From Medscape Medical News

Oral Fingolimod and Cladribine Trials in Multiple Sclerosis Published

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Authors and Disclosures

January 21, 2010 — Final results for 3 large randomized trials of 2 new oral medications for relapsing-remitting multiple sclerosis (MS) were published online January 20 in the *New England Journal of Medicine*.

Two of these trials, FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis (FREEDOMS) and TRial Assessing injectable interferoN vS FTY720 Oral in RrMS (TRANSFORMS), show benefit of the investigational drug fingolimod (FTY720) against placebo and against interferon beta, respectively, in reducing relapse rates and new or enlarging lesions on magnetic resonance imaging (MRI). In FREEDOMS, with 24 months of follow-up, there was also less risk of progression of disability with fingolimod vs placebo.

A third study, the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial of cladribine (*Leustatin*, Ortho Biotech) vs placebo, also showed a significant reduction in annualized relapse rates, risk of disability progression, and MRI measures of disease activity at 96 weeks.

However, adverse effects, although similar between agents, were in some cases serious, even lethal. Herpetic infections, for example, were seen with both drugs and resulted in 2 deaths in the TRANSFORMS trial.

The results of these studies are important for many patients with MS who hope to trade in subcutaneous injections for an oral treatment option.

"The studies in this issue of the *Journal* provide a new horizon for patients with relapsing-remitting multiple sclerosis and a welcome increase in the range of treatment options," William M. Carroll, MB, MD, from the Department of Neurology at Sir Charles Gairdner Hospital in Perth, Australia, writes in an editorial accompanying the publications.

"Clinicians and patients will need to evaluate the risks and benefits of each of these drugs," Dr. Carroll points out. "Given the recent studies documenting the development of progressive multifocal leukoencephalopathy among patients receiving natalizumab ... close postmarketing surveillance will be important to detect any increase in these or other unexpected adverse effects."

In an interview, Dr. Carroll told *Medscape Neurology* that when these drugs become available, it is likely that neurologists will be under a lot of pressure from the "needle-phobic" patient to move to an oral drug. Still, he noted, the adverse effect profiles appear to be more serious than currently available drugs and are simply not completely known as yet.

"Those patients who are not responding that well to conventional therapies, that is, the immunomodulatory therapies [or the disease-modifying therapies], I think will probably be tried on these [oral therapies] fairly soon," Dr. Carroll said.

However, for treatment-naive patients, it is likely that neurologists will be more cautious, he added. "I think there'll be a period where people will, if you like, put their toe in the water and wait and see until there's a bit more experience around."

Fingolimod is a still-investigational agent being developed by Novartis Pharma. A spokesperson for Novartis confirmed that the company has filed a New Drug Application (NDA) with the US Food and Drug Administration (FDA) for fingolimod in MS.

Cladribine is already approved for the treatment of leukemias and lymphomas, and on the strength of the CLARITY findings, the company, Merck Serono, filed an NDA in October 2009 for relapsing-remitting MS. However, in November 2009 they received a "refuse to file" letter, generally issued when the NDA is not considered sufficiently complete by the FDA to permit substantive review.

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"The company will work closely with the FDA to fully understand the FDA's concerns and define a path forward for a successful resubmission of this application at the earliest point in time," Merck Serono president Elmar Schnee said in a statement dated November 30.

Preliminary results of the TRANSFORMS and CLARITY trials were presented at the American Academy of Neurology Annual Meeting and the 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in 2009 and reported by *Medscape Neurology* at that time. Top-line results of FREEDOMS were released by Novartis in September 2009.

FREEDOMS: Fingolimod vs Placebo

Given orally, fingolimod acts as a superagonist to sphingosine-1-phosphate receptors on the surface of thymocytes and lymphocytes, causing them to be sequestered in secondary lymph organs. This reduces the overall number of circulating lymphocytes available to mount an autoimmune reaction to the myelin sheath surrounding axons in MS.

The FREEDOMS trial was a 24-month, double-blind trial of 1272 patients with relapsing-remitting MS with scores of 0 to 5.5 on the Expanded Disability Status Scale, who had had 1 or more relapses in the previous year or 2 or more in the previous 2 years. The lead author on the trial was Ludwig Kappos, MD, University Hospital at the University of Basel, Switzerland.

They were randomized to receive placebo or either 0.5 mg or 1.25 mg of oral fingolimod daily; of these, 1033 (81.2%) completed the study. Causes of study discontinuation included the occurrence of bradycardia and atrioventricular conduction block with fingolimod initiation, the researchers note, as well as macular edema, elevated liver enzyme levels, and mild hypertension.

No increase was seen in cancer risk, as was seen with fingolimod in the TRANSFORMS data, although the researchers caution that longer observation is necessary because the risk for cancer is potentially increased by any immunomodulatory agent.

After 24 months, the annualized relapse rate, the primary endpoint, was significantly reduced with both doses of fingolimod vs placebo.

Table 1. FREEDOMS: Primary Endpoint

Endpoint	Fingolimod, 0.5 mg/day	Fingolimod, 1.25 mg/day	Placebo	*P* Value (for Either Dose vs Placebo)
Annualized relapse rate	0.18	0.16	0.40	<.001

The risk of disability progression during 24 months was reduced with fingolimod in both doses, with hazard ratios of 0.70 and 0.68, respectively, for the 0.5- and 1.25-mg/day groups ($P = .02$ for both doses vs placebo). The cumulative probability of disability progression, confirmed at 3 months, was 17.7% for those in the 0.5-mg group, 16.6% in the 1.25-mg group, and 24.1% with placebo.

On MRI measures, both doses of fingolimod were superior to placebo for outcomes, including new or enlarged lesions on T2-weighted images, gadolinium-enhancing lesions, and brain volume loss, with a $P < .001$ for all comparisons.

"The 2 doses of fingolimod had similar efficacy, and adverse events may be less frequent with the 0.5-mg dose than with the 1.25-mg dose," Dr. Kappos and colleagues note. "Thorough observation and long-term follow-up are necessary for a more informed assessment of the benefits and risks of this new treatment option for relapsing multiple sclerosis."

TRANSFORMS: Fingolimod vs Interferon Beta-1a

In TRANSFORMS, 1292 patients with relapsing-remitting MS were randomized to receive oral fingolimod, in the same doses of 0.5 mg/day or 1.25 mg/day, or interferon beta-1a (*Avonex*, Biogen Idec), 30 µg given intramuscularly once a week. Patients randomized to fingolimod received placebo injections once a week, and those randomized to interferon beta-1a received a placebo pill once a day.

As reported previously, the study met its primary endpoint, with a significant reduction in both fingolimod groups in the annualized relapse rate vs interferon beta-1a.

Table 2. TRANSFORMS: Primary Endpoint

Endpoint	Interferon beta-1a	Fingolimod, 0.5 mg/day	*P* Value	Fingolimod, 1.25 mg/day	*P* Value
Annualized relapse rate	0.33	0.16	<.0001	0.20	<.0001

MRI lesion activity was also reduced in both fingolimod groups vs interferon beta-1a. There was no significant difference seen on progression of disability, but the progression in all groups was small, "as would be expected in a 12-month study," the researchers, with lead author Jeffrey A. Cohen, MD, from the Neurologic Institute, Cleveland Clinic, Ohio, write.

Two deaths occurred during the study, both in the group receiving fingolimod, 1.25 mg/day: one patient with disseminated primary varicella zoster and the other with herpes simplex encephalitis.

Other adverse events in those taking fingolimod included nonfatal herpesvirus infections, skin cancer, and elevated liver enzyme levels,

CLARITY: Cladribine vs Placebo

In the CLARITY trial, 1326 patients received placebo or 1- of 2-dose regimens of cladribine, either 3.5 mg or 5.25 mg per kilogram of body weight, given in 2 or 4 short courses for the first 48 weeks, then in 2 short courses of starting at week 48 and week 52, for a total of between 8 and 20 days per year.

The primary endpoint was relapse rate at 96 weeks. Principal investigator Gavin Giovannoni, MBBCh, PhD, chair of neurology at the Institute of Cell and Molecular Science at Barts and the London School of Medicine and Dentistry in the United Kingdom, reports that both doses of cladribine were associated with a significantly lower relapse rate vs placebo.

Table 3. CLARITY: Primary Endpoint

Dose Group	Relative Reduction In Annualized Relapse Rate vs Placebo, %	Annualized Relapse Rate for Cladribine	Annualized Relapse Rate for Placebo	*P* Value
3.5 mg/kg	57.6	0.14	0.33	<.001
5.25 mg/kg	54.5	0.15	0.33	<.001

Again there was a higher relapse-free rate, a lower risk of 3-month sustained progression of disability, and significant reductions in brain lesion count on MRI, Dr. Giovannoni and colleagues note.

Adverse events that were more frequent with cladribine included lymphocytopenia and herpes zoster.

A "Huge Push" for Oral Agents

Commenting on these new findings for *Medscape Neurology*, Lily Jung, MD, an MS neurologist at the Swedish Neuroscience Institute in Seattle, Washington, who was involved in trials of both agents, pointed out that there is a currently a "huge push" to develop an oral agent for MS. "Patients are tired of injections, and they want more options," she said.

These new results with fingolimod and cladribine represent both good news and bad news, she said. "From the patient standpoint, the good news is that there are 2 oral agents coming down the pipeline that are likely to be approved, bar any new surprises, and from the prescribing neurologist's standpoint, there are more options, which is a good thing."

"But the bad news for both the neurologist and the patients is that the risks are higher," she added. With currently available agents, the main complaints are injection-site reactions and flulike symptoms. "Compared with the higher stakes that we're dealing with here with fingolimod and cladribine and natalizumab, those side effects are nothing."

The challenge, she said, will be to make patients understand the risks and not fixate on the possibility of an oral treatment without acknowledging that they are not benign. "I think there's a huge need for them, and I'm really excited about the possibility of having them on the market, but I think my job as a prescribing neurologist will be much more difficult, because I'm really going to have to carefully weigh for each patient the pros and cons of each of these drugs."

The FREEDOMS study was supported by Novartis Pharma. Dr. Kappos reports receiving consulting or advisory fees from Accorda, Actelion, Allergan, Allozyne, Bayer Schering, Biogen Idec, Biogen-Dompe, Boehringer-Ingelheim, Genmab, GlaxoSmithKline, Medicinova, Merck Serono, Novartis, Roche, Sanofi Aventis, Santhera, Teva Pharmaceuticals, UCB Pharma, and Wyeth; lecture fees from Biogen Idec, Helvea, GlaxoSmithKline, Mediservice, and Merck Serono; and grant support from Bayer Schering, Biogen Idec, CSL Behring, the European Community Research Fund, Genmab, Genzyme, GlaxoSmithKline, Medicinova, Merck Serono, Novartis, Novartis Foundation, the Rubato Foundation, Roche, Santhera, Sanofi-Aventis, and UCB Pharma. Disclosures for coauthors appear in the paper.

The TRANSFORMS trial was supported by Novartis Pharma. Dr. Cohen reports receiving consulting fees from Biogen Idec, Novartis, EMD Serono, and Teva; lecture fees from Sanofi-Aventis and Waterfront Media; and research support from Genzyme., Novartis, and Teva. Disclosures for coauthors appear in the paper.

The CLARITY trial was supported by Merck Serono. Dr. Giovannoni reports receiving consulting fees from Merck Serono, Bayer Schering Pharma, Biogen Idec, Novartis, Teva-Aventis, UCB Pharma, and Vertex Pharmaceuticals; lecture fees from Bayer Schering Pharma, Biogen Idec, Merck Serono, and Vertex Pharmaceuticals; and grant support from Bayer Schering Pharma, Biogen Idec, Ironwood Pharmaceuticals, Merck Serono, Merz, Novartis, and Teva-Aventis. Disclosures for coauthors appear in the paper.

N Engl J Med. Published online January 20, 2010.