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# Oral Disease-Modifying Therapies for Multiple Sclerosis

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Classical multiple sclerosis (MS) treatments using first-line injectable drugs, although widely applied, remain a major concern in terms of therapeutic adherence and efficacy. New oral drugs recently approved for MS treatment represent significant advances in therapy. The oral route of administration clearly promotes patient satisfaction and increases therapeutic compliance. However, these drugs may also have safety and tolerability issues, and a thorough analysis of the risks and benefits is required. Three oral drugs have been approved by regulatory agencies for MS treatment: fingolimod, teriflunomide, and dimethyl fumarate. This article reviews the mechanisms of action, safety, and efficacy of these drugs and two other drugs that have yielded positive results in phase III trials: cladribine and laquinimod. **J Clin Neurol 2015;11(1):9-19**

**Key Words** multiple sclerosis, oral drug, clinical trial, treatment.

## Introduction

Treatments of multiple sclerosis (MS) have undergone a revolution over the past 2 decades. Since its introduction in 1993, interferon (IFN)  $\beta$ -1b, the first therapeutic drug for MS, has been shown to effectively modify the natural course of the disease. The subsequent development of new therapeutic tools has progressed rapidly, affording physicians and patients broader options for disease management.

Classical MS treatments using first-line injectable drugs, although widely applied, remain of major concern in terms of therapeutic adherence and efficacy. The IFNs, the first and (still) most commonly used drugs for MS, have been associated with injection-site reactions, flu-like symptoms, and liver dysfunction, and carry with them the risk of developing neutralizing antibodies that can limit their effectiveness. Glatiramer acetate (GA) has been associated with local injection-site reactions and transient systemic postinjection reactions, which may diminish patient adherence to treatment. In addition to such inconveniences, these injectable drugs only reduce the

relapse rate by approximately 30%; although this is a significant reduction, it is clear that better treatments are needed.

The new orally administered drugs (henceforth referred to as “oral drugs”) approved for MS treatment represent significant therapeutic advances. The oral route of administration clearly promotes patient satisfaction and increases therapeutic compliance; however, as for the injectable drugs, they may also have safety and tolerability issues, and a thorough analysis of their risks and benefits is required. Three oral drugs have been approved by regulatory agencies for the treatment of MS: fingolimod, teriflunomide, and dimethyl fumarate. The mechanisms of action, efficacy, and safety of these drugs and two other drugs that have yielded positive results in phase III trials, cladribine and laquinimod, are reviewed herein (Table 1).

## Fingolimod

Fingolimod (also called FTY720; Gilenya) was the first oral drug approved by the United States Food and Drug Administration (FDA) for the treatment of MS. It is a derivate of myriocin, a metabolite of the ascomycete fungus *Isaria sinclairii*, and is used in Oriental medicine.<sup>1</sup>

## Mechanism of action

Fingolimod is phosphorylated in the bloodstream to resemble

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**Table 1. Efficacy of the oral drugs for MS in phase III clinical trials**

Drugs	Study name and reference	Design	Arms	Primary endpoint	Result of the primary endpoint	Key secondary endpoints and their results
Fingolimod	FREEDOMS <sup>18</sup>	Randomized, double-blind, parallel-group, placebo-controlled study involving 1,272 patients with RRMS for 24 months	0.5 mg, 1.25 mg vs. placebo	ARR	55.0% relative reduction in 0.5-mg group; 60.0% relative reduction in 1.25-mg group	26.6% and 31.1% reductions in EDSS progression (confirmed after 3 months) in 0.5- and 1.25-mg groups, respectively. Reduced Gd-enhanced T1-weighted lesions, new or enlarging T2-weighted lesions, and PBVC in treated groups
	TRANSFORMS <sup>19</sup>	Randomized, double-blind, double-dummy, parallel-group study involving 1,292 patients with RRMS for 12 months	0.5 mg, 1.25 mg vs. intramuscular IFNβ-1a 30 µg weekly	ARR	51.5% relative reduction in 0.5-mg group; 39.4% relative reduction in 1.25-mg group	Confirmed EDSS progression was infrequent in all groups. Reduced and Gd-enhanced T1-weighted lesions and new or enlarging T2-weighted lesions in treated groups
	FREEDOMS II <sup>20</sup>	Randomized, double-blind, parallel-group, placebo-controlled study involving 1,083 patients with RRMS for 24 months	0.5 mg, 1.25 mg (discontinued during the study) vs. placebo	ARR	48% relative reduction in 0.5-mg group; 50% relative reduction in 1.25 mg dose	No significant difference in EDSS progression. Reduced Gd-enhanced T1-weighted lesions, new or enlarging T2-weighted lesions, and PBVC in treated groups
Teriflunomide	TEMSO <sup>38</sup>	Randomized, double-blind, parallel-group, placebo-controlled study involving 1,088 patients with RRMS for 24 months	7 mg, 14 mg vs. placebo	ARR	31.2% relative reduction in 7-mg group; 31.5% relative reduction in 14-mg group	23.7% (not significant) and 29.8% (significant) reductions in EDSS progression in 7- and 14-mg groups, respectively. Reduced Gd-enhanced T1-weighted lesions, new or enlarging T2-weighted lesions, and PBVC in treated groups
	TOPIC <sup>39</sup> (final results not published)	Randomized, double-blind, parallel-group, placebo-controlled study involving 618 patients with CIS over 24 months	7 mg, 14 mg vs. placebo	Conversion to CDMS	37.2% relative reduction in 7-mg group; 42.6% relative reduction in 14-mg group	31.4% and 34.9% reductions in new relapse or new MRI lesion in 7- and 14-mg groups, respectively
	TENERE <sup>40</sup>	Randomized, rater-blinded, parallel-group study involving 324 patients with RRMS over 96 weeks	7 mg, 14 mg vs. subcutaneous IFNβ-1a 44 µg three times weekly	Time to failure	No difference between the groups	No difference in ARR between 14 mg and IFNβ-1a, but ARR significantly higher in 7-mg group; more frequent fatigue in IFNβ-1a group than 7-mg group. Treatment satisfaction higher in teriflunomide groups
	TOWER <sup>41</sup>	Randomized, double-blind, placebo-controlled study involving 1,169 patients with RRMS. Treatment duration was variable, ending 48 weeks after the last patient was included	7 mg, 14 mg vs. placebo	ARR	22.3% relative reduction in 7-mg group; 36.3% relative reduction in 14-mg group	31.5% reduction in EDSS progression in 14-mg group; no difference in 7-mg group
Dimethyl fumarate (BG-12)	DEFINE <sup>57</sup>	Randomized, placebo-controlled study involving 1,234 patients with RRMS over 2 years	240 mg twice, 240 mg three times vs. placebo	Proportion of patients who had a relapse	41.3% relative reduction in twice-daily group; 43.5% relative reduction in three-times-daily group	53% and 48% reductions in ARR, and 38% and 34% reductions in EDSS progression in twice-daily and three-times-daily groups, respectively. Reduced Gd-enhanced T1-weighted lesions, new or enlarging T2-weighted lesions in treated groups

**Table 1. Efficacy of the oral drugs for MS in phase III clinical trials (continued)**

Drugs	Study name and reference	Design	Arms	Primary endpoint	Result of the primary endpoint	Key secondary endpoints and their results
	CONFIRM <sup>58</sup>	Randomized, placebo-controlled study involving 1,417 patients with RRMS over 2 years	240 mg twice, 240 mg three times, GA 20 mg (as a reference comparator) vs. placebo	ARR	44% relative reduction in twice-daily group; 51% relative reduction in three-times-daily group (29% relative reduction in GA group)	21%, 24%, and 7% reductions in EDSS progression in twice-daily, three-times-daily, and GA groups, respectively (not significant). Reduced Gd-enhanced T1-weighted lesions, new or enlarging T2-weighted hyperintense lesions in treated groups
Cladribine	CLARITY <sup>67</sup>	Randomized, double-blind, placebo-controlled study involving 1,326 patients with RRMS over 96 weeks	3.5 mg/kg, 5.25 mg/kg vs. placebo	ARR	57.6% relative reduction in 3.5 mg/kg group; 54.5% relative reduction in 5.25 mg/kg group	30.9% and 29.6% higher relapse-free rate, and 33% and 31% reductions in EDSS progression in 3.5 and 5.25 mg/kg groups, respectively. Reduced Gd-enhanced T1-weighted lesions, active T2-weighted lesions and combined unique lesions in treated groups
	ORACLE MS <sup>68</sup>	Randomized, double-blind, placebo-controlled study involving 617 patients with CIS over 96 weeks	3.5 mg/kg, 5.25 mg/kg vs. placebo	Time to conversion to MS by Poser criteria	67% relative reduction in 3.5 mg/kg group; 62% relative reduction in 5.25 mg/kg group	50% and 57% reductions in the time to conversion to McDonald MS in 3.5 and 5.25 mg/kg groups, respectively. Lower median numbers of new or persisting Gd-enhanced T1-weighted lesions, new or enlarging T2-weighted lesions, and combined unique active lesions in treated groups
Laquinimod	ALLEGRO <sup>78</sup>	Randomized, double-blind, parallel-group, placebo-controlled study involving 1,106 patients with RRMS over 24 months	0.6 mg vs. placebo	ARR	23.1% relative reduction in treated group	29.3% reduction in risk of EDSS progression in treated group. Reduced mean cumulative numbers of Gd-enhanced lesions and new or enlarging T2-weighted lesions in treated group. Reduced PBVC in treated group
	BRAVO <sup>80</sup>	Randomized, double-blind, parallel-group study involving 1,331 patients with RRMS over 2 years	0.6 mg, intramuscular IFNβ-1α 30 µg weekly (as a reference comparator) vs. placebo	ARR	18% relative reduction in laquinimod group (not significant); 26% relative reduction in IFNβ-1α group	31.3% and 40.6% reductions in EDSS progression confirmed at 3 months (not significant) and 6 months (significant), respectively, in laquinimod group; 28% reduction in PBVC in laquinimod group. Nonsignificant reductions in cumulative number of Gd-enhanced T1-weighted lesions and new/enlarging T2-weighted lesions

ARR: annualized relapse rate, CDMS: clinically definite multiple sclerosis, CIS: clinically isolated syndrome, EDSS: Expanded Disability Status Scale, GA: glatiramer acetate, Gd: gadolinium, IFN: interferon, MS: multiple sclerosis, PBVC: percent brain volume change, RRMS: relapsing-remitting multiple sclerosis.

endogenous lysophospholipid sphingosine-1 phosphate (S1P),<sup>2</sup> for which at least five receptors exist. Different receptor subtypes perform various functions. In particular, S1P<sub>1</sub> binding to receptors expressed on lymphocytes regulates the normal egress of lymphocytes from lymphoid tissue,<sup>2,3</sup> whereas S1P receptors expressed in the CNS seem to modulate neurogenesis, neural function, and migration.<sup>4</sup> Fingolimod acts as a receptor superagonist, inducing aberrant internalization. This inhibits the egress of T and B cells from lymph nodes, reducing the numbers of circulating memory T cells by over 70%.<sup>5</sup> Both peripheral lymphocyte counts and recirculation of lymphocytes to the CNS are thus reduced, leading to immunosuppressive effects.<sup>6-9</sup> Fingolimod is lipophilic and easily enters the CNS, where the drug can bind to S1P receptors of several subtypes on different cell types, possibly exerting (as yet poorly understood) neuroprotective or repair effects.<sup>10-12</sup>

### Effectiveness

The efficacy of fingolimod in patients with relapsing-remitting MS (RRMS) was first documented in a 6-month, double-blind, phase II core study and a 6-month extension study, during which both investigators and patients were unaware of the treatment assignments.<sup>13</sup> The median total numbers of gadolinium-enhanced lesions decreased with fingolimod treatment at both 1.25 mg/day (one lesion) and 5.0 mg/day (three lesions) compared with the placebo (five lesions). The annualized relapse rate (ARR) was 0.77 in the placebo group, and 0.35 and 0.36 in the 1.25- and 5.0-mg/day fingolimod groups, respectively, corresponding to relative reductions of 55% and 53%, respectively. Open-label extension studies revealed sustained suppression of both relapse and inflammatory activity for up to 5 years in MS patients.<sup>14-17</sup>

Three large-scale phase III trials have evaluated the long-term safety and efficacy of fingolimod. A double-blind, placebo-controlled study evaluating fingolimod dosages of 0.5 or 1.25 mg/day, termed FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis), revealed a 54% relative reduction in ARR (0.18, 0.16, and 0.40 for 0.5 mg of fingolimod, 1.25 mg of fingolimod, and placebo, respectively).<sup>18</sup> Fingolimod at daily doses of 0.5 and 1.25 mg significantly reduced the risk of disability progression as measured using the Expanded Disability Status Scale (EDSS) over a 24-month period (the hazard ratios were 0.70 and 0.68 for the 0.5- and 1.25-mg doses, respectively). Both of these fingolimod doses were superior to the placebo in terms of MRI-related measures of disease, such as the number of new or enlarged lesions on T2-weighted images and gadolinium-enhanced lesions, and loss of brain volume.<sup>18</sup>

A 12-month, double-dummy phase III study involving patients with RRMS (TRANSFORMS: TRial Assessing INject-

able INterferon vs. FTY720 Oral in RRMS) compared oral fingolimod at daily doses of either 0.5 or 1.25 mg with intramuscular IFN $\beta$ -1a at a weekly dose of 30  $\mu$ g.<sup>19</sup> The ARR were lower in both groups receiving fingolimod (0.16 and 0.20, respectively) than in the IFN group (0.33). MRI findings, including the number of new or enlarged lesions on T2-weighted images, supported the primary results. No significant differences were evident among the three study groups in terms of disability progression.<sup>19</sup>

In the FREEDOMS II study, which commenced at the same time as FREEDOMS and had similar inclusion criteria and equal treatment allocations, the ARR was 0.21 in the 0.5-mg fingolimod group and 0.40 in the placebo group, representing a relative reduction of 48% (0.40–0.66).<sup>20</sup> The 1.25-mg dose was terminated because of the absence of clear additional benefits and a higher risk of safety-related events. All MRI outcome measures, apart from the percentage change in T1-weighted hypointense lesion volume from baseline to 24 months, were significantly better in patients taking fingolimod than in the placebo group. However, no significant reduction in the risk of disability progression was observed.<sup>20</sup> A randomized, double-blind, placebo-controlled study comparing fingolimod with placebo in patients with primary progressive MS is currently ongoing.<sup>21</sup>

### Safety profile

Fingolimod has been associated with transient dose-dependent bradycardia, atrioventricular conduction block (AVB), hypertension, macular edema, elevated liver enzyme levels, lymphocytopenia, and skin cancers.<sup>18,19</sup> In the TRANSFORMS study, two fatal infections occurred in patients receiving the 1.25-mg dose of fingolimod: disseminated primary varicella zoster and herpes simplex encephalitis.<sup>19</sup>

A decrease in heart rate and slowing of atrioventricular conduction following the first dose of fingolimod are recognized pharmacological effects, and are mediated by modulation of the S1P<sub>1</sub> level in atrial myocytes in a manner similar to vagal stimulation. The effect is typically transient due to the internalization of and desensitization to S1P<sub>1</sub>.<sup>22,23</sup> In a phase IIIb open-label study that ran for 4 months, bradycardia occurred in 0.6% of patients and was more frequent in those receiving  $\beta$ -blockers and calcium-channel blockers (3.3%).<sup>22</sup> Most events were asymptomatic, and all patients recovered without pharmacological intervention. Patients with preexisting cardiac conditions tended to have Mobitz type I second-degree AVB and 2:1 AVB at 6 h postdose more frequently (4.1% and 2.0%, respectively) than those without such conditions (0.9% and 0.3%, respectively). Upon predose screening, patients with preexisting cardiac conditions exhibited the same incidence of Mobitz type I second-degree AVB (4.1%) and a slightly lower

incidence of 2:1 AVB (0.7%) than at 6 h postdose. Blood pressure was higher during the first month, and stabilized thereafter.<sup>24-26</sup> Extensive first-dose precautions are currently in place for this drug, as summarized in Table 2.<sup>24,25</sup>

## Teriflunomide

Teriflunomide (Aubagio) is an active metabolite of leflunomide,<sup>27</sup> which is an immunosuppressant drug approved for treatment of mild and moderate rheumatoid arthritis.<sup>28</sup> A role for the drug in MS therapy was first evaluated in the Dark Agouti rat model of experimental autoimmune encephalomyelitis; the drug was shown to delay disease onset, reduce relapse frequency, and improve neurological findings, triggering interest in the reproduction of such findings in clinical trials.<sup>29</sup>

### Mechanism of action

Teriflunomide acts by reversibly inhibiting the enzyme dihydro-orotate dehydrogenase, the rate-limiting mitochondrial enzyme of *de novo* pyrimidine synthesis,<sup>27,30</sup> by noncompeti-

**Table 2.** Summary of cardiovascular monitoring requirements for fingolimod according to the revised European Medicines Agency approved label<sup>26</sup>

Bradyarrhythmia and blood pressure monitoring
ECG and blood pressure measurement before starting treatment.
Observation for 6 h after first dose in all patients:
Continuous ECG monitoring for 6 h.
Check blood pressure and heart rate every hour for 6 h.
Extended monitoring for at least 2 h in patients whose heart rate is lowest at 6 h after first administered dose.
Monitoring should continue at least overnight and until the problems have been resolved for any patients who develop bradycardia, QTc interval $\geq 500$ ms, or new-onset second-degree or higher grade AVB.
Atropine and isoproterenol reverse the negative chronotropic effect of fingolimod; these drugs are therefore recommended to treat symptomatic bradycardia, if necessary.
Fingolimod is not recommended for patients with Mobitz II or higher AVB, ischemic heart disease, or history of symptomatic bradycardia.
Fingolimod is not recommended for patients receiving $\beta$ -blockers and other agents that cause bradycardia because of potential additive effects on the heart rate. However, if treatment is nonetheless considered necessary, advice from a cardiologist should be sought to determine alternative non-heart-rate-lowering medications, or extended overnight monitoring (at least) is recommended after the first dose.
Regular monitoring of blood pressure is recommended during treatment.

AVB: atrioventricular conduction block, QTc interval: corrected QT interval.

tively inhibiting the binding of its substrate, dihydro-orotate, and also by acting as a competitive inhibitor of ubiquinone binding.<sup>31</sup> Thus, the drug exerts cytostatic effects on activated and rapidly proliferating T and B cells responding to autoantigens.<sup>32-34</sup> The pyrimidine salvage pathway is spared, allowing maintenance of protective immunity throughout treatment.<sup>35</sup> RRMS patients treated with teriflunomide exhibited effective immune responses to seasonal influenza vaccination, consistent with preservation of their protective immune response.<sup>36</sup>

### Effectiveness

A randomized, double-blind, parallel-group, placebo-controlled, phase II study involving patients with RRMS and secondary progressive MS with relapses revealed that treatment with teriflunomide (7 or 14 mg/day) significantly reduced the combined numbers of unique active lesions evident upon brain MRI over 36 weeks.<sup>37</sup> Both treatment groups exhibited fewer gadolinium-enhanced lesions and new or enlarging T2-weighted lesions. The deterioration in the EDSS scores was less among those taking the higher dose, even though the ARR was not significantly reduced.

The TEMSO (TEriflunomide Multiple Sclerosis Oral) study was the first Phase III clinical trial to demonstrate the effectiveness of teriflunomide.<sup>38</sup> Patients treated with the drug at dosages of 7 or 14 mg/day exhibited significant ARR reductions (0.54 in the placebo group vs. 0.37 in the 7- and 14-mg/day teriflunomide groups; a decrease of 31%), slower progression of disability (a relative reduction of 29.8% compared with the placebo), and reductions in several MRI measures of disease activity.

Recognition of the potential of teriflunomide in MS therapy has led to new study designs. TOPIC (TEriflunomide vs. Placebo In Patients with First Clinical Symptom of Multiple Sclerosis) was a clinical trial designed to assess whether early commencement of drug therapy in patients experiencing their first neurological symptoms could prevent or delay the conversion to clinically definite multiple sclerosis (CDMS). The preliminary results of that trial have been reported recently. The drug was associated with risk reductions of up to 43%.<sup>39</sup>

The TENERE (TEriflunomide and REbif) study compared teriflunomide with subcutaneous IFN $\beta$ -1a, and showed similar risks of treatment failure.<sup>40</sup> The ARR did not differ between 14-mg teriflunomide and IFN $\beta$ -1a, but was significantly higher with 7-mg teriflunomide. TSQM (Treatment Satisfaction Questionnaire for Medication) scores were also significantly higher with teriflunomide. This evidence, together with prior data, prompted the approval of teriflunomide as the second oral disease-modifying therapy for MS; the favorable clinical profile of the drug was endorsed.

The TOWER (TEriflunomide Oral in People With Relaps-

ing Multiple Sclerosis) trial compared the use of 7- and 14-mg/day teriflunomide with placebo.<sup>41</sup> The ARR was 0.39 and 0.32 in the 7- and 14-mg/day groups, respectively, corresponding to relative rate reductions of 22.3% and 36.3%, respectively (ARR: 0.5). Teriflunomide at 14 mg/day (but not at 7 mg/day) reduced the risk of sustained disability accumulation compared with placebo (hazard ratio: 0.68).

### Safety profile

The most common adverse events associated with teriflunomide use are elevated alanine aminotransferase levels, diarrhea, nausea, influenza, hair thinning or decreased hair density, and peripheral neuropathy.<sup>38,40,41</sup> Such adverse events are dose-dependent and rarely lead to treatment discontinuation. Increased blood pressure, reductions in neutrophil and lymphocyte counts, and skin disorders also develop more frequently in patients receiving the drug. Therefore, it is recommended that liver function is monitored and routine complete blood counts and blood pressure measurements are made in patients receiving this drug.

Another principal concern is teratogenicity, which is evident in animal models.<sup>42</sup> Pregnant women are excluded from treatment, and it is essential that women use effective contraception methods prior to initiation of therapy; males are similarly cautioned to avoid fathering a child whilst on therapy, because teriflunomide has been detected in human semen.<sup>42</sup> If a female becomes pregnant during treatment, it is advisable to substantially reduce drug levels via washout prior to fetal organogenesis, ideally as soon as pregnancy is detected.

## Dimethyl Fumarate

A dimethyl fumaric acid ester compound dimethyl fumarate (also known as BG-12; Fumaderm), which contains four different fumaric acid esters, serves as a second-line agent for the treatment of severe psoriasis. However, similarities in the associated inflammatory cascades have led to the hypothesis that Fumaderm might also exert beneficial effects in patients with CNS autoimmune diseases, and the subsequent recognition of Fumaderm as a promising therapy for MS. In September 2003, Biogen (now Biogen Idec) exclusively licensed the rights to develop and market BG00012 (BG-12, Tecfidera), which is a second-generation fumaric acid compound that contains only dimethylester fumarate in enteric-coated microtablets; adverse gastrointestinal effects are thus supposedly minimized.<sup>43</sup> Two phase III studies have analyzed the long-term efficacy and safety of the drug, and the findings—together with acquired experience on fumaric acid ester use in psoriasis patients—contributed to recent FDA approval being granted to the drug as the newest oral treatment for RRMS.

### Mechanism of action

Various mechanisms have been proposed to explain the effects of dimethyl fumarate in MS patients. The anti-inflammatory effects of the drug have been linked to ultimate reductions in lymphocyte counts and disruption of cell migration. A decrease in circulating lymphocyte numbers is associated with a shift from a T helper (Th) 1 to a Th2 response, increasing the levels of the Th2-like cytokines interleukin (IL)-4, IL-5, and IL-10, which in turn induce apoptosis of activated T cells.<sup>44-46</sup> Restriction of cell migration is attributable to down-regulation of intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin (also termed CD62E), all of which affect the passage of activated T cells through the blood-brain barrier.<sup>47-50</sup>

Dimethyl fumarate may also play a role in neuroprotection. Preclinical work has shown that dimethyl fumarate and its primary metabolite, monomethyl fumarate, activate the nuclear erythroid-2-related factor 2 transcriptional pathway that controls expression of the gene encoding the phase-2 detoxifying enzyme, which plays a crucial role in the oxidative stress response and immune homeostasis.<sup>51-54</sup> Activation of this pathway up-regulates NAD(P)H:quinone reductase and increases the cellular content of glutathione, an important antioxidant that may mitigate cellular damage.<sup>55</sup>

### Effectiveness

In 2006, the findings of an 18-week, open-label, prospective study indicated that dimethyl fumarate significantly reduces the numbers of gadolinium-enhanced lesions.<sup>56</sup> Since that time, dimethyl fumarate has yielded further impressive results. In a second phase II study of BG-12, treatment with 240 mg of BG-12 three times daily reduced the mean total number of new gadolinium-enhanced lesions by 69%, reduced the numbers of new or enlarging T2-weighted hyperintense and new T1-weighted hypointense lesions, and reduced ARR by 32%, all relative to the placebo group.<sup>51</sup>

The DEFINE (Determination of the Efficacy and Safety of Oral Fumarate IN Relapsing-Remitting MS), a 2-year phase III study, demonstrated positive outcomes in terms of relapse, disability, and MRI measures.<sup>57</sup> The ARR was 0.17 in the 240-mg twice daily BG-12 group and 0.19 in the 240-mg three-times-daily BG-12 group, compared with 0.36 in the placebo group, affording relative reductions of 53% and 48%, respectively. Moreover, the risk of confirmed disability progression was also reduced, reaching 38% over the 2-year study period. However, the most notable effect was observed when MRI endpoints were evaluated; BG-12 reduced the numbers of new or enlarging hyperintense lesions on T2-weighted images by up to 85%, and the number of gadolinium-enhanced lesions by up to 94%.

Another Phase III trial, CONFIRM (COmparator aNd an Oral Fumarate In Relapsing-Remitting Multiple Sclerosis), also yielded favorable results.<sup>58</sup> Notably, a GA-treated group was evaluated as a reference comparator, allowing relative risk-benefit analysis of BG-12. The ARR were 0.22, 0.20, and 0.29 in the 240-mg twice-daily BG-12, 240-mg three-times-daily BG-12, and GA groups, respectively, corresponding to relative reductions of 44%, 51%, and 29% compared to the placebo group (ARR: 0.40). Reductions in disability progression with twice-daily BG-12, three times-daily BG-12, and GA versus placebo were not significant. The numbers of new or enlarging T2-weighted hyperintense lesions as well as new T1-weighted hypointense lesions were also reduced in the treated groups. The results showed that the estimated treatment effects of both BG-12 doses tested (240 mg two or three times daily) were equivalent to or better than those achieved with GA in terms of efficacy endpoints. Moreover, the outcomes were consistent with the results of previous BG-12 studies and those of the DEFINE trial, confirming the potential of BG-12 as an initial oral treatment for RRMS patients or as an alternative to currently available therapies.

### Safety profile

Both of the aforementioned phase III trials showed that BG-12 exhibited good safety and tolerability profiles.<sup>57,58</sup> Adverse events that occurred significantly more often in treated patients included gastrointestinal symptoms (specifically, upper abdominal pain, diarrhea, and nausea) and hot flushes, which typically commenced within 30 min of drug administration and subsided within 90 min. However, the incidence of serious adverse events leading to drug discontinuation was similar in patients receiving placebo. Long-term safety data on dimethyl fumarate are available from previous studies using Fumaderm to treat psoriasis. The past observational studies encompass over 50,000 patient-years of experience, distinguishing BG-12 from other novel oral drugs.

## Cladribine

Cladribine (2-chlorodeoxyadenosine) is an adenosine deaminase-resistant purine nucleoside initially licensed as a chemotherapeutic agent used to treat hairy cell leukemia.<sup>59</sup> Early studies evaluated the efficacy of the parenteral form in the treatment of progressive MS and, later, that of the oral form in treating RRMS.

### Mechanism of action

Cladribine enters the cell via the purine nucleoside transporters and is phosphorylated by deoxycytidine kinase.<sup>60,61</sup> In cells in which the ratio of deoxycytidine kinase to deoxynucleotid-

ase is high, such as lymphocytes and monocytes, cladribine is phosphorylated to the active triphosphate deoxynucleotide, 2-chlorodeoxyadenosine-ATP, the accumulation of which disrupts cellular metabolism and damages DNA, causing cell death.<sup>62</sup> These processes lead to lymphocyte depletion and long-lasting lymphopenia.

### Effectiveness

Research assessing the efficacy of cladribine to treat MS was published as early as 1994 and 1996 in two phase II studies involving progressive MS patients, showing that treatment with four monthly courses of 0.7 mg/kg cladribine was associated with significant disease stabilization measured with the EDSS and Scripps Neurologic Rating Scale (SNRS).<sup>63,64</sup> Although these favorable outcomes encouraged evaluation of cladribine in the treatment of progressive MS in a multicenter study, no significant treatment effects were observed in terms of changes in EDSS or SNRS scores.<sup>65</sup>

However, the outcomes of RRMS patients were more impressive. In the first double-blind, placebo-controlled, randomized trial, both the frequency and severity of relapses were reduced and MRI results improved. MRI enhanced lesions were completely suppressed by 6 months of treatment.<sup>66</sup> Prompted by such findings, the phase III CLARITY (CLAdRIbine Tablets Treating Multiple Sclerosis Orally) trial analyzed the long-term efficacy and safety of cladribine tablets (either 3.5 or 5.25 mg/kg) versus placebo.<sup>67</sup> The ARR values (the primary endpoints) were 0.14 and 0.15, respectively, in the two cladribine groups, compared to 0.33 in the placebo group, translating to relative ARR reductions of 57.6% and 54.5%, respectively. The risk of 3-month sustained progression of disability was also lower in the cladribine group (hazard ratio: 0.67 for the 3.5 mg/kg group and 0.69 for the 5.25 mg/kg group). Brain MRI revealed significant reductions in the extent of T2-weighted lesions (by 73.4% and 76.9%, respectively) and gadolinium-enhanced lesions (by 85.7% and 87.9%, respectively).

Preliminary findings of the phase III ORACLE MS (ORAL CLadribine for Early MS) trial on the efficacy of cladribine in delaying conversion to CDMS were released recently.<sup>68</sup> The treated groups exhibited significant delays in such conversion, accompanied by risk reductions of 67.3% and 61.9% in the 3.5- and 5.25-mg/kg cladribine groups, respectively, relative to placebo. Moreover, such treatment also significantly delayed the time to conversion to McDonald MS, compared with the placebo.

### Safety profile

Cladribine is more effective than the traditional drugs used for MS treatment, but several adverse effects have limited its use.

Furthermore, the potential drug-induced long-term suppression of the immune system—creating issues such as malignancy and infection—remains to be elucidated. Dose-dependent myelosuppression, opportunistic infections (herpes zoster and tuberculosis), and malignancies have been linked to cladribine use.<sup>67</sup> Benign uterine leiomyomas and three cases of cancer were noted in patients in the CLARITY study.<sup>69</sup> Furthermore, secondary exacerbation of latent tuberculosis and latent herpes zoster led to implementation of screening measures in all ongoing trials using cladribine. Ultimately, the sponsor received negative feedback from the FDA and the European Medicines Agency, and decided to no longer pursue global approval for cladribine tablets.<sup>10</sup>

## Laquinimod

Laquinimod is an orally administered quinoline-3-carboxamide derived from linomide (roquinimex). Although phase II clinical trials demonstrated that linomide (2.5 mg/day) significantly reduced clinical and MRI activities in RRMS patients,<sup>70</sup> severe adverse events—including cardiopulmonary toxicity and pancreatitis—resulted in abrupt termination of the phase III study.<sup>71,72</sup> However, laquinimod is 20-fold more potent than linomide and exhibits a far more favorable safety profile, increasing the chances that the drug will be found to be acceptable.

### Mechanism of action

The precise mode of action of laquinimod has not yet been fully elucidated, but the drug is known to exert anti-inflammatory and neuroprotective effects. Laquinimod appears to inhibit the infiltration of CD4+ T cells and macrophages into the CNS and to alter the cytokine profile via a shift from the Th1 to the Th2/Th3 phenotype.<sup>73</sup> There is also preliminary evidence of increases in the serum level of brain-derived neurotrophic factor, which may protect neuronal function.<sup>74</sup>

### Effectiveness

Following two positive phase II trials,<sup>75-77</sup> laquinimod was compared with placebo in a randomized, double-blind, phase III study (in which the drug was administered at 0.6 mg/day): the ALLEGRO (Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis) trial.<sup>78</sup> The drug exhibited a modest effect on relapse rate, but had a significantly positive effect in terms of disease progression: a 23% reduction in ARR compared with placebo, a 36% reduction in sustained disability progression assessed using the EDSS, a 37% reduction in gadolinium-enhanced lesions, and a 33% reduction in brain atrophy on MRI. Laquinimod also slowed atrophy of the thalamus and reduced the numbers of permanent

black holes evolving from active lesions at 12 and 24 months, suggesting that the drug modulates certain destructive pathological processes in RRMS patients.<sup>79</sup>

Another phase III trial, BRAVO (Benefit-Risk Assessment of Avonex and Laquinimod), evaluated the efficacy, safety, and tolerability of 0.6 mg/day oral laquinimod, and compared its benefit/risk profile with those of 30- $\mu$ g-weekly IFN $\beta$ -1a (intramuscular) and placebo over a 2-year period.<sup>80</sup> In that study, although laquinimod did not significantly reduce ARR compared with placebo (-18%), the decline in brain volume was significantly reduced (28%). Confirmed worsening of disabilities was infrequent (10% with laquinimod and 13% with placebo). Confirmed worsening of disability in patients taking laquinimod, measured using the EDSS, was -31% compared with placebo. In contrast, IFN $\beta$ -1a significantly reduced the ARR (by 26%).

These findings support the hypothesis that laquinimod both reduces inflammation and exhibits neuroprotection. Such data, combined with the (modest) effect of laquinimod in terms of reducing ARR, triggered planning of a new phase III study, termed CONCERTO (The Third Phase III Placebo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerability of Once-daily Oral Laquinimod in Patients with Relapsing-Remitting Multiple Sclerosis).<sup>81</sup> That study will compare the effects of two dosages of laquinimod (0.6 and 1.2 mg/day) with placebo in approximately 1,800 patients with RRMS for up to 24 months. Disease progression will be the primary endpoint.<sup>82</sup>

### Safety profile

The main adverse effects associated with laquinimod are elevated liver enzyme levels, which are transient and not associated with liver failure or with back or abdominal pain.<sup>78,80</sup> One patient in the phase IIb study developed Budd-Chiari syndrome, raising the concern that the risk of thrombosis is increased in individuals with preexisting thrombophilia.<sup>76</sup> However, the patient was heterozygous for the factor V Leiden mutation, which is associated with venous thrombosis in up to 30% of cases.

## Conclusion

The approval of several new oral drugs will be of benefit to MS patients and afford more convenient routes of administration to them. However, the lack of long-term data on efficacy and several possible adverse events are of concern. Therefore, evaluations of the best treatment for each patient must include overall assessments of its efficacy, safety, tolerability, the need for monitoring, and cost-effectiveness.



## Conflicts of Interest

Dr. H.J. Kim has given talks, consulted and received honoraria and/or research support from Bayer Schering Pharma, Biogen Idec, Genzyme, Kael-GemVax, Merck Serono, Novartis, Teva-Handok, and UCB. He serves on a steering committee for MedImmune and serves as an editorial board member of Multiple Sclerosis Journal - Experimental, Translational and Clinical.

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