

A New Year's Look at the MS Horizon

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The dawn of a new decade brings with it the imminent and long-awaited arrival of oral therapy for relapsing-remitting multiple sclerosis (RRMS). Until a generation ago, MS, an autoimmune disorder characterized by inflammation and neurodegeneration, was a disease without effective therapeutic options. The advent of disease-modifying therapies (DMTs), such as interferon agents and glatiramer acetate, provided the means to alter the course of RRMS, reducing the number of relapses and delaying disability. However, the necessity of injecting these agents created significant barriers to patient acceptance and to long-term adherence.

These new oral agents, once they are approved by regulatory agencies, will present a fresh set of challenges to patients and clinicians as they weigh the pros and cons of treating MS with a pill. Oral MS therapies have mechanisms of action and safety profiles distinct from injectable DMT agents. Working through various immune-mediated pathways, they may offer greater efficacy and convenience than currently available medications, but they also have the potential to cause serious adverse effects including malignancies and infections. The MS nurse will play a key role in helping patients to evaluate the risk/benefit ratio of new oral therapies that have a shorter safety record than injectable DMTs. For patients already taking an

injectable therapy, deciding whether to transition to oral agents is likely to become a major point of discussion in MS management. With oral agents as an option, the choice of first-line therapy for newly diagnosed patients will also become more complex. The educational component of nursing can be expected to deepen, as nurses will be called upon to help patients set realistic expectations for treatment outcomes and tolerability, manage evolving therapeutic regimens, and monitor clinical response to novel agents as well as with any associated adverse effects. The sidebar on page 2 includes questions that may be asked by patients about oral therapy.

Several immunomodulatory agents with anti-inflammatory mechanisms of action are in contention to become the

first oral MS therapies approved by the U.S. Food and Drug Administration (FDA) (Table). Recently, 3 phase III clinical trials have been reported for 2 of these agents, fingolimod and cladribine, with encouraging results. Each study enrolled at least 1,200 patients in up to 32 countries; participants had active relapsing disease for 7 to 9 years, and a median score of 2.0 (in the fingolimod trials) and 2.9-3.0 (in the cladribine trial) on the Expanded Disability Status Scale (EDSS, a range from 0 to 10, with higher scores denoting greater disability). The primary endpoint in all 3 studies—annualized relapse rate—was lower compared to placebo (or, in one trial, to interferon) with both high and low doses of fingolimod and cladribine. Secondary
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Please note that this publication contains reports of medical practices and investigations as presented in the professional and lay literature and scientific meetings. This publication may include discussion of investigational uses of medications that have not been recognized as safe and efficacious by the FDA. In weighing the benefits of treatment against the risks, physicians and nurses should be guided by clinical judgment. Consult complete prescribing information before administering any of the drugs discussed.

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endpoints such as MRI outcomes were also superior for the oral agents over placebo. Safety concerns related to immunosuppression, such as cancers and reactivated infections, were voiced by investigators in each trial. The following is a roundup of data from this first wave of trials of oral MS therapies.

Fingolimod

A sphingosine-1-phosphate-receptor modulator derived from a fungus, fingolimod (FTY720, trade name Gilenya®) effectively traps lymphocytes (white blood cells whose numbers increase in the presence of infection) within lymph nodes. The resulting lymphocytopenia reduces the infiltration of activated T cells across the blood-brain barrier (BBB), curbing inflammation within the central nervous system (CNS). Fingolimod may also promote neuroprotection and neurorepair by modulating sphingosine-1-phosphate receptors on neural cells.

FREEDOMS. In this 24-month, double-blind, randomized trial reported by Kappos et al, patients received oral fingolimod (a dose of 0.5 mg or 1.25 mg daily) or placebo. Of 1,272 enrolled participants, 1,033 (81.2%) completed the study and demonstrated statistically significant decreases in annualized relapse rates for both fingolimod doses (Table). Both doses also significantly lowered the risk of disability progression over 2 years.

Neuroimaging findings were also positive for both fingolimod doses. The 0.5 mg and 1.25 mg doses of fingolimod both demonstrated better results than placebo on MRI endpoints including new or enlarged lesions on T2-weighted images, gadolinium-enhancing lesions, and brain-volume loss ($P < 0.001$ for all comparisons). Adverse events included bradycardia, macular edema, and development of neoplasms and skin cancer (Table). Although fingolimod was associated with an expected reduction in circulating lymphocytes (by approximately 70%), the overall incidence of infection, including herpesvirus, was similar across the 3 study arms. Lower respiratory tract infections, however, were more common with fingolimod than with placebo. Never-

Questions to Anticipate as Oral Therapy Emerges

When will MS therapy be available in a pill?

Although the outcome of a new drug's approval process is not certain, experts anticipate that at least one oral therapy for MS may come to market within the coming year. Several other oral agents are currently in phase III clinical trials and are anticipated to come to market within the next several years.

Do the pills work the same way as injectable DMTs?

Oral therapies currently under testing work differently than injectable medications, but have the same goal: to reduce MS relapses and to delay disability by suppressing some actions of the immune system, which attacks the central nervous system in people with MS.

Are the pills safer than injections?

Not necessarily. Because the new oral agents work by modifying actions of the immune system, they may raise the risk of some serious adverse effects, including cancer and infections. None of the oral agents under study has a documented safety record with a duration as long as the currently available injectable DMTs.

Will oral therapy be more effective than injected therapy?

Phase III clinical trials suggest that the oral MS agents under study will be at least as effective as current injectable DMTs, and possibly more effective in preventing relapses. However, these oral agents may also be associated with an increased amount of potentially serious adverse effects.

Will pills for MS be less expensive than injectable medications?

The new medications have not come to market yet, so it is too early to know how much they will cost.

Will insurance pay for the new oral therapies for MS?

Since no oral agents for MS have yet been approved, it is too soon to know how insurers will respond.

If a patient is doing well on injectable DMT, should he/she switch to oral therapies when they become available?

The choice of a disease-modifying therapy for RRMS depends on many factors that should be evaluated carefully for each individual patient. Once oral agents are available, each care team should discuss treatment options thoroughly to decide whether switching therapies is the right choice for each individual patient.

Will oral therapies help progressive MS?

The clinical trials have primarily studied the use of oral agents in relapsing-remitting MS (RRMS). More study will be needed to determine whether these medications have a role in treating primary-progressive MS (PPMS) or secondary-progressive MS (SPMS).

theless, as the authors cautioned, "As medications used to treat multiple sclerosis become increasingly potent, attention to safety findings is paramount." The safety profile of fingolimod warrants further longer-term assessment, they con-

cluded, and its benefits will need to be weighed against possible long-term risks.

TRANSFORMS. This 12-month double-blind, double-dummy trial reported by Cohen et al randomized 1,292 patients
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Table. Result Summary of Oral MS Therapy Phase III Clinical Trials

Clinical Trial	Agent/Dose Regimen	Key Findings	Adverse Events/Safety Concerns
CLARITY	Oral cladribine 3.5 mg or 5.25 mg per kg body weight or placebo, for a total of 8-20 days/year	At 96 weeks: Annualized relapse rate: 0.14 (3.5 mg/kg) 0.15 (5.25 mg/kg) 0.33 (placebo) ($P < 0.001$ for both comparisons) Fewer MRI lesions ($P < 0.001$) Reduced risk of disability progression ($P = 0.02$ for lower dose, $P = 0.03$ for higher dose)	<ul style="list-style-type: none"> Lymphocytopenia (observed in 21.6% of 3.5-mg cladribine group, 31.5% of 5.25-mg cladribine group, and 1.8% of placebo group) Herpes zoster infections (occurring in 20 cladribine-treated patients vs none in the placebo group; 3 of these cases were classified as serious) Neoplasms were reported in 1.4% of 3.5-mg cladribine group and in 0.9% of 5.25-mg cladribine group (none reported in placebo group) 3 cases of cancer in 3.5-mg group (a melanoma and 2 carcinomas of the pancreas and ovary) 1 case of stage 0 cervical carcinoma <i>in situ</i> (a pre cancerous condition in the 5.25-mg group)
FREEDOMS	Oral fingolimod 0.5 mg or 1.25 mg daily or placebo	At 24 months: Annualized relapse rate: 0.18 (0.5 mg fingolimod), 0.16 (1.25 mg fingolimod), 0.40 (placebo) ($P < 0.001$ for both comparisons) Fewer MRI lesions ($P < 0.001$) Reduced risk of disability progression (both doses, $P = 0.02$ vs placebo)	<ul style="list-style-type: none"> Reduction in circulating lymphocytes Bradycardia/heart block Herpes zoster infections Mild hypertension Macular edema Elevated liver enzymes Malignant neoplasms reported in 4 patients receiving 0.5 mg fingolimod, in 4 patients receiving 1.25 mg fingolimod, and in 10 patients receiving placebo 11 skin cancers were reported: 4 in 0.25-mg fingolimod group, 3 in 1.25-mg fingolimod group, and 4 in placebo group
TRANSFORMS	Oral fingolimod 0.5 or 1.25 mg or IFN β 1-a IM 30 μ g/week	At 12 months: Annualized relapse rate: 0.20 (1.25 mg fingolimod) 0.16 (0.5 mg fingolimod) 0.33 (IFN β 1-a IM) ($P < 0.001$ for both comparisons) Fewer MRI lesions (new or enlarged lesions, $P < 0.001$ for higher dose, $P = 0.004$ for lower dose, vs IFN β 1-a IM) No difference among groups in progression of disability	<p><i>For fingolimod:</i></p> <ul style="list-style-type: none"> Reduction in circulating lymphocytes Bradycardia/heart block Herpes zoster Mild hypertension Macular edema Elevated liver enzymes Ten localized skin cancers reported <ul style="list-style-type: none"> – 5 basal-cell carcinomas in fingolimod groups (3 in 0.5-mg group and 2 in 1.25-mg group) – 3 melanomas in the 0.5-mg fingolimod group Breast cancer was reported in 4 patients (2 in each fingolimod group)

with RRMS to daily fingolimod (1.25 or 0.5 mg) or intramuscular (IM) IFN β 1-a (30 μ g/week). Among the 89% of participants who completed the study, annualized relapse rates were significantly lower in both fingolimod-treated groups (Table). Compared to placebo, secondary MRI endpoints were also reduced further with fingolimod, although progression of disability showed no significant differences, possibly due to the short (12-month) study period.

Adverse events among fingolimod-treated patients were consistent with other studies of the drug and included herpesvirus infections, transient bradycardia, and skin cancer (Table). “The overall number of cancers was too small to determine causality,” commented the authors, and no relationship between fingolimod dose and cancer risk has been shown. They warned, however, that although TRANSFORMS is one of the largest MS studies to date, “a potential shortcoming is that rare or late-appearing adverse events may not have been detected because of their low incidence and the 1-year study duration.” The investigators also noted that the absence of a dose-related difference in efficacy in this trial would require further study.

In February 2010, the FDA granted a priority review for fingolimod. Such a designation can reduce the time to approve a new drug application, although this period may be extended if more information is needed to evaluate the drug’s risks.

Cladribine

An analogue of adenosine already approved as a therapy delivered intravenously or subcutaneously for hairy-cell leukemia, cladribine inhibits DNA synthesis and repair in lymphocytes, resulting in the selective, long-term depletion of inflammatory CD4+ and CD8+ T cells,

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along with a reduction in levels of pro-inflammatory cytokines. Early trials of the oral tablet form of cladribine produced evidence of efficacy for RRMS but not for secondary-progressive MS (SPMS).

The CLARITY trial, conducted in 155 centers in 32 countries, randomized 1,326 patients with RRMS to receive 1 of 2 cumulative doses of oral cladribine (3.5 mg or 5.25 mg/kg of body weight) or placebo, given in short courses for only 8 to 20 days a year. (This dose schedule allows for an extended hematopoietic recovery period before retreatment.) Giovannoni et al reported that, among the 89.3% of participants who completed the 96-week study, cladribine-treated patients had significantly lower annualized relapse rates, lower risks of 3-month sustained progression of disability, and relative risk reductions, compared to placebo (Table). The proportion of patients who remained free of relapses at 96 weeks was significantly higher in both cladribine groups. Neuroimaging also revealed significant reductions in brain-lesion count on MRI ($P < 0.001$ for all comparisons). Both cladribine dose regimens seemed equally efficacious, noted the authors.

Adverse effects included lymphocytopenia and herpes zoster. In addition, 3 cancers (pancreatic, ovarian, and melanoma) were recorded among patients receiving low-dose cladribine (Table). Like other investigational oral MS therapies, cladribine has not yet been approved by the FDA. Ongoing research on this agent includes a 2-year extension of the CLARITY trial; the ORACLE MS study, a 2-year phase III trial of cladribine for clinically isolated syndrome (CIS, a first demyelinating event suggestive of MS); and ONWARD, a phase II placebo-controlled trial of cladribine as add-on therapy for patients who experience relapses on interferon treatment.

Laquinimod

Laquinimod, a quinolone-carboxamide, has immunomodulatory effects under investigation for several autoimmune diseases including MS. It is believed to work by shifting the cytokine profile from pro-inflammatory Th1 cells to anti-inflammatory Th2 cells. A structurally modified derivative of roquinimex (an investigational agent for RRMS whose study was suspended due to toxicity concerns), oral laquinimod has shown favorable tolerabil-

ity and safety in phase II studies, along with a significant reduction in MRI disease activity (Comi et al, *Lancet*. 2008;371:2085-2092). The drug was given a fast-track review by the FDA in 2009, and 2 phase III trials, BRAVO and ALLEGRO, are underway to evaluate laquinimod 0.6 mg/day in RRMS.

Teriflunomide

Teriflunomide, a metabolite of leflunomide, which is a drug used to treat rheumatoid arthritis, reduces activated B- and T-cell proliferation by inhibiting the synthesis of pyrimidine. It has anti-inflammatory and immunomodulatory properties. After a promising phase II trial (O'Connor, *Neurology*. 2006;66:894-900), the agent is now in phase III trials to treat RRMS and CIS. Some safety concerns have been voiced: according to a review by Spain et al, teriflunomide has been associated with hypertension, rash, and alopecia, and requires pre-treatment with cholestyramine or activated charcoal.

Dimethyl Fumarate

An oral formulation of dimethyl fumarate, a topical treatment for psoriasis, may exert anti-inflammatory and neuroprotective effects in MS through antioxidant activity. In a study of 257 patients randomized to placebo or to 1 of 3 dose regimens of oral fumarate, patients receiving the highest dose (240 mg 3 times daily) had a 69% reduction in the mean total number of new gadolinium-enhancing lesions from study weeks 12 to 24 compared with placebo (1.4 vs 4.5 lesions, $P < 0.0001$) (Kappos et al, *Lancet*. 2008; 372:1463-1472). Adverse effects included

abdominal pain, flushing, and hot flush, but the safety profile was deemed favorable, and the agent is now under investigation in a phase III trial.

Altogether, oral immunomodulatory agents are part of a new treatment horizon for patients with RRMS. In an editorial accompanying the new trial data for fingolimod and cladribine, Carroll commented, "Oral therapies further support a change in treatment approach to directly prevent immune-mediated injury." The long-term efficacy of oral agents in delaying MS disability has yet to be determined, he added, and adverse effects will require close surveillance. Approaching this next horizon, the management of MS with oral therapies will involve setting realistic expectations for therapy, monitoring safety, and tracking adherence and cost issues yet to be determined.

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CLINICAL INSIGHTS

- ✎ *In their role as educators, MS nurses will be challenged to help patients evaluate the risks and benefits of new oral therapies for RRMS as they become available, and to set realistic expectations for treatment.*
- ✎ *The first oral disease-modifying agents for RRMS to complete phase III clinical trials, fingolimod and cladribine, both showed significant reductions in relapse rates and MRI burden of disease compared to placebo.*
- ✎ *Oral MS agents are likely to present a tradeoff: potency and convenient administration vs a lack of long-term safety data. Currently unknown are the disease-modification effects and the safety profiles of any of the oral agents over a period of 3 or more years.*
- ✎ *Injectable DMTs for RRMS remain the standard of care for reducing relapses and MRI lesions and for delaying disease progression.*

*This summary was reviewed by
Cira Fraser, PhD, RN, ACNS-BC.*