg 13%, 0.3 mg 18%</td>
</tr>
<tr>
<td>Laquinimod</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3 or 0.6 mg/day</td>
<td>306</td>
<td>• Chest pain: 0.3 mg, n = 2; 0.6 mg, n = 4</td>
</tr>
<tr>
<td>Comi et al, 200881</td>
<td></td>
<td>• Arthralgia: 0.3 mg, n = 4; 0.6 mg, n = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Herpes simplex/herpes zoster: more frequent than PL only in 0.3 mg group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LFT elevations: PL 11%, 0.3 mg 23%, 0.6 mg 33% (2 times normal level in 2%, 8%, 13%, respectively)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fibrinogen level elevation: PL 29%, 0.3 mg 33%, 0.6 mg 44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CRP elevation: PL 18%, 0.3 mg 11%, 0.6 mg 13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Budd-Chiari syndrome: n = 1 (0.6 mg)†</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 or 14 mg/day</td>
<td>179</td>
<td>• Higher incidence with teriflunomide than PL: nasopharyngitis, alopecia, nausea, ALT elevations,</td>
</tr>
<tr>
<td>O’Connor et al, 200686</td>
<td></td>
<td>paresthesia, back or limb pain, arthralgia, diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Numbers of serious AEs similar with teriflunomide and PL (eg, neutropenia, hepatic dysfunction,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rhabdomyolysis, trigeminal neuralgia): PL, n = 7; 7 mg/day, n = 5; 14 mg/day, n = 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Study withdrawal due to adverse events: PL, n = 4; 7 mg, n = 3; 14 mg, n = 8 (see text)</td>
</tr>
<tr>
<td>BG00012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 mg/day and 120 mg TID or 240 mg TID</td>
<td>257</td>
<td>• Significantly more common with BG00012 (all doses) than with PL: upper abdominal pain (9% vs 3%), flushing (47% vs 9%), hot flash (6% vs 0%)</td>
</tr>
<tr>
<td>Kappos et al, 200882</td>
<td></td>
<td>• More common with 240 mg TID than PL: nausea (16% vs 8%), diarrhea (11% vs 5%), headache (21% vs 11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dose-related AEs with BG00012: headache, fatigue, feeling hot</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GI AEs (nausea, diarrhea, upper abdominal pain): PL 25%, 120 mg/day 30%, 120 mg TID 39%, 240 mg TID 41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infections similar in all groups: 34%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SAEs in PL 12%, all treatment groups 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serious infection (pelvic inflammatory disease) n = 1 in 120 mg TID group</td>
</tr>
</tbody>
</table>

*Table only includes AEs occurring more than with placebo and likely drug related, unless otherwise noted
†Thrombotic venous outflow obstruction of the liver; this patient had Factor V Leiden mutation
ESR=erythrocyte sedimentation rate; LFT=liver function tests; PL=placebo.
in the teriflunomide groups were single cases of rash and abdominal pain (7 mg/day) and single cases of alopecia, erythema multiforme, urticaria, condyloma acuminatum, and hypertension (14 mg/day). Out of 14 noteworthy laboratory value changes, 10 patients had elevated LFTs (n = 4 in placebo, n = 4 in 7 mg/day, n = 2 in 14 mg/day).

Teriflunomide likely is teratogenic and should be avoided in those trying to conceive or in pregnant females. A washout procedure with cholestyramine or activated charcoal can remove teriflunomide in women who wish to become pregnant; in the absence of this washout, it may take 2 years for teriflunomide plasma levels to fall below 0.02 ng/mL after discontinuation, a level considered to present minimal teratogenic risk.36,89

**Oral Fumarate (BG00012)**

Kappos et al assessed the efficacy and safety of oral fumarate (BG00012) in patients with RRMS. In a placebo-controlled, phase IIb trial (N = 257), patients were randomized to BG00012 120 mg/day, 120 mg 3 times per day (TID), or placebo for 24 weeks. In a safety assessment extension, patients who were randomized to placebo received BG00012 240 mg TID for another 24 weeks. Results showed that a dose of BG00012 240 mg TID was more effective than lower doses (120 mg/day or 120 mg TID) in reducing the number of Gd-enhancing lesions during weeks 12-24.82 This dose also reduced the mean total number of Gd-enhancing lesions by 69% vs placebo (P < 0.0001) and decreased the annualized relapse rate by 32% vs placebo (P = 0.272). This study showed that BG00012 generally is well-tolerated (Table 5) although AEs were significantly more common in patients on BG00012 vs placebo. The proportion of infections with BG00012 was similar to placebo (34%). Gastrointestinal adverse events mainly were seen during the early phase of treatment and contributed to the higher discontinuation rate of 9.5% after 6 months in the high-dose 240 mg TID BG00012 group.

**Adverse Effects of Currently Available DMTs**

To provide an indirect comparison with the new oral agents, the principle AEs of currently available injectable DMTs are shown in Table 6.14,17-19,22,73,80,89-103

**Discussion**

**Benefit vs Risk**

The head-to-head comparison of IM IFN beta-1a and oral fingolimod in TRANSFORMS provides the best evidence to date for directly assessing the risk/benefit of an oral agent. However, direct comparisons of oral agents with the SC IFN beta agents or other approved DMTs in similar, sufficiently powered, large, placebo-controlled trials such as TRANSFORMS are lacking.

Although further head-to-head comparative trials are underway, such as ONWARD (comparing SC IFN beta-1a alone and combined with cladribine), CONFIRM (GA vs dimethyl fumarate), and a trial comparing laquinimod and IFN beta-1a,72,80,89 currently clinicians are only able to draw indirect comparisons of available study results to judge benefits vs risks of oral agents. It is important for clinicians to remember that relapse rate reductions of only 29%-34% were achieved with IFN beta preparations or GA in RRMS in the early, placebo-controlled pivotal trials.13,18,19,104 With the caveat of differing trial demographics, this is about half of relapse-rate reductions (50%-60%) observed with cladribine and fingolimod vs placebo in TRANSFORMS, FREEDOMS, and CLARITY. A more informed assessment of risks and benefits will be made possible by long-term efficacy and safety results of ongoing studies with all oral agents.

**Treatment Decisions**

As oral agents become available, MS patients may request a switch from their injectable therapy to an oral drug. In the initial period after FDA approval, making this decision may be challenging for clinicians, especially if the patient is clinically stable on their current injectable DMT. If patients are doing well on their injectable MS therapy, should clinicians risk more serious AEs by switching to an oral agent? In this scenario, the risk/benefit ratio increases, and the patient should be informed that staying on their present injectable medication is prudent, at least until more information and clinical experience are gained with oral therapy over the next several years. Patients also should be informed that oral drugs are not curative and are only partially effective; it is not possible to predict how a patient will respond or which AEs may occur.

In contrast, an oral agent might be considered over other second-line therapies in patients with more severe breakthrough disease. Indications of breakthrough disease include continued MRI activity, relapses, accruing cognitive impairment, and/or disease progression during treatment with first-line agents or an injectable second-line drug, especially if the patient has problems with adherence.

First-line therapy with an oral agent in RRMS could be delayed in most patients until more long-term safety data are available. For each case, both the clinician and patient must evaluate the risks vs benefits of each new oral agent, whether used as first- or second-line therapy for MS (Tables 4-6). Clinical trial data and clinician experience in using oral MS drugs over time will help guide treatment decisions in the future.

**The Immune System and Oral Therapies**

Investigational oral agents for MS may have different mechanisms of action than established first-line treatments, which could prevent immune-related injury early in the disease course.71 However, some oral agents may suppress the immune system in the long term, and this may persist even after early discontinuation of treatment. Issues of immune suppression and if or when to start oral MS therapy demonstrate the need for a consensus-based algorithm that takes into account risks/benefits. This will help clinicians with decision making aspects regarding oral agents while also considering all other available treatment options.
Overview
An effective dialogue between the clinician and patient is essential when deciding whether to treat a CIS early or to use a new drug in any subtype of MS. This interaction builds patient trust, prevents breakdowns in care, and facilitates patient adherence to therapy. However, adequate clinical time is required for effective provider-patient interaction to ensure that patients fully understand their condition, address why therapy is or is not recommended, address patient expectations of that therapy, and ensure adequate follow-up. In particular, the introduction of oral MS drugs will place greater demands on clinical time and will create new issues and challenges for both patients and providers.

MRI in CIS
As discussed above, in patients with a CIS, MRI is an important tool predictive of future development of MS. Using MRI, clinicians may recommend early treatment of a CIS to delay the next relapse, reduce MRI-disease activity, and minimize disability. Patients with a CIS or MS should be fully informed about their condition, their need for treatment, and realistic expectations of treatment; they also should be involved in the decision-making process (Table 7). Experts agree that the clinician-patient interaction provides the patient with a sense of

Table 6. Adverse Effects of Current Injectable DMTs Observed in Clinical Trials

<table>
<thead>
<tr>
<th>IFN Beta Agents†</th>
<th>Glatiramer Acetate‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Headache</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>Injection-site reactions</td>
</tr>
<tr>
<td>Blood dyscrasia, leukopenia, lymphopenia, anemia</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>LFT elevations</td>
<td>Postinjection systemic reaction (dyspnea, chest tightness, tachycardia, anxiety)</td>
</tr>
<tr>
<td>Depression</td>
<td>(Antibodies but do not affect clinical response) Pain</td>
</tr>
<tr>
<td>(NAbs)‡</td>
<td>Nausea</td>
</tr>
<tr>
<td>GI upset</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Peripheral vascular symptoms</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Menstrual disorders</td>
<td>Rash</td>
</tr>
<tr>
<td>Seizures</td>
<td>Uncommon: Lipatroph, injection-site necrosis, lymphadenopathy, modified immune response</td>
</tr>
<tr>
<td>Depression, anxiety</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Natalizumab</th>
<th>Mitoxantrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Headache</td>
<td>Menorhea</td>
</tr>
<tr>
<td>Infections</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>URI</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Infusion reactions (more frequent if persistent antibodies to natalizumab)</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>(Anti-natalizumab antibodies)**</td>
<td>GGT elevations</td>
</tr>
<tr>
<td>Depression</td>
<td>Systolic dysfunction (asymptomatic)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Menstrual disorders</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Changes in blood-cell counts</td>
<td>Uncommon: TRAL, CHF</td>
</tr>
</tbody>
</table>

Uncommon: PML, hepatotoxicity, melanoma

†SC IFN beta-1a, SC IFN beta-1b, IM IFN beta-1a. Injection-site reactions and LFT elevations more common with SC preparations than IM IFN beta-1a; flu-like symptoms more frequent with IM IFN beta-1a than SC agents.
‡If persistent, can reduce biologic activity and clinical efficacy.
*Does not usually cause LFT elevations, flu-like symptoms, or hematologic abnormalities seen with IFN betas
**May reduce efficacy and increase chance of infusion reactions
CHF=congestive heart failure; LFT=liver function tests; GGT=gamma-glutamyl transferase; NAbs=neutralizing antibodies; PML=progressive multifocal leukoencephalopathy; TRAL=therapy-related acute leukemia
**Table 7. Patient Interaction: What Should be Discussed With the CIS Patient**

- Definition of a CIS
- The importance and implications of a CIS
- Are you confident in the diagnosis of CIS?
- Brief natural history of CIS and MS
- What MRI does and what findings mean with respect to underlying disease activity, progression to MS, and subsequent disability
  - Brain lesions at time of a CIS mean a much higher risk of progressing to a diagnosis of MS
  - Early MRI abnormalities are predictive of a greater risk of long-term disability
- Risk in each patient and whether immediate treatment with a DMT is recommended
- Realistic expectations to be derived from treatment
- Brief discussion of controlled clinical-trial literature in a CIS and MS (which has been found to be a useful guide for clinical discussion with patients)
- Discussion of pros and cons of early vs later treatment with a DMT (if a DMT is recommended, emphasizing that early treatment may delay progression to diagnosed MS, minimize further lesions on MRI, and slow disability in short term; the underlying disease process will continue if treatment is not initiated)
- The importance of patient adherence to treatment in order to limit underlying disease progression
- AEs that may be expected from IFN beta or GA
- Is the patient ready for treatment with injectable therapy?
- Does the patient have a fear of needles?
- Describe your rationale on selection of an initial DMT (an IFN beta or GA) based on adverse effect profile or individual needs; eg, a SC IFN beta is more effective than IM IFN beta but causes higher frequency of some AEs
- Instruction on injection preparation and administration technique
- Importance of regular follow-up visits and additional MRIs
- Patient’s main concerns

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self-control, increases patient confidence in the care provided, and enhances the likelihood of commitment and adherence to injectable DMTs.73,75,105,106

“What did the physician just say?” is a common question made by the newly diagnosed CIS or MS patient to nurses entering the examination room after the physician has explained what is being done and why. Information regarding the diagnosis and different treatments are foreign concepts to most individuals. Many are trying to grasp the reality of a potentially disabling diagnosis, while the discussion has moved ahead to disease modification. There is a large amount of information to present and often little time for adequate explanation. Having a nurse available to help explain the information and clear up misconceptions and misinformation is helpful to establish a firm foundation of knowledge and understanding of the disease and treatment. The information is best presented in increments and may need a variety of learning strategies for optimal understanding. Providing written information that can be reviewed after the office visit and following up with the patient to address questions and concerns is of high importance.

Following a diagnosis of a CIS or MS, patients may experience a variety of emotions, including anger, confusion, and denial. They may be unwilling to continue with the diagnostic workup or commit to a treatment. It is important for providers to understand that patients may not be able to start treatment until they have been able to incorporate the diagnosis into their life. It may take time for patients to understand various treatment options and the associated side effects.

The initial patient interaction and education process typically will begin with the physician, but all members of the health care team (eg, nurses, MS nurses or specialists, physician assistants, pharmacists, rehab specialists, and case managers) should contribute to the educational process.106 This can be dispensed over a short period of time (eg, 3 days) to minimize information overload. Educational strategies in or out of the office (eg, handouts, videos, websites, local educational meetings) and a phone line dedicated to answering questions also can enable greater patient understanding of a CIS and MS over time. Follow-up visits with the physician can re-emphasize important points and explain additional aspects not covered at the first visit.

**Balancing Expectations**

Despite providing patients with the best information, treatment adherence rates can be poor; studies show that many patients discontinue treatment within the first 6 months, often due to perceived lack of efficacy or AEs.73 A balance of expectations is needed when counseling patients because what they hear does not always fit with what they have anticipated. Health-related quality of life (HRQOL) is most important to the patient.107,108 As in established MS, a poor HRQOL also may be seen in the patient with a CIS.109,110

Clinicians should address patient concerns and outcomes relevant to the individual, as well as the more objective medical aspects of the MS disease state. For example, it should be explained that although results have been mixed, GA and IFN beta may have a favorable effect on HRQOL in many patients.111 Also, many or most of the AEs of GA or IFN beta can be managed with minimal effect on daily life and HRQOL. For example, “hidden-needle” autoinjectors are available if the patient has a needle phobia. Flu-like side effects to interferons can be managed by initial dose titration, the use of antipyretics, and evening dosing. Rotating injections can help to prevent or minimize injection-site reactions. This type of counseling can minimize poor patient adherence to therapy and improve patient outcomes. Out-of-pocket costs of therapy and insurance issues should be discussed as they also are causes of nonadherence. Social workers and MS societies can provide guidance in this area, and some pharmaceutical companies can assist with drug provision at lower cost.
Oral MS Therapies

**Figure 5** is a timeline that shows the approval dates of the currently approved DMTs for MS, as well as some of the research pipeline agents in late-stage development. Dalfampridine is a recently approved symptomatic medication for MS that may temporarily improve walking in MS patients.\(^\text{100}\) This potassium channel blocking drug is not a DMT that can alter the natural history of MS. Other agents in Figure 5 are potential DMTs. As all of the currently approved medications are Injectable, the approval of oral therapies is bound to excite the MS patient community. Many patients may wish to switch from their current injectable treatment to an oral medication.

It will be important for clinicians to become familiar with new treatments and their mechanisms of action, drug interactions, possible AEs, any required monitoring, and potential toxicities. Experience with new therapies may reveal additional AEs and/or toxicities. Patients will need to know the realistic expectations of the new therapy and potential side effects. While any new treatment will be efficacious, none of the ones in late-stage development are cures for MS. It is not known yet if a new treatment will be superior to an existing treatment in an individual or whether the new agents will be first or second line. Clinicians will need to know how and when to use the new agents in various forms of MS, which mechanisms will provide the best approach in individual patients, and how to best monitor clinical response over time.

Other changes are envisioned for when oral therapies are released. Additional time for patient counseling will be a central issue. Most of the elements presented in the earlier discussion on oral MS drugs will need to be discussed with patients (**Table 8**). Effective communication and education may be the most important aspects of the introduction of new oral agents. Currently, most clinicians spend time discussing the various available treatments. Will that approach be possible if there are 4 or 5 new treatments available? Written or video information will be needed for patients so they can understand the new treatments. Advocacy groups, such as the National MS Society (NMSS), MS Association of America (MSAA), and MS Foundation (MSF), will need to provide unbiased information about any new treatments. Switching treatment in MS will require time with patients to explain the change and the monitoring requirements of the new agent.

In the United States, third-party insurance reimbursement may be challenging for patients as well as clinicians. Insurers may choose to cover some, but not all, available treatments. Lack of insurance or inadequate insurance may limit an individual’s ability to take any of the medications. While programs likely will be in place to assist with payment, applications may add another layer to administrative time for clinicians and anxiety for patients.

Similar to the patient presenting with a CIS, collaborative and other educational approaches to minimize information overload should be considered with the introduction of new oral agents. Adding nurses to existing office staff, while potentially useful, will be very costly and not possible for many clinicians. Pharmaceutical hotlines as well as online, written, and video information will be needed to complement the introduction of new agents by the clinician. Maintaining patient trust through reasonable dialogue can maintain the patient relationship and improve adherence to any treatment regimen. For example, upon receiving a negative response about switching to an oral therapy, some patients may seek to change providers for a different opinion and could be lost to follow-up. Achieving a balance in patient expectations is important in relation to new oral drugs.

Studies show that RRMS patients are more concerned about their HRQOL than their physical capacity, pain related to MS, or potential costs of the disease.\(^\text{107,108,112}\) Side effects and toxicities to medications can impact HRQOL negatively and will need to be monitored. It is believed that long-term adherence, which will maximize the benefits of the treatment, will help to maintain and potentially improve HRQOL, as well as offer the best chance for a good clinical outcome.

**CONCLUSION**

Progress in MS management is moving at a rapid pace. Clinicians need to be aware of how eMRI can play a significant role in treatment decision making for patients with a CIS. Conventional MRI is predictive of subsequent MS and disability, and clinicians may be able to diagnose MS on a single scan in many patients. Investigational oral drugs offer potentially greater clinical- or MRI-measured efficacy compared with current DMTs, but the risk of severe adverse events may be
Table 8. Patient Interaction: What Should Be Discussed With Patients Regarding Investigational Oral MS Drugs*

- Oral MS drugs offer new options for both patient and physician. Oral drugs may improve patient adherence to therapy, which is needed to ensure achievement of treatment goals.
  - This is still up to the patient.
  - Ongoing adherence to an oral drug is essential if therapy is started.

- Oral drugs will not cure MS and still are only partially effective.
- Brief review of clinical efficacy and safety—oral agents have had a positive impact on clinical and MRI measures of disease activity in RRMS.
- Risk/benefit suggests these agents are possibly more effective than current DMTs but carry greater risk for severe AEs including possibility of cancer.
- Long-term efficacy and safety data are unavailable at this time.
- Safety of oral drugs is a primary concern in starting therapy.
- Discuss AEs that may occur with the selected oral agent and compare with adverse effect profile of currently available DMTs (comparative tables of adverse events will be useful).
- For patients requesting a switch to oral therapy but who are stable on current injectable DMT: Experts indicate that staying on present medication is best choice at present; switching could be a step backward considering potential for suboptimal response and greater risk of more severe adverse events.
  - Are patients willing to resume injectable therapy if oral drug is ineffective or intolerable after 6 months?
  - Only one oral drug may be approved initially; there may not be extensive choices of oral preparations for several years.
- Stress importance of time for clinicians to gain experience using oral drugs, which ultimately will benefit the patient. May not be able to approve a switch for this reason alone.
- Expectations: At present, it is not possible to predict which patients will respond to an oral drug or which AEs may emerge, if any; effect on HRQOL also is unknown.
- Monitoring of therapy (office visits, MRIs) with oral agents is as, if not more, important than with current DMTs; oral agents may involve more intense monitoring, tests, and more frequent office visits.
- Insurance issues and appropriate referrals for financial guidance.

*Based on suggestions from MS specialists.

Greater. This must be balanced against potential benefits in each patient.

Effective clinician-patient interaction and communication provides patients with information and education on their diagnosis, treatment options, and prognosis and can improve treatment adherence and clinical outcomes in the patient with a CIS or MS. Although these interactions deplete clinical time, which already is scarce in practice, they are of high priority in achieving treatment goals.

References


Supplement to the International Journal of MS Care


5. Serious or potentially serious adverse events associated with fingolimod in phase III trials include:
   a. macular edema, hypotension, herpes zoster infection, cancer potential.
   b. AV block, herpes simplex infections, hepatic failure, lymphocytopenia.
   c. AV block, serious bradycardia, cancer potential, fatal pneumonia, macular edema.
   d. AV block, serious bradycardia, herpes zoster infection, potential for malignancy, macular edema.
   e. hypertension, lymphocytopenia, renal insufficiency, herpes virus infections.

6. Which of the following statements is true regarding the clinical efficacy and safety of investigational oral MS drugs based on clinical trials to date in RRMS patients?
   a. Cladribine has been shown to be more effective than mitoxantrone and natalizumab but is more likely to cause severe adverse events.
   b. Fingolimod is more effective than SC IFN beta-1a but has a greater patient risk for severe adverse events.
   c. Laquinimod and teriflunomide are as effective as cladribine with less risk of toxicity.
   d. Fingolimod is more effective than IM IFN beta-1a but has a greater patient risk for severe adverse events.
   e. Cladribine is more effective than glatiramer acetate but with greater risk of severe adverse events.

7. Which of the following is false about providing information and education to patients with a CIS?
   a. It should be done incrementally.
   b. It is of minimal importance as long as the patient agrees to adhere to treatment.
   c. It can enhance adherence and commitment to a prescribed DMT, which can help ensure a good outcome.
   d. It should include explanation of the meaning of cMRI findings with respect to progression to MS and long-term disability.
   e. It should include involvement of the patient in the decision making process.

8. When oral MS drugs are introduced, important practical considerations will include:
   a. the need for more time to interact with and educate patients.
   b. a collaborative team approach.
   c. a period of adjustment to assess efficacy and safety in selected patients due to no clinician experience in the use of oral drugs.
   d. accommodating the increase in time spent with patients by making changes to necessary office and staff.
   e. All of the above are considerations.

9. Health-related quality of life (HRQOL) is:
   a. less important to patients with RRMS than physical capacity or pain from the disease.
   b. impaired in some patients with a CIS.
   c. not improved by DMTs.
   d. not affected by adverse effects.
   e. (a) and (d) are correct.
Today’s Practice, Tomorrow’s Potential: Evidence-Based Debates in MS Management

Consensus Medical Communications and Medical Education Resources (MER) respect and appreciate your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

Please answer the following questions by circling the appropriate rating:

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Extent to Which Program Activities Met the Identified Objectives

• Describe current approaches to the clinical management of patients with MS and the evidence base for these practices ........................................ 5 4 3 2 1
• Discuss the rationale for making changes to treatment protocols in patients with MS ................................................................. 5 4 3 2 1
• Evaluate emerging treatments for MS and the potential impact they may have with first-line use in newly diagnosed patients .......... 5 4 3 2 1
• Explain how magnetic resonance imaging supports treatment decision making in patients with a clinically isolated syndrome ............. 5 4 3 2 1

Please indicate if this activity was free from commercial bias.  Yes  No
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Overall Effectiveness of the Activity

• Objectives were related to overall purpose/goal(s) of activity................................................................. 5 4 3 2 1
• Enhanced my current knowledge base ................................................................................................................. 5 4 3 2 1
• Will help me improve patient care .......... ........................................................................................................... 5 4 3 2 1
• Provided new ideas or information I expect to use .......................................................................................... 5 4 3 2 1
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• Addressed my most pressing questions .......................................................................................................... 5 4 3 2 1

Please indicate any changes you plan to make in your practice of medicine as a result of information you received from this activity.

How committed are you to making these changes? .................................................................................. (Very committed)  5  4  3  2  1 (Not at all committed)
In what time frame do you anticipate making these changes?  Immediately  1-2 months  3-6 months  At some point in the future

Based on my participation in this CME/CE activity, I will now incorporate the following new clinical strategies: (Check all that apply.)

☐ Understanding of the impact of early treatment on the quality of life in patients with a CIS and concurrent MRI changes
☐ Knowledgeable in the appropriate use of DMT’s to maximize successful outcomes
☐ Confident in the interpretation and application of the clinical data associated with the use of oral-based therapy to maximize successful outcomes
☐ I already do all these things.

If this activity did not give you strategies to be better able to practice medicine, please list the factors acting as barriers.

This activity was designed to help the participant master the ABMS/ACGME core competency of patient care and medical knowledge.

How well did this activity address this competency?........................................................................... 5  4  3  2  1

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There are no prerequisites or fees for participating in and receiving credit for this activity. During the eligibility period of October 2010 and October 2011, participants must 1) study the educational activity, 2) complete the posttest by recording the best answer to each question in the answer key on this form, 3) complete the evaluation form, and 4) mail or fax the completed form to Medical Education Resources at 720-449-0217.

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Posttest Answer Key

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