# Recent advances in oral therapies for relapsing-remitting multiple sclerosis

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ABSTRACT. Oral therapies for multiple sclerosis have been highly sought after by patients and their physicians. Recently, the results of several important phase III clinical trials studying oral formulations of fingolimod and cladribine were published. In addition, a symptomatic oral treatment, dalfampridine, has been developed for use in MS patients with ambulatory impairment. The efficacy and potential adverse effects of these medications are discussed.
*Key words: multiple sclerosis, relapsing-remitting, treatment, oral delivery, fingolimod, cladribine, dalfampridine.*

RESUMEN. Los tratamientos orales para la esclerosis múltiple han sido muy deseados, tanto por los pacientes como por los médicos. Recientemente, se han publicado los resultados de los estudios en fase III con fingolimod y cladribina oral. Además, se ha desarrollado un tratamiento oral, dalfampridina, para el uso en pacientes de EM con alteraciones de la marcha. Se discute en este trabajo, la eficacia y los efectos adversos de estos fármacos.
*Palabras clave: esclerosis múltiple, recurrente-remitente, tratamiento, vía oral, fingolimod, cladribina, dalfampridina.*

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Since the early 1990's, a succession of medications have been approved for the treatment of relapsing-remitting multiple sclerosis (MS). These initially consisted of injectable medications in the form of interferon beta-1a (intramuscular and subcutaneous), interferon beta-1b (subcutaneous), and glatiramer acetate (subcutaneous). Natalizumab and mitoxantrone, both of which are delivered by infusion, were later approved and typically used as escalation therapies. Patients who are treated with one of the interferon beta medications or glatiramer acetate face potential adverse effects that include injection-site skin reactions, post-injection side effects such as flu-like symptoms in the case of the interferons, and lipoatrophy and transient systemic reactions in the case of glatiramer acetate[1]. These adverse effects make these drugs less convenient, reduce compliance, and can potentially lead to the discontinuation of disease-modifying treatment.

In a prospective three-year study by Milanese *et al* of 1481 relapsing-remitting MS patients, drop-out rates for injectable immunomodulatory treatment due to any reason ranged from 15.3% in patients receiving intramuscular interferon beta-1a to 41.1% in patients taking subcutaneous interferon beta-1b[2]. A retrospective study by Rio *et al* of 632 MS patients followed for a mean duration of 47.1 months and receiving either one of the beta-interferon medications or glatiramer acetate found that 107 patients (17%) stopped treatment[3]. Furthermore, 34 of the 632 patients (5.4%) did so not because of therapeutic inefficacy but as a result of flu-like symptoms or their own decision. Oral immunomodulatory treatments have therefore been highly desired by both patients and their health care providers.

Recently, the results of pivotal phase III trials of fingolimod and cladribine were published[4-6]. Fingolimod has subsequently been approved in the United States in September of 2010 for the treatment of relapsing-remitting multiple sclerosis while cladribine's application was rejected. Dalfampridine, a symptomatic MS treatment, was approved in the United States in January of 2010 following the published results of a phase III trial[7]. In this review, the efficacy of these drugs in patients with relapsing-remitting MS will be covered but perhaps just as importantly, their potential side effects will be discussed. We will conclude with possible strategies on how to incorporate medications such as fingolimod into the known armamentarium of established and approved MS treatments.

## ❑ Fingolimod

Fingolimod (FTY720) is an oral derivative of a fungal metabolite, myriocin, that when phosphorylated in vivo becomes a modulator of sphingosine-1-phosphate (S1P) receptors[8-10]. It causes the internalization of S1P receptors such as $S1P_1$ and ultimately results in what has been deemed functional antagonism. Since $S1P_1$ receptors aid in the migration of lymphocytes out of lymph nodes, fingolimod impedes the egress of activated T-cells from peripheral lymphoid organs into the central nervous system[11, 12]. Peripheral circulating lymphocytes are reduced in number. The

functioning of lymphocytes already in circulation appears to remain unchanged. Other mechanisms are likely to be at work. For example, $S1P_5$ receptors appear to aid in the survival of mature oligodendrocytes in vitro and by functioning as an agonist, fingolimod may exert a beneficial effect[13].

Clinical trials in humans were preceded by evidence in mice with experimental autoimmune encephalitis that fingolimod had a favorable effect[14]. In 2006, the results of a phase II clinical trial involving 255 patients with relapsing-remitting MS were published[15]. In the study, patients were randomly assigned to three groups: placebo (n=81), 1.25 mg daily (n=83), and 5.0 mg daily (n=77) for six months. Among the primary MRI endpoints, there was a reduction in the cumulative number of gadolinium-enhancing lesions and the number of patients who remained free of gadolinium-enhancing lesions at the end of six months in the patients receiving either the 1.25 mg or 5.0 mg doses. The annualized relapse rates of the 1.25 mg and 5.0 mg groups were 0.31 (55% relative reduction) and 0.29 (53% relative reduction), respectively, with prolongation of the time to first relapse in both fingolimod groups.

Adverse events that were noted in the phase II clinical trial described above included clinically asymptomatic lymphopenia (20 to 30% of baseline) and elevated alanine aminotransferase (ALT) levels (greater than 3 times the upper limit of normal). Transient bradycardia following the initial dose occurred in 3 patients in the 5.0 mg group and none in the 1.25 mg group. It has been proposed that $S1P_1$ receptors on atrial myocytes are the cause of this bradycardia that is generally asymptomatic with reductions in heart rate of less than 20 beats per minute[16]. One case of posterior reversible encephalopathy syndrome occurred in the 5.0 mg group.

A six-month long extension study was subsequently carried out with randomization of the placebo study patients to either the 1.25 mg or 5.0 mg daily dose while the patients receiving the 1.25 mg dose were maintained at that dosage and the patients receiving the 5.0 mg dose were reduced to the 1.25 mg dose due to the increased incidence of side effects at the higher dosage. There continued to be a reduction in the annualized relapse rate of the treated patients. In the end, this clinical trial was not powered to detect a treatment effect in terms of its relapse end points and so was regarded as a proof-of-concept study.

Extending upon their 2006 work, Kappos *et al* recently published the results of a phase III trial (FREEDOMS) that was a 24-month, double-blind, randomized study of patients with relapsing-remitting MS who had one or more relapses in the year before or two or more relapses in the past two years[4]. A total of 1272 patients were randomized to placebo (n=418), 0.5 mg daily (n=425), or 1.25 mg daily (n=429). The primary end point was the annualized relapse rate over 24 months, and both treatment groups had significantly lower mean relapse rates ($p<0.001$) of 0.18 (55% relative reduction) for the 0.5 mg group and 0.16 (60% relative reduction) for the 1.25 mg group compared with 0.40 for the placebo group. Among the various MRI-related secondary end points, there were fewer gadolinium-enhancing lesions at 24 months in both treatment groups compared with placebo with mean values of 0.2 for both 0.5 mg and 1.25 mg groups compared with 1.1 for the placebo group ($p<0.001$). There were also fewer new or enlarged lesions on T2-weighted images between baseline and 24 months in the fingolimod treated groups.

The adverse effects that were reported in the FREEDOMS trial were largely consistent with what had been found in the earlier 2006 phase II trial by Kappos *et al*. Lymphocytopenia was noted in the fingolimod treatment groups with a reduction in peripheral blood lymphocyte count of about 75 percent. Liver function test abnormalities in the form of an elevated ALT greater than three times the upper limit of normal were again seen more commonly in the groups who received fingolimod. Transient bradycardia after administration of the first dose was more likely to happen with fingolimod. Cases of atrioventricular block were rare. Macular edema occurred in seven patients on 1.25 mg daily of fingolimod and five of those cases developed within three months of initiating treatment. Six of the seven cases resolved after discontinuation of treatment. Herpesvirus infections occurred in a similar fraction of patients in all three groups. While there were three deaths during the study with two in the placebo group (pulmonary embolism and traffic accident) and one in the fingolimod treatment groups (suicide), none of those events were thought to be related to the medication.

Another Phase III clinical trial (TRANSFORMS) compared oral fingolimod against intramuscular interferon beta-1a in a 12-month, double-blind, active-controlled study that enrolled 1292 patients with relapsing-remitting MS who had one or more relapses in the year before or two or more relapses in the past two years[5]. The patients were randomly assigned to 0.5 mg daily of fingolimod (n=431), 1.25 mg daily of fingolimod (n=426), or 30 µg weekly of intramuscular interferon beta-1a (n=435). The primary endpoint was the annualized relapse rate, and this was significantly lower for fingolimod with mean values of 0.16 (52% relative reduction) for the 0.5 mg group and 0.20 (39% relative reduction) for the 1.25

mg group compared with 0.33 for interferon beta-1a ($p<0.001$). Both the proportion of patients who remained relapse-free during the study period and the time to first relapse favored the fingolimod-treated patients. One of the secondary MRI outcomes was the number of gadolinium-enhancing lesions on T1-weighted images. The interferon beta-1a group had a mean number of 0.51 gadolinium-enhancing lesions during the 12-month study period while the two fingolimod treatment groups had a mean of 0.23 lesions in the 0.5 mg group ($p=0.004$) and 0.14 lesions in the 1.25 mg group ($p<0.001$). Another secondary MRI outcome was the number of new or enlarged hyperintense lesions on T2-weighted images; the two fingolimod groups performed better with a mean of 1.7 lesions in the 0.5 mg group ($p<0.001$) and 1.5 lesions in the 1.25 mg group ($p<0.001$) in comparison to the interferon beta-1a group that had a mean of 2.6 lesions over 12 months.

Serious adverse events included two fatalities with one patient who developed a disseminated primary varicella zoster infection and another who had herpes simplex encephalitis. After the study concluded, two additional fatalities were attributed to metastatic breast cancer in one of the patients and progressive neurological deterioration with aspiration pneumonia in the other. Herpesvirus infections were documented in 9 patients in the 0.5 mg group (2.1%), 23 patients in the 1.25 mg group (5.5%), and 12 patients in the interferon beta-1a group (2.8%). As in previous studies, episodes of transient bradycardia occurring within an hour following the first dose of fingolimod were noted. Second-degree atrioventricular block was noted in four patients during the first day of treatment. Macular edema also occurred in six patients on fingolimod with five of those six cases discovered within the first four months after starting treatment. Three cases of melanoma were found in the 0.5 mg group.

Up to this point, TRANSFORMS has been the only clinical trial directly comparing fingolimod against an established MS medication. One may speculate as to whether or not there would have been a more comparable reduction in annualized relapse rate if fingolimod had been tested against glatiramer acetate, subcutaneous interferon beta-1a, or subcutaneous interferon beta-1b. The Independent Comparison of Interferon (INCOMIN) trial that was published in 2002 compared weekly intramuscular interferon beta-1a against every-other-day subcutaneous interferon beta-1b in 188 patients with relapsing-remitting MS who were randomly assigned to one of two open-label treatment groups[17]. The annualized relapse rates over two years were 0.70 for intramuscular interferon beta-1a and 0.50 for subcutaneous interferon beta-1b, and both results were higher than what was found in treatment groups in the TRANSFORMS trial. In the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial published in 1998 that studied 533 relapsing-remitting MS patients in a double-blinded and placebo-controlled manner, the annualized relapse rates for subcutaneous interferon beta-1b were 0.91 in the 22 mcg treatment group, 0.87 in the 44 mcg treatment group, and 1.28 in the placebo group[18]. More recently, the Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose (BEYOND) trial that was published in 2009 studied 2244 patients with relapsing-remitting MS[19]. Patients were randomized to 20 mg daily of glatiramer acetate or either 250 mcg or 500 mcg every other day of subcutaneous interferon beta-1b. Annualized relapse rates in these three groups were 0.34, 0.36, and 0.33, respectively, and similar to what was found for subcutaneous interferon beta-1a in the TRANSFORMS trial. A summary of the two fingolimod trials and the cladribine trial discussed below along with the earlier studies mentioned above can be found in Table I.

## ❑ Cladribine

Cladribine is a purine nucleoside analogue whose active metabolite, 2-chlorodeoxyadenosine triphosphate, is an adenosine deaminase inhibitor that primarily affects lymphocytes by disrupting their metabolism and causing apoptosis[20]. $CD4^+$ T cells are affected to a greater extent than $CD8^+$ T cells, and there also appear to be downregulatory effects upon inflammatory cytokines such as interleukin-8 and RANTES[21]. Originally used to treat hairy cell leukemia and other hematological malignancies, cladribine was studied in the mid-1990's in patients with chronic progressive MS who received the medication by infusion[22, 23]. A placebo-controlled trial published in 2000 enrolled 159 patients with primary progressive MS and secondary progressive MS but found no significant difference in disability outcome[24].

The results of a phase III study (CLARITY – Cladribine Tablets Treating Multiple Sclerosis Orally) were published in 2010[6]. This was a 96-week, double-blind, placebo-controlled, multicenter study that enrolled patients with relapsing-remitting MS and at least one relapse within a year before study entry. 1326 patients were randomized to placebo (n=437), a 3.5 mg/kg cumulative dose (n=433), or a 5.25 mg/kg cumulative dose (n=456). During the first 48-week period, the patients on medication were given either two courses in the 3.5 mg/kg group or four courses in the 5 mg/kg group, and during the second 48-week period, both groups received anoth-

**Table I** Summary of selected relapsing-remitting MS treatment trials mentioned in the text

| Trial | Year | Treatments compared | Study design | Patients | Duration | Annualized relapse rate |
|---|---|---|---|---|---|---|
| PRISMS Study Group[18] | 1998 | 44 mcg interferon beta-1a SC three times a week<br>22 mcg interferon beta-1a SC three times a week<br>Placebo | Prospective, randomized, double-blind, placebo-controlled | 184<br>189<br>187 | 24 mo | 0.87<br>0.91<br>1.28 |
| Durelli *et al.* (INCOMIN)[17] | 2002 | 250 mcg interferon beta-1b SC every other day<br>30 mcg interferon beta-1a IM weekly | Prospective, randomized, double-blind, active-controlled | 96<br>92 | 24 mo | 0.50<br>0.70 |
| O'Connor *et al.* (BEYOND)[19] | 2009 | 500 mcg interferon beta-1b SC every other day<br>250 mcg interferon beta-1b SC every other day<br>20 mg glatiramer acetate SC daily | Prospective, randomized, double-blind, active-controlled | 887<br>888<br>445 | 24-42 mo | 0.33<br>0.36<br>0.34 |
| Kappos *et al.* (FREEDOMS)[4] | 2010 | 1.25 mg fingolimod PO daily<br>0.5 mg fingolimod PO daily<br>Placebo | Prospective, randomized, double-blind, placebo-controlled | 429<br>425<br>418 | 24 mo | 0.16<br>0.18<br>0.40 |
| Cohen *et al.* (TRANSFORMS)[5] | 2010 | 1.25 mg fingolimod PO daily<br>0.5 mg fingolimod PO daily<br>30 mcg interferon beta-1a IM weekly | Prospective, randomized, double-blind, active-controlled | 426<br>431<br>435 | 12 mo | 0.20<br>0.16<br>0.33 |
| Giovannoni *et al.* (CLARITY)[6] | 2010 | 5.25 mg/kg cumulative dose of cladribine<br>3.5 mg/kg cumulative dose of cladribine<br>Placebo | Prospective, randomized, double-blind, placebo-controlled | 456<br>433<br>437 | 24 mo | 0.15<br>0.14<br>0.33 |

*SC = subcutaneous; IM = intramuscular; PO = oral, see text for the full trial names.*

er two courses. Each course consisted of one or two 10 mg cladribine tablets given once daily for 4 or 5 days out of a 28-day period. The primary end point was the annualized relapse rate at 96 weeks and the mean values were 0.14 (58% relative reduction) for the 3.5 mg/kg group and 0.15 (55% relative reduction) for the 5.25 mg/kg group compared with 0.33 for the placebo group ($p<0.001$ for both). Secondary end points such as the relapse-free rate and time to first relapse were in favor of the patients who received cladribine. Lesion activity on brain MRI was significantly reduced with a 85.7% reduction in the mean number of gadolinium-enhancing lesions in the 3.5 mg/kg group (87.9% for the 5.25 mg/kg group).

Adverse effects that were reported in the CLARITY trial included lymphocytopenia that was detected in a quarter of patients in both cladribine treatment groups. Headaches were more common in subjects who received cladribine. Herpes zoster infections occurred in 20 patients treated with cladribine and none in the patients who received placebo. Of the 20 patients just mentioned, 3 were deemed to have serious adverse reactions. Neoplasms occurred in 1.4% of patients in the 3.5 mg/kg group and 0.9% of patients in the 5.25 mg/kg group compared with none in the placebo group.

A randomized, double-blind phase III clinical trial investigating the use of oral cladribine (1.75 mg/kg/yr or 3.5 mg/kg/yr) in patients with clinically isolated syndrome entitled ORACLE (Oral Cladribine in Early Multiple Sclerosis) is currently underway with an estimated enrollment of 600 patients.[25] There is also a phase II study that will study the addition of cladribine to interferon-beta for the treatment of relapsing-remitting MS patients[26].

## ❑ Dalfampridine

Dalfampridine (4-aminopyridine) is a voltage-gated potassium channel blocker that likely prolongs action potentials in demyelinated nerve fibers[27, 28]. It has been studied as a symptomatic treatment in MS patients with ambulatory impairment. Early clinical trials of 4-aminopyridine were carried out in MS patients in the 1980's[29, 30]. In 1994, a randomized and double-blinded crossover trial of 24 patients found 4-aminopyridine to be superior to 3,4-aminopydrine[31]. Later, Schwid *et al* studied the use of a timed 8-meter walk test and found it to be superior to the Expanded Disability Severity Scale (EDSS) in providing a quantitative assessment of ambulatory impairment in MS patients taking sustained

release 4-aminopyridine[32]. This has since been used as a primary outcome in recent trials in the slightly modified form of a timed 25-foot (7.5-meter) walk (T25FW) test.

In 2009, the results of a phase III study were published by Goodman *et al*[7]. This was a randomized, double-blinded, placebo-controlled, and parallel-group study of patients with clinically defined MS who were able to complete a T25FW test in an average of 8 to 45 seconds. Out of 301 patients, 72 were randomized to the placebo arm while 229 were randomized to treatment with 10 mg twice daily. Between these two groups, it was found that 8.3% of the placebo group had a significant response as measured by improvement in walking speed while 34.8% of the treatment group showed a significant response. Furthermore, the average improvement in walking speed in the responders of the treatment group was 25.2% (95%CI: 21.5-28.8).

Prior to initiating dalfampridine, a baseline T25FW test time should be obtained for future comparison. Measurement of creatinine clearance is recommended as dalfampridine is predominantly excreted renally. Patients with moderate-to-severe renal impairment with a creatinine clearance below 50 ml/min should not take dalfampridine as peak serum levels of the drug will be elevated. Seizures are a concerning side effect of dalfampridine and its use has been contraindicated in patients with a history of seizures. The incidence of seizures may be dose-dependent and in the United States, the manufacturer (Acorda Therapeutics) has recommended a fixed dose of 10 mg twice daily. At that dose, the seizure rate is about 0.25% per 100 patient-years[33]. Additional possible adverse effects of dalfampridine include imbalance, insomnia, headache, dizziness, nausea, fatigue, and urinary tract infections[7, 34].

## ❑ Conclusion and approach to clinical management

Both fingolimod and cladribine portend a future in which MS therapies will be delivered orally rather than by injection. It remains to be seen whether sequestered lymphocytes in peripheral lymphoid organs by fingolimod when released upon discontinuation of the medication might result in a "rebound effect" attributable to a sudden surge of T-cells into circulation. Whether or not reduced immune surveillance due to the sequestration of lymphocytes will have long-term consequences remains an open question. Immunosuppressive therapies such as natalizumab along with other monoclonal antibodies such as rituximab and efalizumab have been associated with progressive multifocal leukoencephalopathy (PML) due to the JC virus[35]. Uncommon side effects may come to light over time and recent case reports of patients being treated with fingolimod have described the occurrence of hemorrhaging focal encephalitis and critical vasospasm[36, 37]. Longer follow-up of patients treated with these oral medications will be needed to discern if their use will be justified by the higher rates of infection and other potentially life-threatening side effects. The lack of an apparent dose-related difference in efficacy between the various fingolimod daily doses that have been studied (0.5 mg, 1.25 mg, and 5 mg daily) has allowed for a ten-fold reduction in dosage over successive trials, and this reduction in dose may improve the overall safety of the drug. An extension study entitled FREEDOMS II with an estimated enrollment of 1080 patients that follows the study design of FREEDOMS may be completed by early 2011 and should help to provide further insight into the safety profile of fingolimod[38].

In the meantime, clinicians that opt to start fingolimod in their patients should obtain baseline complete blood counts and liver function tests that should then be repeated every three to six months. Due to the possibility of transient bradyarrhythmias and atrioventricular block after the first dose of fingolimod, patients will need to be observed for six hours after receiving their initial treatment. Their cardiac history will need to be reviewed before the drug is given. Since macular edema has been observed in patients within the first three to four months of treatment, an ophthalmological evaluation should be performed before starting fingolimod and then repeated after four months of therapy. If patients develop breathing difficulties, spirometry may be needed to check for a reduction in forced expiratory volume over one second (FEV1). Patients may be more prone to developing infections while in a lymphopenic state and the manufacturer (Novartis AG) has recommended checking for antibodies to varicella zoster virus before starting treatment. If found to be negative in a patient, vaccination should be considered before starting fingolimod at least a month later[39].

The well-established track record of the interferon medications and glatiramer acetate suggests that they will remain first-line treatments for relapsing-remitting MS. Pending the release of additional long-term safety information about fingolimod, a conservative approach would be to use this as second-line therapy unless a patient has an insurmountable phobia to needles or has other reasons for which an oral medication would be preferable. For example, the detection of a high titer of neutralizing antibodies in a patient who is not responding well to interferon treatment could prompt consideration of the use of a different medication such as fingolimod. The greater wholesale cost of

fingolimod when compared with the injectable medications will also need to be taken into account. Drug manufacturers will seek to capitalize on the more preferable form of delivery of oral medications and will market them accordingly, but the risks and benefits of using them must be carefully weighed.

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