

Emerging Oral Agents for Multiple Sclerosis

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The emergence of a new generation of multiple sclerosis (MS) agents is likely to cause a significant shift in the MS treatment landscape. Many of these new agents are in the later stages of development or have recently been approved for use by the US Food and Drug Administration (FDA). Much anticipation has centered around new oral formulations, which could make the administration of MS therapies significantly easier for patients, with likely beneficial effects on treatment adherence. Not surprisingly, injection anxiety is the central barrier to adherence with current first-line agents, interferon beta-1a (IFNB-1a), interferon beta-1b (IFNB-1b), and glatiramer acetate.¹ A survey of patients who use injectable agents for MS reported several injection-related factors that contribute to a lower rate of treatment adherence, including simple disinclination to perform an injection, “being tired” of taking injections, and skin and pain reactions to injection.² Adherence rates for the interferons and glatiramer acetate have been estimated between 50% and 80%.^{1,4} It remains to be seen whether the new oral agents will displace current first-line treatments or if the selection of MS therapies will be more diffuse or divided among oral and nonoral agents, with choice of treatment being based upon a variable equation of efficacy, adverse-event (AE) profile, and convenience. This article focuses on the efficacy and safety of 4 emerging agents for the treatment of MS: cladribine, laquinimod, fingolimod, and dalfampridine.

Cladribine

Mechanism of Action

Cladribine is a purine nucleoside analogue prodrug that is selectively toxic for lymphocytes and monocytes and appears to be able to cross the blood-brain barrier (BBB), although it is unclear if penetration is only possible when the BBB is damaged.^{5,6} Cladribine's mechanism of action is believed to derive from its reduction of lymphocyte subtypes, specifically CD4+ T cells, CD8+ T cells, and B cells.⁷ Cladribine also reduces pro-inflammatory chemokine levels.⁸ CD4+ T cells play a mediating role in the inflammatory cascade and are believed to contribute to the destruction of oligodendrocytes, resulting in axonal demyelination, whereas CD8+ T cells are implicated in the destruction of target cells expressing specific antigens.⁹ Furthermore, CD4+ T cells have been observed in acute lesions in MS, and CD8+ T cells are often seen in chronic lesions.¹⁰ There is

Abstract

A variety of emerging therapies for the treatment of multiple sclerosis (MS) are currently in development or have recently been approved by the US Food and Drug Administration (FDA). These new agents offer novel mechanisms of action and potentially improved efficacy over existing first-line MS therapies. Much attention has been given to emerging therapies delivered orally which, at minimum, will likely improve long-term adherence over existing agents delivered via injection. This article reviews the mechanisms of action, efficacy, and safety and tolerability of 4 emerging oral therapies for MS: cladribine, laquinimod, fingolimod, and dalfampridine. The first 3 of these agents are in late development and may enter the market within the next year and a half. Cladribine, laquinimod, and fingolimod have demonstrated impressive efficacy in terms of clinical outcomes, such as annualized relapse rate and change in disability scores, as well as magnetic resonance imaging variables. Dalfampridine, which has already been approved by the FDA, is indicated as a symptomatic therapy to improve walking in MS patients. Based on existing data, these agents appear to have tolerable side-effect profiles, although the long-term safety profiles of these drugs have yet to be elucidated. It remains to be seen whether the safety profiles of these disease-modifying drugs will allow them to displace existing first-line therapies or if agents such as dalfampridine will become additional options alongside current dominant therapies.

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also evidence to suggest that B cells play an important role in both inflammation and demyelination in MS.¹¹ At present, oral cladribine is not approved as an MS therapy, but a parenteral form of cladribine is approved as a treatment for hairy cell leukemia.¹²

Clinical Trials of Cladribine in MS

Research into the use of cladribine for MS has been ongoing since the 1990s; early studies included patients with primary progressive MS, secondary progressive MS, and relapsing-remitting MS (RRMS). Early studies involved subcutaneous (SC) administration; the oral formulation of cladribine is a relatively recent innovation. In a study of 51 patients with progressive MS, Beutler et al found that SC cladribine was significantly more effective than placebo in producing changes in disability, as measured by the Expanded Disability Status Scale (EDSS) and magnetic resonance imaging (MRI) parameters.¹³ However, a subsequent study in 159 patients with progressive MS found no advantage with subcutaneous cladribine for treatment of disability, although modest improvements were seen in MRI variables.¹⁴ Two subsequent analyses of data from this study found no significant efficacy associated with cladribine with respect to T1 (ie, hypointense) black holes or changes in brain volume, 2 of the key markers for disease progression and neuroprotection.¹⁵⁻¹⁷

An 18-month randomized controlled trial of SC cladribine in RRMS ($n = 52$) showed significant benefit with cladribine versus placebo for both frequency and severity of relapses, as well as improvement in MRI variables.¹⁸ It is worth noting, however, that a small safety study of SC cladribine in progressive MS ($n = 19$) found that although cladribine appeared to be well tolerated, it had significant suppressive effects on total lymphocyte count, as well as CD4+ and CD8+ cell subsets, with the doses tested.¹⁹ A 2-year study in 89 patients with progressive MS also found a significant reduction in lymphocyte count.²⁰ Although lymphopenia would be an expected outcome for a drug that is toxic to lymphocytes, excessive suppression could be a cause for concern.

The subsequent creation of an oral formulation moved cladribine into a new stage of importance in the MS treatment landscape. Results from a phase 3 clinical trial of oral cladribine, the CLARITY (CLAdRIbine Tablets in Treating MS Orally) study, were published in 2010. The study included 1326 patients with RRMS who were randomized to receive cladribine in 1 of 2 doses (3.5 or 5.25 mg/kg body weight) or placebo in a 1:1:1 ratio for 96 weeks.²¹ The primary end point, annualized relapse rate (ARR), was significantly reduced in both cladribine groups: 57.6% ($P < .001$)

in the 3.5-mg/kg group and 54.5% ($P < .001$) in the 5.25-mg/kg group (Figure 1).²¹ Risk of 3-month sustained progression, a secondary end point, was significantly reduced in both cladribine groups: 33% ($P < .02$) in the 3.5-mg/kg group and 31% ($P < .03$) in the 5.25-mg/kg group. MRI results also favored cladribine. Both treatment groups experienced fewer gadolinium (Gd+)-enhancing T1 lesions, active T2 lesions, and combined unique lesions ($P < .001$ for all comparisons vs placebo).²¹

As expected, lymphocytopenia was far more common in the cladribine groups: 21.6% in the 3.5-mg/kg group and 31.5% in the 5.25-mg/kg group versus 1.8% in the placebo group.²¹ The overall effect on lymphocytes was notable. The lowest median lymphocyte count in the 3.5-mg/kg group occurred at week 9 and constituted a 45.8% reduction from baseline.²¹ The nadir for the 5.25-mg/kg group constituted a 64% reduction and occurred at week 16.

Serious AEs in the form of infections and infestation—possibly as a result of immunosuppression—occurred in 2.3% and 2.9% of the lower and higher dose cladribine groups, respectively, compared with 1.6% in the placebo group.²¹ In addition, 6 patients in the 3.5-mg/kg group (1.4%) and 2 patients in the 5.25-mg/kg group developed neoplasms, compared with none in the placebo group. Five of the 10 neoplasms were benign uterine leiomyomas, whereas the remaining 5 cases consisted of 1 each of the following: cervical carcinoma (stage 0), malignant melanoma, myelodysplastic syndrome, ovarian cancer, and metastatic pancreatic carcinoma.²¹ There were 2 deaths in each of the 3 groups, 1 of which, in the 3.5-mg/kg cladribine group, resulted from metastatic pancreatic carcinoma.²¹

For its approved use in hairy cell leukemia, cladribine has been designated as pregnancy category D and has been shown to be teratogenic in mice and rabbits.¹² On November 30, 2009, it was announced that the FDA had issued a refuse-to-file letter for cladribine's New Drug Application (NDA).²² A new NDA for cladribine was submitted in June 2010, and it has been accepted for review.²³

Laquinimod

Mechanism of Action

Laquinimod is an immunomodulator related to, but chemically distinct from, linomide, an agent that has demonstrated efficacy in the treatment of MS, but has been associated with substantial adverse effects.²⁴⁻²⁷ The efficacy of laquinimod in MS is believed to be at least partially a result of its shift in the balance of T helper cells, Th1/Th2, which produces an immunomodulatory, but not immunosuppressive, effect.²⁸ A recently published in vitro study comparing the effects

of laquinimod in the peripheral blood mononuclear cells (PBMC) of healthy subjects and patients with RRMS found that laquinimod induced suppression of genes associated with antigen presentation and the resulting inflammatory pathways.²⁹ Analysis of PBMC subpopulations further determined that laquinimod activated the Th2 response in CD14+ and CD4+ cells, while suppressing CD8+ production.

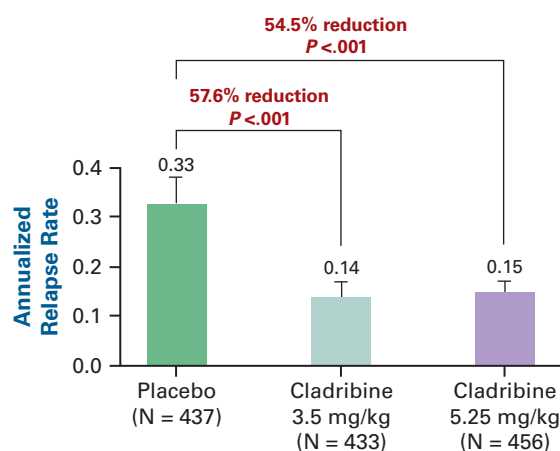
Clinical Trials of Laquinimod in MS

Clinical trials of laquinimod in MS have yielded positive efficacy results and a mild side-effect profile. Polman et al conducted a 24-week multicenter trial of laquinimod (0.1 or 0.3 mg/day) versus placebo in RRMS (n = 209).²⁴ The primary efficacy variable was cumulative number of Gd+-enhancing MRI lesions. At the end of 24 weeks, the mean cumulative number of active lesions was 44% lower in the 0.3-mg group compared with placebo—a difference that was significant ($P = .049$). The difference between placebo and the 0.1-mg group was not significant.²⁴ Exacerbations were rare during the study and disability measurements remained stable; there were no significant differences between the laquinimod groups and placebo.²⁴

Comi et al subsequently conducted a phase 2b trial of laquinimod (0.3 and 0.6 mg/day) for 36 weeks in 306 patients with RRMS.³⁰ The primary efficacy measure was cumulative number of Gd+-enhancing lesions at 24, 28, 32, and 36 weeks. At the end of the study, patients receiving laquinimod 0.6 mg experienced a 40.4% reduction in the mean cumulative number of Gd+-enhancing lesions compared with placebo ($P = .0048$); no significant reduction was noted in the laquinimod 0.3-mg group (Figure 2).³⁰ Among secondary end points, laquinimod was associated with a 51% reduction in T1-hypointense lesions. No significant improvements over placebo were noted in the other secondary clinical end points, EDSS and relapse rate.³⁰ Although AEs occurred with similar frequency in all groups, there was a dose-dependent elevation of alanine aminotransferase (ALT) in patients given laquinimod compared with those given placebo: 23.4% in the 0.3-mg/day group, 33.0% in the 0.6-mg/day group, and 10.8% in the placebo group. Two patients given laquinimod 0.3 mg/day discontinued treatment due to ALT elevations.³⁰

A 36-week double-blind extension trial of this phase 2b study involved maintaining patients on laquinimod and randomizing those who

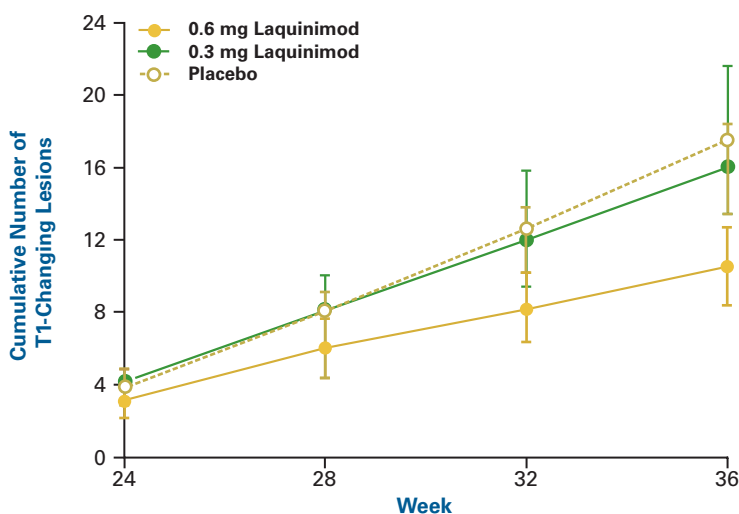
■ **Figure 1.** Annualized Relapse Rate in RRMS With 2 Doses of Cladribine Versus Placebo: CLARITY Study²¹



CLARITY indicates CLAdRiBine Tablets in Treating MS Orally; RRMS, relapsing-remitting multiple sclerosis. Reprinted with permission from Giovannoni G, et al. *N Engl J Med*. 2010;362(5):416-426.

had initially received placebo to treatment with either the higher or lower laquinimod dose.³¹ Patients who switched from placebo to laquinimod experienced significant reductions in the mean number of Gd+-enhancing lesions with both the 0.3-mg/day dose ($P < .03$) and the 0.6-mg/day dose ($P < .009$). Taken together, patients initially assigned to placebo experienced a 52% reduction in Gd+-enhancing

■ **Figure 2.** Cumulative Number of Gadolinium-Enhancing Lesions From the Final 4 Scans (Weeks 24 Through 36) in Patients With RRMS Given Laquinimod or Placebo³⁰



RRMS indicates relapsing-remitting multiple sclerosis. Reprinted with permission from Comi G, et al. *Lancet*. 2008;371(9630):2085-2092.

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lesions ($P < .0007$). Patients originally receiving laquinimod also experienced significant reductions in cumulative lesions: 0.3 mg/day ($P = .0013$) and 0.6 mg/day ($P = .0062$). AEs were similar to those observed in the original phase 2b trial.

After a total of 18 months (the original study and double-blind extension trial), 209 patients were enrolled in a 24-month, open-label extension trial in which all patients received laquinimod 0.6 mg/day.³² The mean ARR for all patients after the entire 42 months was 0.46, compared with an ARR of 0.53 for the first 18 months (ie, the 2 double-blind studies combined). Broken down by initial dosage from the first double-blind study, the ARR was 0.45 for the original laquinimod 0.6-mg/day group, 0.50 for the original 0.3-mg/day laquinimod group, and 0.42 for the original placebo group. Confirmed disability progression, as measured by the EDSS, occurred in 10.5% of patients over the 42-month period compared with 14.8% during the first 18 months. At month 42, 61% of patients were free of Gd+-enhancing lesions. Treatment was reported as safe and tolerable, although few details were given. In the 24-month, open-label extension trial, 24% of patients discontinued, although AEs did not appear to play a central role in most cases.

Laquinimod is now being studied in 2 phase 3 trials. The ALLEGRO (Assessment of Oral Laquinimod in Preventing Progression of MS) trial is a 2-year, double-blind, multinational study comparing laquinimod 0.6 mg/day with placebo. A total of 1107 patients with RRMS have been enrolled.³³ The primary outcome is ARR over 2 years; other end points include disability progression and number of MRI lesions. The 2-year BRAVO (Benefit-Risk Assessment of Avonex and Laquinimod) trial is designed to compare laquinimod, intramuscular IFNB-1a, and placebo.³⁴ The primary outcome for BRAVO is number of confirmed relapses (vs placebo); other end points include disability progression, number of MRI lesions, and changes in low-contrast visual acuity. Laquinimod has received fast-track review status from the FDA; it may reach the market in late 2011.³⁵

Fingolimod

Mechanism of Action

Fingolimod is a synthetic analogue of the fungus *Isaria sinclairii*.³⁶⁻³⁸ Fingolimod possesses a novel mechanism of action involving the modulation of sphingosine 1-phosphate receptors on lymphocytes and neural cells and inhibition of lymphocyte egress from lymph nodes.³⁶ As a result, circulating mature lymphocytes are sequestered to lymphoid tissues and recirculation of lymphocytes between lymphoid tissue and blood is modified. This is believed to reduce the infiltra-

tion of antigen-specific T-cells at inflammatory sites, with a consequent immunosuppressive effect.^{36,37}

Clinical Trials of Fingolimod in MS

Kappos et al conducted a multicenter, placebo-controlled, phase 2 study in 281 patients with RRMS. Patients were randomly assigned to receive fingolimod 1.25 mg/day, or fingolimod 5 mg/day, or placebo, for 6 months. This study was followed by a 6-month, blinded extension trial, in which patients given placebo were randomized to receive 1 of the 2 fingolimod doses.³⁹ The number of cumulative T1-weighted, Gd+-enhancing lesions, the primary end point, were significantly less in both the fingolimod 1.25-mg group ($P < .001$) and the 5.0-mg group ($P = .006$) compared with placebo.³⁹ Significantly more patients given fingolimod were lesion free versus placebo ($P < .001$ for both doses).³⁹ Other secondary MRI outcomes, including Gd+-enhanced lesion volume per patient, number of T2-weighted lesions per patient, and change in T2 lesions volume, also favored fingolimod.³⁹ With regard to clinical outcomes, the ARR was significantly better in patients given fingolimod ($P = .009$ for 1.25 mg and $P = .01$ for 5 mg vs placebo), but EDSS scores were not.³⁹

The extension study demonstrated continued benefits, with 80% of those receiving fingolimod lesion free at 12 months (ie, the initial 6-month study plus the 6-month extension).³⁹ AEs were significantly more common with the higher dose of fingolimod, but not the lower dose, compared with placebo. AEs primarily consisted of nasopharyngitis, dyspnea, and diarrhea.³⁹ Serious AEs occurred most frequently with fingolimod 5 mg/day.³⁹ Three patients given fingolimod 5 mg/day experienced bradycardia. Two patients receiving fingolimod 5 mg/day and 1 receiving fingolimod 1.25 mg/day had chest pain.

The extension study continued beyond the original 6-month period and, earlier this year, interim results were reported in those who completed 36 months of treatment ($n = 173$).⁴⁰ During months 15 through 24, all patients given fingolimod 5 mg/day were switched to 1.25 mg based on determination that the lower dose provided equivalent efficacy while conferring a lower risk of AEs.⁴⁰

At baseline (ie, day 0 of the first trial), 52% of patients initially given fingolimod 1.25 mg/day and 48% of those initially given fingolimod 5 mg/day were free of Gd+-enhancing lesions; at 6 months, the proportions were 77% and 82%, respectively; at 36 months, the percentages were 88% and 89%.^{39,40} The proportion of patients initially given placebo and free of Gd+-enhancing lesions was 50% at baseline, 47% at month 6, and 89% at month 36. The ARR at month 36 was 0.20 in the 1.25-mg group, 0.21 in the 5/1.25-

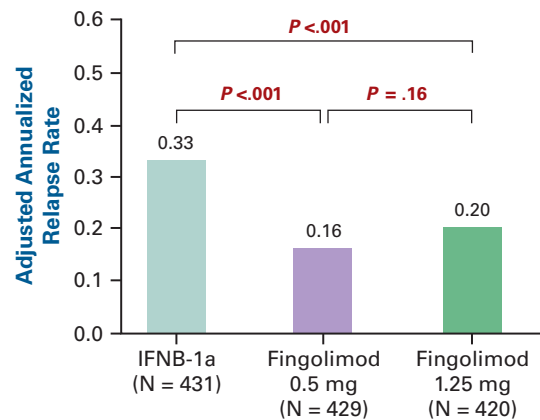
mg group, and 0.31 in the placebo/fingolimod group.⁴⁰ Nasopharyngitis was the most common AE, occurring in more than one third of all patients, whereas headache occurred in 30% of patients.⁴⁰ The greater the exposure to fingolimod, in terms of time and dose, the greater the risk of nasopharyngitis; the same was not true for headache. Elevated ALT levels were reported in 14.9% of patients. A total of 16% of patients experienced serious AEs. Eleven cases of skin cancer were noted between months 0 and 36, 8 of which occurred after month 24.⁴⁰

The FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis) study was a 24-month, multicenter, placebo-controlled trial. A total of 1272 patients with RRMS were randomized to receive fingolimod 1.25 mg/day, fingolimod 0.5 mg/day, or placebo.⁴¹ The primary end point, ARR, was 60% lower in the 1.25-mg group and 54% lower in 0.5-mg group compared with placebo (both $P < .001$).⁴¹ Key secondary end points were absence of confirmed disability progression (per EDSS) at 3 and 6 months. After 3 months of persistent disability, the cumulative probability of disability progression was 16.6% in the 1.25-mg group, 17.7% in the 0.5-mg group, and 24.1% in the placebo group ($P = .01$ vs placebo and $P = .03$ vs placebo, respectively). After 6 months of persistent disability, the probability of cumulative disability progression was 11.5%, 12.5%, and 19.0%, respectively ($P = .004$ vs placebo and $P = .01$ vs placebo, respectively).⁴¹ MRI variables also favored both fingolimod treatment groups compared with placebo.⁴¹

AEs occurred at a similar rate in all 3 groups. Sixty-one (14.2%) patients in the fingolimod 1.25-mg/day group discontinued the study due to AEs compared with 32 (7.5%) patients in the fingolimod 0.5-mg/day group and 32 (7.7%) in the placebo group.⁴¹ For serious AEs, bradycardia occurred in 3 patients given fingolimod 1.25 mg/day, 4 patients given fingolimod 0.5 mg/day, and 1 patient given placebo.⁴¹

The efficacy and safety of fingolimod was also assessed in a head-to-head trial with IFNB-1a. In the 12-month TRANSFORMS (TRial Assessing injectable interferoN vS FTY720 Oral in RrMS) study, 1292 patients with RRMS were randomized to receive fingolimod (1.25 or 0.5 mg daily) or intramuscular IFNB-1a (30 µg weekly).⁴² ARR, the primary end point, was significantly lower for both fingolimod doses versus IFNB-1a ($P < .001$ for both) (Figure 3).⁴² In one of the 2 key secondary end points, fingolimod 1.25 mg/day and 0.5 mg/day were associated with significantly fewer new or enlarged T2-weighted hyperintense lesions compared with IFNB-1a ($P < .001$ for

■ **Figure 3.** Annualized Relapse Rate in RRMS With 2 Doses of Fingolimod Versus Interferon Beta-1a (IFNB-1a) After 12 Months: TRANSFORMS Study⁴²



RRMS indicates relapsing-remitting multiple sclerosis; TRANSFORMS, TRial Assessing injectable interferoN vS FTY720 Oral in RrMS. Reprinted with permission from Cohen JA, et al. *N Engl J Med*. 2010; 362(5):402-415.

both doses).⁴² The other key secondary end point, time to confirmed disability progression, was similar in all 3 groups.⁴²

Six cases of localized skin cancer occurred in patients given fingolimod 0.5 mg/day; there were 2 cases in both the fingolimod 1.25-mg/day group and the IFNB-1a group.⁴² Two patients in each of the fingolimod groups, and none in the IFNB-1a group, were diagnosed with breast cancer. There were 2 deaths in the fingolimod 1.25-mg/day group (1 due to disseminated primary varicella zoster infection and 1 due to herpes simplex encephalitis) and none in the other groups.⁴²

The FDA's Peripheral and Central Nervous System Drugs Advisory Committee recommended approval of fingolimod in June 2010, and full approval is expected in September 2010.⁴³ The Advisory Committee recommended that fingolimod be approved as a first-line therapy at the 0.5-mg/day dose and stipulated that (1) patients be monitored during the first dose for lowering of heart rate in addition to other potential heart effects, and (2) potential AEs related to macular edema and lung function must also be assessed.⁴³ The committee further suggested that the FDA should consider requiring a study to determine whether a lower dose might be as effective as the recommended dose but have a lower risk of AEs.

Dalfampridine

Mechanism of Action

Dalfampridine (also known as fampridine) is a selective potassium channel blocker that has been hypothesized to

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relieve MS symptoms by restoring conduction in demyelinated axons via voltage-dependent potassium channel blockade.⁴⁴ It was approved by the FDA for treatment of MS in January 2010, and is unique among MS agents in having an indication specifically for improving walking (as opposed to reducing relapses or improving disability).⁴⁵ Dalfampridine has not proven efficacious in any other domains apart from improved walking.

Clinical Trials of Dalfampridine in MS

Dalfampridine has been studied in 2 phase 3 clinical trials. The first phase 3 trial was a multicenter study in 301 patients (27% with RRMS and 73% with progressive MS). Patients were randomly assigned in a ratio of 3:1 to receive dalfampridine 10 mg or placebo twice daily for 14 weeks.⁴⁶ The primary end point was change in walking speed (feet per second), as measured by the 25-foot walk test (T25FW). Patients were evaluated 4 times with the T25FW during a 2-week, single-blind, placebo run-in period. During the double-blind treatment phase, patients were evaluated at weeks 2, 6, 10, and 14.⁴⁶ They were also evaluated 2 weeks after discontinuation of treatment. Patients were designated as T25FW “responders” if their walking speed in 3 of the 4 T25FW assessments during the double-blind phase was faster than the maximum speed they achieved during the 5 off-drug assessments. A total of 35% of patients receiving dalfampridine were responders compared with 8% of those given placebo ($P < .0001$).⁴⁶

Sixteen (7%) patients given dalfampridine experienced serious AEs compared with none given placebo. Urinary tract infections and MS exacerbations occurred in 2 patients each; all other serious AEs occurred in 1 patient each.⁴⁶ One patient experienced a focal seizure that was believed to be related to treatment.

The second phase 3 trial ($n = 239$) was similar in design, but consisted of a treatment period of 9 weeks, and the ratio of those assigned to dalfampridine or placebo was 1:1.⁴⁷ After 9 weeks, 42.9% of patients given dalfampridine were T25FW responders compared with 9.3% of those given placebo ($P < .001$).⁴⁷

Because of its association with seizures, the FDA, in approving dalfampridine's use in MS, required the manufacturer to study the efficacy of doses lower than the approved dose of 10 mg twice daily. A warning for seizure risk, and a contraindication for people with a history of seizures, is included in the prescribing information for dalfampridine.⁴⁵

Conclusions

Of the 4 emerging oral MS therapies discussed, 3 agents—

cladribine, laquinimod, and fingolimod—may represent the future of MS therapy, with the potential to displace existing first-line injectable therapies. The fourth, dalfampridine, may become widely used, but the limited indication for its use limits its potential to become a dominant MS therapy. These oral therapies may offer significant advantages in terms of ease and convenience of administration. Cladribine, laquinimod, and fingolimod all possess encouraging efficacy profiles. It remains to be seen whether their efficacy in the larger patient population will sustain them over the long term, and if their safety profiles allow them to become first-line therapies used in the broad MS population.

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Authorship Information: Concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and supervision.

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