Emerging multiple sclerosis oral therapies

ABSTRACT

Currently, patients suffering from multiple sclerosis (MS), a chronic demyelinating disorder of the CNS, must be injected with medication to provide modest relief for their symptoms. Five orally available therapies are being evaluated in phase II/III clinical trials. If these therapies prove safe and tolerable, oral compounds may improve patient endorsement and compliance. Fingolimod, a novel immunosuppressant, significantly lowered annual relapse rates in phase II/III trials. Laquinimod, an immunomodulator, reduced the cumulative number of active lesions at the highest dose tested (0.6 mg/d) in a phase II trial. Cladribine, another immunomodulator, reduced annual relapse rates by >50% and gadolinium-positive lesions by >70% at both doses tested in a phase III trial. Oral fumarate, with immunomodulatory and antioxidant properties, also lowered the number of lesions in a phase II trial. Finally, teriflunomide, an immunomodulator, significantly reduced MRI lesion activity and reduced annual relapse rates in a phase II trial. In this report, we weigh the beneficial outcomes of these compounds against their risks of adverse effects. NEUROLOGY 2010;74(Suppl 1):S47–S53

GLOSSARY

ARR = annual relapse rate; EAE = experimental allergic encephalitis; EDSS = Expanded Disability Status Scale; FDA = Food and Drug Administration; IFN = interferon; MS = multiple sclerosis; MSFC = MS Functional Composite; Nrf2 = nuclear factor-E2–related factor 2; RRMS = relapsing-remitting MS; SC = subcutaneously; S1P = sphingosine-1-phosphate.

INTRODUCTION

The era of disease-modifying therapies for multiple sclerosis (MS) commenced with the introduction of injectable human interferon (IFN)β-1b. Glatiramer acetate and (GA) IFNβ-1a, both administered through injection, round out the current standard of care for relapsing-remitting MS (RRMS). Glatiramer acetate is injected subcutaneously (SC); generally, side effects include a lump at the injection site, fever, chills, and aches, which subside within 30 minutes.1 IFNβ-1a is injected SC or IM. Common side effects with the IFNβ therapies include flu-like symptoms and injection-site reactions.2-4

Treatment with the monoclonal antibody natalizumab is approved by the Food and Drug Administration (FDA) under a special prescription program. Administered every 28 days, natalizumab has been shown to reduce relapses in patients with MS by as much as 68%.5 Other promising antibodies include rituximab, alemtuzumab, and daclizumab. By their nature, these compounds must be administered through IV infusion. Atacicept is a recombinant fusion protein that contains the soluble transmembrane activator and CAML interactor receptor, which is expressed on B and T cells, and neutralizes or sequesters survival factors or proliferators of B-cell survival.6 Although the phase II trial of this drug was voluntarily terminated after it was observed that patients on atacicept experienced an increase in MS activity, this trial and trials of other therapies suggest that target B cells represent a renewed interest in B-cell involvement in MS. Another IV compound approved to treat MS is mitoxantrone, which has been shown to alleviate symptoms. However, its myelosuppressive and cardiotoxic effects preclude widespread administration.7 Other therapies directed toward neuroprotection, repair, and prevention are still in preclinical stages of research.

Today, many oral therapies, including fingolimod, laquinimod, oral cladribine, fumarate...
(BG00012), and teriflunomide are in phase III trials and show promise as efficacious treatments for MS. Effective, safe, and well-tolerated oral therapies may improve compliance and empower patients with a level of independence not presently possible. In this article, we review the most promising oral agents currently undergoing clinical trials.

**THE AGE OF ORAL AGENTS Fingolimod (FTY720).**

A structural analogue of sphingosine, FTY720 targets receptors for sphingosine-1-phosphate (S1P), a potent signaling lipid. Migration of lymphocytes from secondary lymphoid organs (SLP) to the periphery is determined by the density of S1P on their surface. Higher density of S1P results in release of cells from SLP, and vice versa. Mature dendritic cells have been shown to migrate to SLP, and this migration is hindered in the presence of FTY720. Both S1P and FTY720 engage S1P receptors as phosphorylated metabolites. Because of its lipophilic nature, FTY720 readily crosses the blood-brain barrier to interact with S1P receptors, which are widely expressed throughout the CNS.

FTY720 is a nonselective S1P agonist and activates 4 of its 5 receptor isotypes: S1P1, S1P3, S1P4, and S1P5. S1P receptors have a broad tissue distribution and are the dominant subtype found on lymphocytes. S1P receptors regulate a wide variety of cellular functions, including cell motility and cytoskeletal arrangements. S1P is present at high nanomolar basal concentrations in serum, and it is released by platelets at sites of inflammation.

FTY720 improves myelination in animal models of experimental allergic encephalitis (EAE) and is beneficial in a wide variety of graft-rejection and autoimmune models. In these models, FTY720 imparts reductions in clinical disease score and infiltration of macrophages to the CNS, conserves expression of myelin genes, and is active in prophylactic and therapeutic regimens. In experimental models, it has even been shown to reverse demyelination.

Lymphocytic migration to individual compartments depends on the differential release of chemokines. Lymphocyte egress from lymphoid tissue is dependent on S1P3 signaling, and S1P1 expression is regulated to control the release of newly generated effector T cells from secondary lymphoid organs (figure 1). FTY720 has also been shown to sequester naïve and central memory T cells in the lymph nodes, whereas effector memory T cells remain in circulation. The reduction of blood leukocytes caused by FTY720 is reversible. FTY720 increases endothelial barrier integrity, which may convey vasoprotection. Furthermore, given at therapeutic doses, FTY720 does not impair activation, proliferation, or effector functions of immune cells, but rather hampers their ability to infiltrate peripheral tissues.

A 24-month extension of a phase II trial assessed the efficacy of once daily oral dosing of either 5 or 1.25 mg/d of FTY720 for RRMS. Each dose of FTY720 significantly reduced both Gd-enhanced (Gd+) lesions and annual relapse rate (ARR) compared with placebo (table). After the 6-month core study was complete, patients originally assigned to placebo were rerandomized to receive either dose of FTY720. Results from the extension phase showed similar proportions of patients were free of Gd+ lesions at month 12 in the patients treated with FTY720 for either 6 or 12 months. These results indicated that, for up to 24 months, FTY720 treatment was associated with lower lesion activity and a lower relapse rate in patients with MS.

In the phase III TRANSFORMS study, the effects of FTY720 were compared with IM IFNβ-1a. Both doses of FTY720 significantly reduced ARR compared with the current standard of treatment (as shown in table), which indicates that even lower doses may provide an improved risk-benefit ratio. With regard to disability progression, 92%–94% of patients in the 2 FTY720 groups and the IM IFNβ-1a group were free of 3-month confirmed disability at 12 months. Mean Expanded Disability Status Scale (EDSS) scores and MS Functional Composite (MSFC) z scores slightly improved in the 2 FTY720 groups and slightly deteriorated in the IM IFNβ-1a group from baseline. Two ongoing phase 3 clinical trials, FREEDOMS and FREEDOMS II, both double blind and randomized with 3 arms (FTY720 5 mg and FTY720 1.25 mg vs placebo) will follow over 1,000 RRMS patients for 2 years. The primary outcome measure for both trials will be the ARR at 24 months. MRI will also be used to assess the burden of disease.

**Laquinimod.** Laquinimod (Teva Pharmaceuticals, Ltd, Petach Tikva, Israel; Active Biotech AB, Lund, Sweden) is an orally available immunomodulator that has been granted fast-track review status from the FDA, with a planned release in late 2011. A derivative of linomide, laquinimod is more potent at inhibiting MS symptoms than its parent compound, and causes less of the debilitating side effects associated with the latter. Although its pharmacological target has not yet been identified, laquinimod alleviates EAE (measured by clinical score and disease development) without causing general immunosuppression. Treatment with laquinimod induces the release of transforming growth factor-β and shifts the immune response in favor of other Th2 cytokines. This T-cell shift indicates that the beneficial effects of laquinimod...
mod occur because of a deviation, rather than suppression, of the immune response.

In a phase IIb trial assessing the effects of laquinimod on patients with RRMS with superimposed relapses, 98 patients received 0.3 mg/d of laquinimod, 106 patients received 0.6 mg/d, and 102 patients received a placebo for 36 weeks.27 Primary outcome measures included the cumulative number of active lesions seen on monthly brain MRI scans. Treatment with 0.6 mg/d of laquinimod resulted in a 40.4% (p = 0.0048) reduction in the baseline adjusted mean total of Gd+ lesions, whereas treatment with 0.3 mg/d showed no significant effect compared with placebo. During a 36-week extension phase in which patients receiving placebo were switched to either dose of laquinimod, there was a 52% (p < 0.0007) decrease in Gd+ lesions in patients formally on placebo, and the reductions were sustained in both laquinimod groups.28 A 24-month open-label extension in which all patients received 0.6 mg/d laquinimod continued to show a decrease in the number of Gd+ lesions as well as a reduction in relapses and disability progression.29

Two randomized, phase III trials of laquinimod are currently under way. BRAVO, a 2-year, multinational trial with 3 arms (0.6 laquinimod vs placebo vs 30 μg IM IFNβ-1a), is measuring the effect of laquinimod treatment on relapse rate compared with placebo (double blind) as its primary outcome measurement.30 Disability progression, MRI lesions, and safety are other measured outcomes, and a comparative benefit/risk assessment between laquinimod and IM IFNβ-1a (rater blind) is also being conducted. ALLEGRO, a 2-year, double-blind, multinational trial with 2 arms (0.6 mg laquinimod vs placebo), is measuring the number of confirmed relapses (primary outcome), disability progression, radiographic lesions, and safety.31

Cladribine. When administered orally, cladribine (Merck Serono SA, Geneva, Switzerland) has been shown to be effective in the treatment of RRMS.

Figure 1  Mechanism of action of FTY720

The egress of mature T cells from the lymph nodes into the efferent lymph depends on S1P1 receptor signaling by S1P. (A) In case of antigen-specific activation of naïve T cells within the lymph node, S1P1 receptor expression on lymphocytes is transiently downregulated, and the naïve T cells are unresponsive to the egress signal provided by the existing S1P concentration gradient between the lymph node and lymph. After proliferation and differentiation, activated T cells upregulate their S1P1 receptors. Those T cells that bind higher amounts of S1P become responsive to the egress signal and eventually reach the blood by migration through the sinus-lining endothelium into the lymphatic sinuses and then efferent lymphatic vessel. Those cells that have low levels of S1P do not egress. S1P also modulates the permeability of the sinus-lining endothelium. (B) FTY720 inhibits lymphocyte egress from the lymph node by 2 potential mechanisms: the downregulation of S1P1 receptors on activated T cells, which blocks the ability of the receptor to support the S1P-dependent egress; and activation of S1P1 receptors on sinus-lining endothelial cells, which enhances the barrier’s function and reduces the transmigration of T cells into the lymphatic sinuses, efferent lymphatic vessel, and eventually into the blood. T cells that have FTY720 bound to receptors do not egress. S1P = sphingosine-1-phosphate. Adapted from Expert Rev Neurother 2008;8:699-714 with permission from Expert Reviews Ltd.
A comparison with IFN
*Placebo control.
†A comparison with IFNβ.
ARR = annual relapse rate; NS = nonsignificant; IFN = interferon.

Table: Data reported from phase II and III trials of oral compounds for the treatment of MS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Phase II</th>
<th>Phase III TRANSFORMS</th>
<th>Phase III CLARITY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 mo</td>
<td>24 mo</td>
<td></td>
</tr>
<tr>
<td>FTY720</td>
<td>0.36*</td>
<td>0.16 (p &lt; 0.001)*</td>
<td>0.14 (p &lt; 0.001)*</td>
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<tr>
<td></td>
<td>0.35*</td>
<td>0.20 (p &lt; 0.001)*</td>
<td>0.15 (p &lt; 0.001)*</td>
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<tr>
<td></td>
<td>0.77</td>
<td>0.33</td>
<td>0.33</td>
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<tr>
<td>ARR 12 mo</td>
<td>53%</td>
<td>58%</td>
<td>58%</td>
</tr>
<tr>
<td>Relative reduction (%)</td>
<td>7%*</td>
<td>7%*</td>
<td>7%*</td>
</tr>
<tr>
<td>Gd + lesions (mean)</td>
<td>5.7 (p &lt; 0.006)*</td>
<td>2.6 (p &lt; 0.0048)*</td>
<td>&gt;73% (p &lt; 0.001)*</td>
</tr>
<tr>
<td>Relative reduction (%)</td>
<td>38%*</td>
<td>38%*</td>
<td>&gt;73% (p &lt; 0.001)*</td>
</tr>
<tr>
<td>Cladribine</td>
<td>3.5 mg/kg</td>
<td>5.25 mg/kg</td>
<td>3.5 mg/kg</td>
</tr>
<tr>
<td>Relative reduction (%)</td>
<td>&gt;73% (p &lt; 0.001)*</td>
<td>&gt;73% (p &lt; 0.001)*</td>
<td>3.5 mg/kg</td>
</tr>
<tr>
<td>BG00012</td>
<td>120 mg 3x/d</td>
<td>240 mg 3x/d</td>
<td>120 mg 3x/d</td>
</tr>
<tr>
<td>ARR</td>
<td>0.78 (p &lt; 0.572)*</td>
<td>0.44 (p &lt; 0.272)*</td>
<td>0.78 (p &lt; 0.572)*</td>
</tr>
<tr>
<td>Relative reduction (%)</td>
<td>32%</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>Gd + lesions (mean new)</td>
<td>3.1 (p &lt; 0.068)*</td>
<td>1.4 (p &lt; 0.0001)*</td>
<td>3.1 (p &lt; 0.068)*</td>
</tr>
<tr>
<td>Relative reduction (%)</td>
<td>69%</td>
<td>69%</td>
<td>69%</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>7 mg/d</td>
<td>14 mg/d</td>
<td>7 mg/d</td>
</tr>
<tr>
<td>Relative reduction (%)</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

Teriflunomide tablets are given once daily for 5 days per course, for a total of 10 to 20 days per year of treatment. The manufacturer applied for FDA approval in late 2009 with an anticipated projected launch in 2010–2011. Cladribine has also been approved for fast-track status by the FDA.

Cladribine, or 2-chlorodeoxyadenosine, is an adenosine deaminase-resistant purine nucleoside. It targets CD4+ cells rather than CD8+ T cells and spares other hematologic and immune cells such as B cells and natural killer cells. Oral cladribine treatment was associated with dose-dependent improvements on both clinical assessment and MRI analysis. Cladribine given SC has also been shown to reduce the levels of proinflammatory cytokines and chemokines in the CSF of patients with MS in remission, indicating that its effects may extend beyond lymphocyte suppression and suppress resident immune cells of the CNS. Although generally well tolerated, cladribine treatment must be considered with caution because it may have potential carcinogenic, teratogenic, and bone marrow effects.

A recently completed phase III trial for oral cladribine (CLARITY) randomized 1,326 patients with RRMS into 3 groups: low dose (3.5 mg/kg) vs high dose (5.25 mg/kg) vs placebo. The relapse rate was reduced by 58% (p < 0.001) in the low-dose group and 55% (p < 0.001) in the high-dose group compared with placebo (Table). In both treatment groups, the proportion of patients without relapses was significantly lower (80% and 79% of the low- and high-dose groups, respectively, compared with 61% of placebo; p < 0.001), the risk of disability progression was reduced by 33% and 31% in the low- and high-dose groups, respectively, and the mean number of Gd+, active T2, and combined unique lesions was reduced by 73%–88% in both groups (all p < 0.001) compared with placebo.

To assess the efficacy of cladribine to slow or halt the progression of MS at an early stage of the disease, the phase III ORACLE trial will include 642 patients who have experienced an initial clinical event suggestive of MS. Efficacy of 2 regimens of cladribine, 1.75 mg/kg/y and 3.5 mg/kg/y, will be assessed using both the McDonald (primary outcome) and Poser (secondary outcome) criteria and compared with placebo. The estimated completion date for this trial is October 2012.

The ONWARD phase II clinical trial was designed to determine the efficacy of combination therapies and will compare a) a combination of low-dose cladribine with 44 µg SC IFNβ-1a, b) a combination of high-dose cladribine with 44 µg SC IFNβ-1a, and c) 44 µg SC IFNβ-1a with a placebo. The projected completion date for this trial is October 2013. The primary outcome will be measuring the safety and tolerability of these compound combinations. Efficacy, MRI lesion activity, relapse rate, and progression of disability will also be assessed.
understood, preclinical studies have shown that BG00012 activates the nuclear factor-E2–related factor 2 (Nrf2) transcriptional pathway. Downstream effectors of the Nrf2 signaling cascade can control gene expression of phase 2 detoxification enzymes and may upregulate antioxidative response elements. Recently published results from a phase II clinical trial show that 240 mg of BG00012 given 3 times a day decreased the mean number of new lesions by 69% compared with placebo (p < 0.0001). At this higher dose, the number of new or enlarging lesions per scan, fewer new or enlarging T2 lesions per scan, and less T2 lesions, when compared with placebo. Patients receiving teriflunomide showed a relative reduction in ARR (Table). In another study, 117 patients, all on stable doses of IFNβ-1a SC, were given placebo, 7 mg/d, or 14 mg/d teriflunomide for 24 weeks. The number of lesions was significantly reduced in both the 7 mg (56%) and 14 mg teriflunomide groups, when compared with placebo (both comparisons p < 0.001). Tolerance and safety in both teriflunomide groups were acceptable. The proportion of patients with a reported treatment-emergent adverse event of increased alanine transaminase was higher in the 14 mg group (28.9%) than in the 7 mg (13.5%) and placebo (12.2%) groups.

The large-scale phase III TEMSO trial was designed to determine the efficacy and safety of teriflunomide for patients with MS. Patients will be treated for 108 weeks with placebo, 7 mg/d, or 14 mg/d teriflunomide with measurements of clinical disability (EDSS, MSFC, and Fatigue Impact Scale) every 12 weeks and biannual MRI scans. The study is expected to be completed at the end of 2009 with results published in 2010. Recruitment for another phase III trial, which will test the efficacy of teriflunomide to delay onset of MS in patients with syndromes consistent with demyelination, began in 2007. In this trial, patients will be randomized into

Figure 2 Mechanism of action of cladribine

Cladribine (2CdA) is transported into the cell and resists deamination by adenosine deaminase (ADA). In cells that have a higher amount of deoxycytidine kinase (dCK) than 5'-nucleotidase (5'-NT), cladribine is phosphorylated and becomes 2-chlorodeoxyadenosine triphosphate (2CdATP) by dCK, adenosine monophosphate kinase (AMK), and nucleoside diphosphate kinase (NDK). The accumulation of 2CdATP leads to breaks in DNA strands, inhibition of DNA synthesis, and cell death (apoptosis). Lymphocytes tend to have a higher ratio of dCK to 5'-NT and are targeted by cladribine. In cells that have equal levels of 5'-NT and dCK, cladribine enters and leaves the cells without causing cell death.

Teriflunomide. As the active metabolite of leflunomide, teriflunomide, an FDA-approved treatment for rheumatoid arthritis, reversibly inhibits dihydroorotate dehydrogenase, the rate-limiting step in the de novo synthesis of pyrimidines. Teriflunomide has also been shown to suppress proinflammatory factors, inhibit tyrosine kinase activity, prevent T-cell interactions with antigen-presenting cells, and suppress nuclear factor-κB activation. Thus, teriflunomide may impede T-cell activation in a multifaceted manner. Teriflunomide has been suggested to have teratogenic, hepatotoxic, and bone marrow suppressive effects. Therefore, this drug is contraindicated for women of childbearing years, and monthly to bimonthly monitoring of liver enzymes is required.

A completed 9-month phase II study in patients with RRMS assessed the efficacy of 7 and 14 mg/d teriflunomide compared with placebo. After 36 weeks of treatment, there was a statistically significant reduction in the median number of combined unique active lesions per MRI scan. Patients receiving teriflunomide had significantly fewer T1-enhancing lesions per scan, fewer new or enlarging T2 lesions per scan, and less T2 lesions, when compared with placebo. Patients receiving teriflunomide also showed a relative reduction in ARR (Table). In another study, 117 patients, all on stable doses of IFNβ-1a SC, were given placebo, 7 mg/d, or 14 mg/d teriflunomide for 24 weeks. The number of lesions was significantly reduced in both the 7 mg (56%) and 14 mg teriflunomide groups, when compared with placebo (both comparisons p < 0.001). Tolerance and safety in both teriflunomide groups were acceptable. The proportion of patients with a reported treatment-emergent adverse event of increased alanine transaminase was higher in the 14 mg group (28.9%) than in the 7 mg (13.5%) and placebo (12.2%) groups.

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CONCLUSION Although newer treatment options for patients with MS have improved efficacy over first-generation therapies, they still necessitate the use of weekly or monthly injections. Oral agents would not only eliminate the need for painful injections and would provide patients with MS with a more user-friendly alternative to currently approved choices, but also these compounds show promise in reducing clinical markers of MS, such as ARRs and the number and volume of brain lesions. An additional promising phase III trial of an oral MS medication showed that Fampridine-SR improved walking ability in patients with MS, even though the drug is not considered as a disease-modifying therapy. Although the results of oral therapy trials are encouraging, all agents have significant side effects that may outweigh benefits in certain individuals. Thus, these oral therapies may not replace the existing platform therapies. As results from these trials of oral therapies become available within the next few years, further characterization of their safety, tolerability, and efficacy will provide additional means to combat MS.

DISCLOSURE Dr. Rammohan has served on scientific advisory boards for EMD Serono, Genentech, and Novartis; has received honoraria for speaking from Acorda, Bayer, EMD Serono, Novartis, and Teva; and has received grant/research support from Acorda, Bayer, Biogen, EMD Serono, Genentech, Novartis, and Teva. Dr. Shoemaker reports no disclosures.

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