

SYNOPSIS

Highlights From the Literature

Update on Oral Therapy for MS

Kappos L, Radue E-W, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med.* 2010;362:387-401.

Fingolimod is an oral sphingosine-1-phosphate receptor modulator currently under investigation for the treatment of multiple sclerosis (MS). Preclinical work has suggested that this agent may have neuroprotective effects and may promote reparative processes in the central nervous system. In a phase II clinical trial and open-label extension, fingolimod reduced relapse rates and suppressed inflammatory disease activity for up to 5 years.

Building on this foundation, a phase III, double-blind trial, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS), was undertaken to assess the effects of daily fingolimod therapy in 1,272 patients with relapsing-remitting MS (RRMS). The recently reported results indicate that the annualized relapse rate over 24 months (the primary endpoint) was significantly reduced by daily fingolimod doses of 0.5 or 1.25 mg as opposed to placebo ($P < 0.001$ for both comparisons). The relapse rate was 0.18 (95% confidence interval [CI], 0.15 to 0.22) with the lower dose; 0.16 (95% CI, 0.13 to 0.19) with the higher dose; and 0.40 (95% CI, 0.34 to 0.47) with placebo. Hazard ratios for disability progression after 3 months (a key secondary endpoint) were 0.70 (95% CI, 0.52 to 0.96) with fingolimod 0.5 mg/d and 0.68 (0.50 to 0.93) with 1.25 mg/d vs placebo ($P = 0.02$ for both comparisons). Both fingolimod doses demonstrated superiority over placebo with respect to outcomes on magnetic resonance imaging (MRI), including number of new or enlarged lesions on T_2 -weighted images, number of gadolinium-enhancing lesions, and loss of brain volume ($P < 0.001$ for all comparisons at 24 months).

The incidence of adverse events was similar in the actively treated groups and placebo group. However, adverse events prompting study discontinuation (including abnormal

findings on laboratory tests) occurred more frequently with fingolimod 1.25 mg/d (14.2% of patients) than with fingolimod 0.5 mg/d (7.5%) or placebo (7.7%).

In light of these results, the FREEDOMS investigators called for more thorough and longer-term follow-ups of patients treated with oral fingolimod so as to obtain a greater understanding of benefits and risks.



Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med.* 2010;362:402-415.

Both articles indicate the need for further long-term studies of fingolimod to assess its safety profile. Serious adverse events (≥ 2 patients in any group) observed in both trials included infection, neoplasms, and cardiovascular disorders.

The Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) was undertaken to evaluate 1,153 patients who had a recent history of at least 1 relapse. This 12-month, double-blind, comparative trial demonstrated greater efficacy with oral fingolimod than with intramuscular (IM) interferon (IFN) β -1a.

The primary endpoint, the annualized relapse rate, was 0.16 (95% CI, 0.12 to 0.21) with fingolimod 0.5 mg/d; 0.20 (95% CI, 0.16 to 0.26) with fingolimod 1.25 mg/d; and 0.33 (95% CI, 0.26 to 0.42) with IM IFN β -1a in a weekly dose of 30 μ g. The differences between both fingolimod doses and IM IFN β -1a were statistically significant ($P < 0.001$). Findings on MRI indicated that the lower and higher fingolimod doses were also significantly superior with regard to the number of new or enlarged lesions on T_2 -weighted images ($P = 0.004$ and $P < 0.001$ for fingolimod 0.5 and 1.25 mg/d, respectively, vs IM IFN β -1a). In addition, significantly fewer gadolinium-enhancing lesions were apparent on T_1 -weighted imaging with fingolimod 0.5 and 1.25 mg/d as opposed to IM IFN β -1a ($P < 0.001$ for both comparisons). The 2 fingolimod doses were comparably effective. Progression of disability did not differ by treatment.

Serious adverse events (AEs) occurred in similar proportions of patients in the 3 study groups. Two fatal infections occurred in the 1.25-mg/day fingolimod group: disseminated primary varicella zoster and herpes simplex encephalitis. Other AEs seen in the fingolimod groups were nonfatal herpes virus infections, bradycardia and atrioventricular block, hypertension, and macular edema.

The authors of the TRANSFORMS report commented that an oral treatment option for RRMS is highly desirable from the standpoint of reducing side effects, improving convenience, and enhancing patient adherence. In view of the absence of dose-related differences in efficacy in this study, they called for further evaluation of the relative attributes of fingolimod 0.5 and 1.25 mg/d in other phase III trials.



Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362:416-426.

Cladribine is an oral medication that provides immunomodulation through selective targeting of certain subtypes of lymphocytes. The recently published results of the 96-week, phase III, double-blind, placebo-controlled Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) study confirmed the significant efficacy of this agent in RRMS.

The 2 oral cladribine doses assessed (3.5 or 5.25 mg/kg) were selected based on the results of previous clinical studies of a parenteral formulation of the drug. To provide an extended interim period of hematopoietic recovery before patients moved on to subsequent retreatment, cladribine was administered in short courses within separate 48-week periods, rather than giving the aggregate treatment as 6 to 8 consecutive monthly courses. This regimen resulted in only 8 to 20 days of treatment per year.

The primary endpoint, relapse rate at 96 weeks, was significantly reduced by both cladribine doses (0.14 with 3.5 mg and 0.15 with 5.25 mg compared to 0.33 with placebo; $P<0.001$ for both comparisons). Similarly, the proportion of patients who remained free of relapse at 96 weeks was significantly higher with cladribine 3.5 and 5.25 mg than with placebo (79.7% and 78.9% vs 60.9%, respectively; $P<0.001$ for both comparisons).

Furthermore, the time to first relapse was significantly longer with both cladribine doses compared to placebo (hazard ratios of 0.44 [95% CI, 0.34 to 0.58] for 3.5 mg and 0.46 [95% CI, 0.36 to 0.60] for 5.25; $P<0.001$ for both comparisons). The risk of 3-month sustained progression of disability was

33% with cladribine 3.5 mg and 31% with 5.25 mg, representing significant reductions when compared to placebo ($P=0.02$ and $P=0.03$, respectively). Both cladribine doses also significantly reduced measures of MRI activity, including number of gadolinium-enhancing T_1 lesions, active T_2 lesions, and combined unique lesions ($P<0.001$ for all comparisons vs placebo).

The most commonly reported adverse event in patients receiving either dose of cladribine was lymphocytopenia, which occurred more often than with placebo but was generally mild to moderate in severity. Adverse events prompting treatment discontinuation occurred in 3.5% and 7.9% of patients receiving cladribine 3.5 and 5.25 mg, respectively, and 2.1% of those receiving placebo. The CLARITY investigators added that the benefits of cladribine remain to be fully weighed against the risks.



Carroll WM. Oral therapy for multiple sclerosis—sea change or incremental step? N Engl J Med. 2010;362:456-458.

An editorial accompanying recent reports on clinical trials of oral therapies for MS noted that these studies “provide a new horizon for patients with relapsing-remitting multiple sclerosis and a welcome increase in the range of treatment options.” Although current therapies remain highly effective (especially when administered early in the course of disease) and have well-characterized side effect profiles, oral therapies offer another approach to the prevention of immune-mediated injury. Ever since the first pivotal trial of IFN β -1b was published in 1993, the author observed, clinicians and patients alike have been anticipating the approval of oral therapies for MS because of the relative ease of administration, which would be expected to “improve adherence and reduce restrictions on lifestyle.” However, the commentator pointed out that only time will tell whether oral medications will be effective over the long term for delaying the development of irreversible disability. In this respect, the lack of a definable endpoint “remains a contentious issue for clinicians and health care funders alike.”



Bremer J, Baumann F, Tiberi C, et al. Axonal prion protein is required for peripheral myelin maintenance. Nat Neurosci. 2010;13:310-318.

Prions cause transmissible neurodegenerative diseases, and the brains of patients affected by such disorders exhibit characteristic histopathologic changes. Nonetheless,

the molecular pathogenesis of these diseases has remained largely undetermined. In light of the fact that prion diseases are associated with accumulation of PrP^{Sc}, a misfolded and aggregated form of the cellular prion protein PrP^C, researchers have been interested in dissecting the molecular basis of the function of PrP^C to uncover possible pathways involved in neurodegeneration. Their findings in mouse models have revealed that neuronal expression and regulated proteolysis of PrP^C play crucial roles in the maintenance of peripheral myelin.

This conclusion was based on work in strains of mice in which PrP^C was ablated. Ablation of this prion protein led to the development of a chronic demyelinating polyneuropathy (CDP). This condition was brought about by depleting PrP^C

specifically in neurons and was suppressed by the expression of PrP^C in neurons. In contrast, depletion of PrP^C in Schwann cells alone did not trigger CDP, and expression of the protein in these cells did not protect against the disease.

Taken together, the results obtained by restricting expression of PrP^C to neurons and selectively depleting PrP^C from neurons indicated that neuronal expression of PrP^C is essential for maintaining the long-term integrity of peripheral myelin sheaths. The researchers commented that clarification of the molecular basis of these observations may result in an improved understanding of peripheral neuropathies and may pave the way toward new therapeutic targets for these debilitating diseases.



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