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Review Article

Oral Therapies for Multiple Sclerosis in Recent Years

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Abstract

The injectable immunomodulators interferon and glatiramer acetate have dominated the multiple sclerosis (MS) market for the past two decades. Recently, new oral drugs have been approved by the US Food and Drug Administration for the treatment of MS. In this review, we discuss four new oral therapies for MS: fingolimod, laquinimod, BG-12, and teriflunomide, including their mechanisms of action, clinical trial efficacy, and safety profile, as well as the implications for clinical practice.

Introduction

Multiple Sclerosis (MS) is a chronic progressive disorder characterized by demyelination, axonal transection, and progressive neurodegeneration in the central nervous system (CNS), leading to long-term disability. There are four clinical types: relapsing–remitting, secondarily progressive, primarily progressive, and relapsing– progressive courses. Among these, the relapsing–remitting form (RRMS) is the most common, affecting ~85% of patients; it is characterized by attacks of inflammation and partial or complete remission of clinical symptoms followed by periods of stable symptomatology until the next relapse [1]. Disease-modifying therapies (DMTs) have been available since the early 1990s, and are able to alter the natural history of RRMS because of their anti-inflammatory effects on the immune system. Their development is the biggest change over the past 20 years in the treatment of MS. These agents have shown efficacy in the reduction of relapse frequency and the reduction in CNS inflammation, as well as having a variable ability to reduce the progression of disability [2]. Currently approved immunomodulator therapies for RRMS include glatiramer acetate (GA), recombinant interferons (IFNβ, IFNβ-1a Avonex®, IFNβ-1a Rebif®, IFNβ-1b Betaseron®). Natalizumab (Tysabri®) and mitoxantrone (Novantrone®) are also available for treatment of MS as second-line therapy in more severe disease. Natalizumab is used in RRMS patients who are unresponsive to immunomodulatory treatment or have severe relapsing–remitting forms of the disease. Mitoxantrone is generally reserved for the secondary progressive and severe relapsing–remitting forms [3]. Though the DMTs are potentially more effective based on a number of trials, many factors influence their application in individual treatment [4]. Uncontrolled side-effects of injectable DMTs, such as flu-like symptoms, depression, and immediate post–injection reactions, may result in periods of treatment disruption or inconsistent administration. Evidence shows that there is a risk of progressive multifocal leukoencephalopathy, a potentially fatal viral brain infection in patients receiving natalizumab who are positive for John Cunningham virus antibody. However, several pivotal reports have provided promising results for new oral therapies. This review highlights the mechanism of action, clinical trial efficiency, safety profile, and implications for clinical practice of four new oral therapies (fingolimod, laquinimod, BG-12, and teriflunomide). Due to a number of safety concerns with malignancy and hematologic toxicity, discussion of cladribine is not included in this report [4].

Four New Oral Agents

Fingolimod

Mechanism of Action

Fingolimod (FTY720) is an oral sphingosine-1-phosphate (S1P) receptor modulator [5], approved by the US Food and Drug Administration (FDA) for treating patients with RRMS. It is converted *in vivo* to its biologically active phosphate ester (FTY720-P), which acts as a high-affinity agonist for four of the five known G-protein-coupled S1P receptors, S1P1 and S1P3-5 [6-9]. The S1P1 receptor is predominantly expressed by immune cells, neural cells, endothelial cells, and smooth muscle cells [10-12]. FTY720-P subsequently induces S1P1 down-regulation and alters the ability of lymphocytes to recognize and respond to the S1P1 gradient of S1P, keeping them within lymphoid tissues and preventing them for exiting from the nodes, known as "lymphocyte sequestration" [8]. Moreover, in a recent study involving patients with relapsing MS, FTY720 was found to prevent the egress of CCR7-positive naive T-cells and central memory *cells* (TCM) from the lymph nodes, but spares CCR7-negative effector memory cells [13]. Retaining desirable immunological function may be important for immune surveillance and memory immune responses in peripheral tissues [13-15].

Clinical Trials

The first phase II proof-of-concept study evaluating the safety and efficiency of FTY720 was a randomized, double-blind, placebo-controlled, 6-month study that enrolled patients to receive oral FTY720 at 1.25 mg or 5.0 mg, or a once-daily placebo. As the primary end-point, the median total number of gadolinium-enhanced (Gd+) lesions on MRI was lower with 1.25 mg (1 lesion, $P < 0.001$) and 5.0 mg (3 lesions, $P = 0.006$) than with placebo (5 lesions). The annualized relapse rate (ARR) was 0.77 *vs* 0.35 *vs* 0.36 in the placebo, 1.25 mg ($P = 0.009$), and 5.0 mg ($P = 0.001$) groups, respectively [16].

Patients receiving 5.0 mg FTY720 were switched to 1.25 mg for months 15-24, and this demonstrated that the placebo-switched patients exhibited clear reductions in ARR and lesion counts compared with the placebo phase; ARR and lesion counts remained low in patients who continued FTY720 treatment. After 24 months, 79-91% of patients were free of Gd+ lesions and up to 77% remained relapse free [17]. Then the phase II study of oral FTY720 for 3 years reported that most patients were free from Gd+ (88-89%) or new T2 lesions (70-78%) at month 36. Patients receiving continuous FTY720

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treatment sustained low ARRs of 0.20-0.21, and 68-73% remained relapse-free at month 36 [18].

Based on the results of the phase II study, the FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study was a 24-month, double-blind, placebo-controlled study comparing two doses of FTY720, 0.5 mg or 1.25 mg *versus* placebo. The same doses of FTY720 were compared with intramuscular IFNβ-1a in the Trial Assessing injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) study. The FREEDOMS study found that all clinical and MRI-related measures where better than placebo, with no significant differences in efficacy between the two doses. The ARR was lower with 0.5 mg (0.18) and 1.25 mg (0.16) FTY720 than with placebo (0.40). In addition, the risk of relapse was significantly lower in the FTY720 groups than with placebo, and proportionately more treated patients remained relapse-free during the 24-month period (70.4 *vs* 74.7 *vs* 45.6%, in the 0.5 mg, 1.25 mg, and placebo groups, respectively; $p < 0.001$ for all comparisons). The cumulative probability of disability progression (confirmed after 3 months) was 17.7 *vs* 16.6 *vs* 24.1% ($p = 0.002$ for each FTY720 dose *versus* placebo). Patients in either FTY720 group had significantly fewer Gd+ lesions than those in the placebo group at 6, 12, and 24 months, as well as fewer new or enlarged lesions on T2-weighted MRI scans at 24 months ($p < 0.001$) [19].

The TRANSFORMS experiment reported that the ARRs at the end-point were significantly lower in both FTY720 groups compared with the IFNβ-1a group (0.16 *vs* 0.20 *vs* 0.33 in the 0.5 mg, 1.25 mg, and IFNβ-1a IM groups, respectively; $p < 0.001$ for both comparisons). At 12 months, patients in the two FTY720 groups had significantly fewer new or enlarged hyperintense lesions on T2-weighted images (1.7 ± 3.9 and 1.5 ± 2.7 in the 0.5 mg and 1.25 mg FTY720 groups *versus* 2.6 ± 5.8 in the IFNβ-1a IM group; $p = 0.04$ and $p < 0.01$) and fewer Gd+ lesions (0.23 ± 0.97 and 0.14 ± 0.58 for the 0.5 mg and 1.25 mg groups *versus* 0.51 ± 1.86 in the IFNβ-1a IM group; $p < 0.001$ for both comparisons). This study showed that once-daily oral FTY720 has superior efficacy to IFNβ-1a administered by weekly intramuscular injection.

The results of two phase III extension studies confirmed improvements in clinical and MRI outcomes (including brain atrophy) in patients who switched from placebo to FTY720, and demonstrated sustained low clinical and MRI disease activity in patients in the continuous FTY720-treatment group [20].

Safety and Profile

The two doses of FTY720 have similar efficacy, and adverse events may be less frequent with 0.5 mg than with 1.25 mg and 5 mg. Especially, the phase III study abandoned the 5-mg dose after assessing the frequency and severity of the side-effects in this group [16]. Adverse events (AEs) associated with FTY720 include nasopharyngitis and dyspnea, headache, diarrhea, nausea, transient decreases in heart rate, elevations in liver ALT levels, and infrequent macular edema. Most of the events were mild to moderate in severity [16,19,20]. Though the overall incidence of infection was similar across the three study groups, the finding that two fatal herpes infections occurred in TRANSFORMS with the 1.25-mg dose may indicate an association with the ~70% reduction in circulating lymphocytes [20]. Cardiovascular effects included slowing of the heart rate and blocking of atrioventricular conduction at the time of the first dose. Symptomatic bradycardia occurred in one patient in the phase II study at a dose of 5.0 mg [16] and 7 cases of skin cancer with 2 melanomas in the 36-month follow-up [17] remain a potential risk. These effects appear to be dose-dependent and specifically related to the binding to S1P receptors in cardiac tissue. Interactions with S1P receptors in smooth muscle may account for the mild increase in blood pressure seen during long-term treatment, but the long-term relevance of this finding is unclear [19]. However, association with cardiovascular complications has led to a more cautious approach in its initial use, now requiring cardiac monitoring for the first 6 h as well as subsequent monitoring of blood pressure and macular edema [40].

Summary

Oral FTY720 has better efficacy than intramuscular IFNβ-1a, along with significantly lower ARRs and smaller hyperintense lesions. On the other hand, findings associated with the safety profile such as increased risk of fatal herpes infections, skin cancers, and macular edema remains a concern.

Teriflunomide

Mechanism of Action

Teriflunomide inhibits dihydro-orotate dehydrogenase (DHODH), the rate-limiting mitochondrial enzyme in *de novo* pyrimidine synthesis, by non-competitively antagonizing the binding of its substrate, dihydro-orotate [21-23]. In the resting state, lymphocytes replenish their pyrimidine pools by salvaging pyrimidines from catabolic processes; this is sufficient for the synthesis of phospholipids (membrane maintenance and second messengers) and glycoproteins (adhesion molecules). However, when lymphocytes start blasting and proliferating, the need for pyrimidines increases disproportionately, and their *de novo* synthesis becomes necessary to fuel the synthesis of new DNA. Teriflunomide is a high-affinity inhibitor of the key enzyme DHODH, which targets proliferating (but not resting) lymphocytes in a semi-selective manner [24]. Interestingly, although an exogenous supply of uridine (a pyrimidine nucleoside) can overcome this cellular inhibition and allow lymphocyte proliferation, the other lymphocyte functions remain impaired [25].

Clinical Trials

In the first phase II study, to evaluate the safety and efficacy of oral teriflunomide in MS with relapses, patients with RRMS or secondary progressive MS were randomized to receive placebo or teriflunomide at 7 mg/day or 14 mg/day for 36 weeks. Both doses significantly suppressed MRI activity (>61% *vs* placebo), including: fewer combined unique active lesions, T1 Gd+ lesions, and new or enlarging T2 lesions. Moreover, treatment with 14 mg/day significantly reduced the T2 disease burden. And compared with placebo, a lower ARR (77% *vs* 62%) and fewer relapsing patients (14 mg/day only) were found with teriflunomide treatment [26]. Following up the first phase II study, an extension study up to 8.5 years showed that ARRs decreased throughout the 372-week evaluation period in both teriflunomide groups. Expanded Disability Status

Scale (EDSS) scores were higher in the 7-mg group at baseline, and this difference remained throughout the study. MRI activity remained low throughout the course of the extension, providing evidence that the previously-reported beneficial effects of teriflunomide on clinical and MRI endpoints are maintained over the long-term, for up to 8.5 years. There was a trend towards a dose-dependent benefit with 14 mg on several MRI parameters (including T2 burden of disease, cerebral volume, newly enlarging T2 lesions, and newly active lesions), which is also consistent with previous teriflunomide clinical trials [27].

The first phase III clinical trial assessing the efficacy of teriflunomide — the Teriflunomide Multiple Sclerosis Oral (TEMSO) trial — involved 1088 patients who were randomly assigned (in a 1:1:1 ratio) to placebo, 7 mg teriflunomide, or 14 mg teriflunomide once daily for 108 weeks. TEMSO demonstrated that teriflunomide significantly reduced the ARR (0.54 for placebo *vs* 0.37 for teriflunomide at either 7 or 14 mg), with relative risk reductions of 31.2% and 31.5%, respectively (P <0.001 for both comparisons with placebo). The proportion of patients with confirmed disability progression was 27.3% with placebo, 21.7% with teriflunomide at 7 mg (P = 0.08), and 20.2% with teriflunomide at 14 mg (P = 0.03). Both doses improved several MRI measures of disease activity compared with placebo: Ga+ lesions per T1-weighted scan, unique active lesions per scan, and total lesion volume from baseline. The magnitude of the benefits in patients receiving teriflunomide was modest but similar to those of the approved injectable therapies for RRMS [28].

The second pivotal phase III trial, TOWER, for the comparison of teriflunomide at 7 mg/day and 14 mg/day *versus* placebo, showed that teriflunomide led to reductions of 22.3% and 36.3% in ARR (7 mg and 14 mg group, respectively) — the primary end point — compared to placebo. Patients free from confirmed relapse were 55.4 *vs* 51.5 *vs* 37.7% (7 mg, 14 mg, and placebo groups, respectively). In the 14-mg group, there was a 31.5% reduction compared with placebo (p = 0.04). On the other hand, there was no statistically significant difference in disability accumulation in the 7-mg treatment group compared with placebo [28].

To investigate the value of teriflunomide as an adjunct treatment with IFN-β, a phase II study assigned patients with relapsing MS to receive teriflunomide 7 mg or 14 mg teriflunomide for 24 weeks. There was a pronounced reduction in the number of T1-Gd+ lesions per scan in both teriflunomide groups compared with the placebo group (relative risk reduction, 84.6% (p = 0.0005) and 82.8% (p <0.0001) of placebo, in the 7- and 14-mg groups, respectively). The corresponding relative reduction in total T1-Gd+ lesion volume was 72.1% (P = 0.11) and 70.6% (P = 0.02) in the 7 mg and 14 mg add-on treatment groups. Furthermore, there was a reduction trend in ARR among the three groups — 36.4% relative decrease with 7 mg and 65.4% relative decrease with 14 mg *versus* placebo. Teriflunomide was well-tolerated with a low and similar incidence of treatment-emergent AEs (TEAEs) across the placebo, 7-mg, and 14-mg groups, as with the incidence of treatment discontinuation (4.9 *vs* 8.1 *vs* 7.9% of patients, respectively) [29]. Although the population in each group was small, subgroup analyses revealed that the additive effects of teriflunomide with IFN were more pronounced in the subgroup with more active disease at baseline. This raises the possibility that, in patients experiencing disease activity, the addition of teriflunomide may be a safe treatment option, providing superior control with less risk to the patient than switching to therapies with less favorable safety profiles.

Recently, a phase III, rater-blinded study compared teriflunomide with IFNβ-1a, in which patients with relapsing MS were randomized (1:1:1) to 7 or 14 mg oral teriflunomide, or 44 μg subcutaneous IFNβ-1a. No difference in time to failure — the primary composite endpoint — was observed. There was no difference in ARR between 14 mg teriflunomide and IFNβ-1a, but the ARR was significantly higher with 7 mg teriflunomide. The Fatigue Impact Scale scores indicated more frequent fatigue with IFNβ-1a, though differences were only significant with 7 mg teriflunomide. The Treatment Satisfaction Questionnaire for Medication (version 1.4) scores was significantly higher with teriflunomide. This trial did not demonstrate a significant difference between teriflunomide and IFNβ-1a on the primary composite endpoint of time to failure. Formal conclusions on effectiveness are challenging, as a larger patient population, longer treatment duration, and MRI outcomes would be needed for a more robust comparison. Overall, patients reported greater satisfaction and less fatigue with teriflunomide than with IFNβ-1a. Based on these outcomes, teriflunomide can be considered as an alternative therapy for patients with RRMS for whom treatment with interferon is being considered [30].

Safety and Profile

Common AEs are predominantly gastrointestinal (including abdominal pain, diarrhea, dyspepsia, nausea, vomiting, and oral ulcers), elevated liver enzymes, alopecia, skin rashes, and hypertension. The incidence of diarrhea, nausea, alopecia, and elevated liver enzymes is dose-related [28].

Severe AEs (SAEs) include elevated liver function tests, hepatic dysfunction, neutropenia, rhabdomyolysis, and trigeminal neuralgia. The incidence of these events was similar in the placebo and treatment groups. There was a higher frequency of AEs leading to study withdrawal in the 14-mg teriflunomide group. The reported TEAEs of asymptomatic laboratory findings related to white blood cell (WBC) counts included decreases in WBCs, neutrophils, and lymphocytes. Infections were mainly of upper respiratory tract origin, including nasopharyngitis and upper respiratory tract infection. Influenza and urinary tract infection were also commonly reported [27].

As the reproductive toxicity is not understood, strict contraceptive measures are recommended. Women who wish to become pregnant should undergo a washout procedure with either cholestyramine or activated charcoal after stopping treatment. A teriflunomide assay must be performed following completion of the washout procedure to confirm a plasma level of <0.02 g/L. Liver function tests are mandatory before commencing treatment and need to be performed monthly for 6 months and every 2 months thereafter. Blood pressure also needs to be monitored whilst on teriflunomide.

Regarding comparison with IFNβ-1a, both drugs varied in tolerability, with flu-like symptoms more frequent, effects on laboratory evaluations, including liver enzymes and hematological parameters, more pronounced with IFNβ-1a than with teriflunomide. Diarrhea and hair-thinning were more common with teriflunomide [30].

Summary

This agent was recently approved by the FDA for use in relapsing MS. Furthermore, the addition of teriflunomide may be a safe treatment option for first-line DMTs with less favorable safety profiles. Although teriflunomide's safety profile based on the existing clinical trials is relatively benign, considering the rare SAEs seen with the long-term safety data available for leflunomide, more post-marketing surveillance of teriflunomide is needed.

BG-12

Mechanism of Action

In early studies, BG-12, a dimethyl fumaric acid ester (FAE), had been shown to be effective in patients with psoriasis, a Th1-mediated skin disease. It has now been submitted to the FDA as a potential treatment for relapsing MS. Data showed that it promotes the polarization of the immune system from a Th1 phenotype to a Th2 phenotype of CD4 T cells [31], increasing the production of Th2-driving molecules [32] such as IL-4, IL-10, and IL-5 [32-34], as well as reducing proinflammatory cytokines such as IL-2 and TNF-α. BG-12 also downregulates intracellular adhesion molecules (ICAM)-1 and VCAM expression that are involved in the movement of lymphocytes across endothelial barriers [35].

Otherwise, BG12 has been reported to inhibit LPS-induced NF-κB-driven gene activation in dendritic cells [36] and endothelial cells *in vitro* [37]. In an animal model of chronic MS, FAEs exert neuroprotective effects in neuroinflammation *via* activation of the Nrf2 antioxidant pathway [30,31,38].

Clinical Trials

An exploratory, prospective, open-label study of FAE was conducted in patients with RRMS. This consisted of a 6-week baseline; 18-week treatment (720 mg/day), 4-week washout, and a second 48-week treatment phase (360 mg/day). The mean number of Gd+ lesions and median Gd+ lesion volume were significantly decreased during 70 weeks. All clinical measures (EDSS, Ambulation Index, and 9-Hole Peg Test) either remained stable or showed improvement during the study. The changes in IL-10 and apoptotic rates suggest that FAE therapy positively influences cytokine responses in $CD4^+$ cells [39]. The results of this exploratory study suggest that further studies of FAE in patients with MS are warranted.

To assess the efficacy and safety of BG-12, patients with RRMS were assigned to receive 120 mg once daily, 120 mg three times daily, or 240 mg three times daily, or placebo for 24 weeks [40]. The group on 120 mg/day had fewer total plus new Gd+ lesions (69% reduction) at weeks 12, 16, 20, and 24 combined compared with the placebo (1.4 *vs* 4.5, $p < 0.0001$) and fewer new Gd+ lesions (1.3 *vs* 4.8, $p < 0.0001$). Cumulative new Gd+ lesions and mean number of new or enlarging T2-hyperintense lesions (48% reduction) were all reduced in the 120 mg/day group (44% reduction). Furthermore, the mean number of T1-hypointense lesions after 24 weeks of treatment was lower (53% reduction) in the 120 mg/day group than in the placebo group. During the first part of the study, the ARR for the 120 mg/day group decreased by 32%. Subsequently, subgroup analyses from the phase IIb study showed that 240 mg BG-12 three times daily significantly reduced the number of new Gd+ lesions compared with placebo in the following subgroups [41].

Two randomized, double-blind, placebo-controlled phase III studies involving patients with RRMS were conducted at 240 mg BG-12 twice daily, three times daily, or placebo. The results from the DEFINE study showed that in patients with RRMS, BG-12, compared with placebo, significantly reduced the proportion of patients who had a relapse by 2 years (27 *vs* 26 *vs* 46% in the 480 mg/day, 720 mg/day, and placebo groups, respectively), as did the ARR (0.17 *vs* 0.19 *vs* 0.36). These estimated proportions of patients also confirmed the progression of disability (16 *vs* 18 *vs* 27%, respectively). BG-12 also significantly reduced the number of Gd+ lesions and new or enlarging T2-weighted hyperintense lesions ($P < 0.001$ for each BG-12 regimen compared with placebo) [42].

The second phase III study, CONFIRM, in which GA was also included as a reference comparator, the ARR was reduced by 44% and 51% compared with placebo. Moreover, the treatments reduced the estimated proportion of patients with a relapse from 41% with placebo to 29% and 24% with the two doses of BG-12. Similarly, in the CONFIRM trial, there were fewer MS lesions on MRI scans in patients who received BG-12 than in those who received placebo [43]. These efficacy results are consistent with the results of previous BG-12 studies [40-42]. Although both doses of BG-12 had a significant effect on disability progression in the DEFINE study, neither BG-12 (at either dose) nor GA had a significant effect on disability progression in the CONFIRM study. A potential contributor to the difference in findings is that, in the CONFIRM study, the proportion of patients with disability progression in the placebo group (17%) was lower than that in the DEFINE study (27%).

Safety and Profile

The overall incidence of AEs was similar across study groups. AEs were reported more frequently with BG-12 than with placebo and included flushing, gastrointestinal events (diarrhea, nausea, and upper abdominal pain), upper respiratory tract infections, and erythema [43].

The most common AEs were flushing and MS relapse. Flushing and gastrointestinal AEs took place mainly in the early phase of treatment. And in general, flushing started within 30 min of drug administration, subsided within 90 min, and was mild and not related to dose [40].

BG-12 is not associated with an increased risk of serious infections, opportunistic infections, or malignant neoplasms. In DEFINE there were decreases in lymphocyte counts and elevations in liver aminotransferase levels in the patients who received BG-12 [42]. The safety profile of BG-12 in the CONFIRM study was similar to that in the DEFINE study. The AEs reported more frequently in the GA group than that in the placebo group were injection-related: injection-site pain (0 *vs* 8%, placebo and GA) and injection-site erythema (0 *vs* 9%, placebo and GA) [43].

Laboratory assessments, including mean white-cell and lymphocyte counts in both BG-12 groups, decreased during the first year and then plateaued, remaining within the normal range. The incidence of liver aminotransferase levels at least three times higher than the upper limit of the normal range was similar across the study groups [43].

A recent study assessing Health-related Quality of Life (HRQoL) in CONFIRM revealed that patients receiving placebo had a decline in their HRQoL while that for patients treated with BG-12 generally improved or remained stable [43].

Summary

Preclinical studies have shown that BG-12 reduces inflammatory responses and provides protection against oxidative stress. These mechanisms may contribute to the beneficial effects in patients with RRMS, including reductions in clinical relapses and MRI measures of disease activity with BG-12 in comparison with placebo, in both the CONFIRM and DEFINE studies. Overall, these findings support BG-12 as a potential initial oral treatment for patients with RRMS or as an alternative to currently-available therapies. Regarding the safety, BG-12 is mainly associated with flushing and gastrointestinal side-effects, and has a lower risk of infections such as respiratory tract infection, influenza, and flu-like symptoms compared to FTY720. Otherwise, a systematic review and analysis suggested that BG-12 could be a valid alternative treatment to all DMTs except for natalizumab in terms of efficacy outcomes in this patient population [43].

Laquinimod

Mechanism of Action

Laquinimod, N-ethyl-N-phenyl-5-chloro-1, 2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinoline-carboxamide, is a new synthetic immunoregulator derived from roquinimex, an immunomodulatory drug that was first developed in the early 1980s. Laquinimod is pharmacologically and chemically distinct from roquinimex [44]. Though the precise mechanism of action of laquinimod has not yet been fully elucidated in MS, some evidence is available. At first, laquinimod has anti-inflammatory effects rather than suppressive effects on the immune response. It inhibits the infiltration of both CD4+T cells and macrophages into central nervous tissues, induces a Th1-to-Th2/3 shift, and suppresses Th17 responses by inhibiting IFN-α, TNF-β, IL-12, or IL-17 and enhancing IL-4 and TGF-β [45-47]. The decreased infiltration involves the ability of VLA-4 on T cells to integrate chemokine signals and to generate a high binding-affinity to VCAM-1 under flow, a critical step for T cells to adhere to and cross endothelial barriers [47]. It has also been reported that the anti-inflammatory potency of laquinimod is realized through the suppression of the NFkB pathway that concordantly leads to the activation of apoptosis in immuno-competent cells [48].

Otherwise, there is evidence that laquinimod has a neuroprotective effect [49,50]. Notably, it is a direct neuroprotective activity. One study showed that it is able to limit axonal damage *via* the modulation of neuronal excitability and the limitation of excitotoxic damage induced by changes in synaptic transmission [50]. Another study indicated the potential neuroprotective properties of laquinimod by up-regulation of brain-derived neurotrophic factor production, which is essential for the development and maintenance of neurons and axons in the CNS [46].

Besides a potential direct action of laquinimod on T cells, these effects could be mediated indirectly through the modulation of T T-cell responses by dendritic cells [49,50]. Data show that inhibition of the NF-κB pathway results in down regulation of the immunogenicity of dendritic cell responses, by which laquinimod exhibits its disease-modulating activity in MS [49].

Laquinimod inhibits experimental **autoimmune encephalomyelitis** (EAE) in mice [51] and Lewis rats [44] and various experimental autoimmune inflammatory-mediated animal models [52]. In acute EAE, based on exposure to the free drug, laquinimod is 100 times more potent in inhibiting the disease than roquinimex [51]. With potency in inhibiting the migratory capacity of lymphocytes, demyelination, and axonal damage, laquinimod is therefore a potential candidate for the effective treatment of MS.

Clinical Trials

In a phase II study, 256 patients with relapsing MS received 0.1 mg or 0.3 mg or placebo as three daily tablets for 24 weeks. The 0.3 mg laquinimod group showed a significant reduction active lesion by 44% when compared to the placebo. In the subgroup of patients with at least one active lesion at baseline the reduction was slightly more pronounced (52%). No differences in clinical variables (relapses and disability) were found [53]. A phase IIb study with 306 eligible patients included placebo and laquinimod at 0.3 or 0.6 mg/day. Patients treated with 0.6 mg showed an ARR of 0.52 ± 0.92 *versus* 0.77 ± 1.25 for the placebo group ($p = 0.0978$) and a ratio of 75/106 (70.8%) relapse-free patients *versus* 64/102 (62.7%) in the placebo group ($p = 0.3297$). EDSS changes from baseline did not show significant differences among any of the laquinimod treatment groups and the placebo group. The cumulative number of new T2 lesions in the last four scans was reduced by 44% in the 0.6 mg group *versus* placebo. But against the results of the phase IIa study, there was no significant difference between 0.3 mg laquinimod and placebo for the primary endpoint, or for any of the secondary or exploratory clinical and MRI endpoints, which may be explained by the mild treatment effect being offset by the ongoing inflammation. This needs to be validated in further studies [54].

To determine the sustainability and reproducibility of the safety and efficacy profiles of laquinimod as shown in the phase II study, a phase IIb extension was performed. The results showed that Gd+ T1 lesions were significantly reduced in placebo-switched patients at 0.3/0.6 mg (52%, $p = 0.0006$). In patients initially randomized to 0.6 mg in phase II, the reduction of MRI activity in the placebo-controlled phase was maintained in the extension. The proportion of Gd+-free patients for those who switched from placebo increased from a baseline of 31% to 47% at the end of the extension phase ($p = 0.01$). The effects of 0.6 mg laquinimod on reducing MRI activity as seen in the placebo-controlled phase of the study were sustained in this extension phase. In addition, these effects were reproduced in placebo-switched patients during the extension phase. Considering the absence of effects of the 0.3 mg dose in the placebo-controlled phase of the study, the significant decrease of MRI activity in patients shifting from placebo to 0.3 mg (and in-patients who continued on low-dose laquinimod) was unexpected. The data from the extension phase of this trial suggest that extending treatment may have increased the likelihood for the effect of the lower dose to become apparent. Moreover, a significant reduction of the MRI activity in the extension phase was noted not only in patients continuing treatment with the same dose (interpretable as a delayed effect of the low dose compared with the high dose), but also in patients exposed for the first time to 0.3 mg laquinimod [55].

A randomized, double-blind, phase III study [56] with 1106 patients was conducted in which they received oral laquinimod at 0.6 mg once daily or placebo for 24 months. Treatment with laquinimod compared with placebo showed a modest reduction in the mean ARR (0.30 ± 0.02 *vs* 0.39 ± 0.03, P = 0.002) along with a reduction in the risk of confirmed disability progression (11.1 *vs* 15.7%; hazard ratio, 0.64; 95% confidence interval, 0.45-0.91; P = 0.01). The mean cumulative numbers of Gd+ lesions and new or enlarging lesions on T2-weighted images were lower in patients receiving laquinimod than in those receiving placebo (1.33 ± 0.14 *vs* 2.12 ± 0.22 and 5.03 ± 0.08 *vs* 7.14 ± 0.07, respectively; P <0.001 for both comparisons). The percentage of relapse-free patients was 62.9% in the laquinimod group and 52.2% in the placebo group (P <0.001). The time to the first relapse during the study was longer for patients receiving laquinimod than for those receiving placebo, and the risk of relapse was significantly reduced with laquinimod (hazard ratio, 0.72; 95% confidence interval, 0.59-0.87; P <0.001). We conclude that oral laquinimod administered once daily slows the progression of disability and reduces the rate of relapse in patients with RRMS.

However, in the second phase III trial, a double-blind, placebo-controlled study in RRMS patients with a rater-blinded reference arm of interferon β-1a (Avonex®) (BRAVO) which compared 0.6 mg laquinimod with an oral placebo and IFNβ-1a (30l g/week IM injection) failed to reach its primary end-point and showed no reduction in ARR compared to placebo on unadjusted statistical comparison.

The ongoing open-label extension of ALLEGRO involving 844 patients will provide further useful safety data. The data and safety monitoring committee has not reported any new safety signals so far in this extension study.

Safety and Profile

In all studies, the most prominent safety signal was reversible elevations of liver enzymes, not associated with clinical, imaging, or laboratory signs of liver failure.

In the initial phase II trial, including phases IIa and b, 0.3 mg/day laquinimod was well-tolerated over 24 weeks and there were no undesirable inflammatory AEs. Mild and transient increases appeared in the frequency of erythrocyte sedimentation rate and liver function test abnormalities [53,54].

Table 1: Summary of oral therapies for the treatment of multiple sclerosis.

Oral drugs	Mechanism of Action	Side effects	Main results of phase III trails			
			Relapse rate reduction	Relative reduction in new T2 MRI activity	Relative reduction in (Gd+) MRI activity	Relative reduction in EDSS
Fingolimod	Agonist at the G protein-coupled S1P1on lymphocytes: downmodulating thereceptor, the cells become unresponsive to S1P, required to egress from the limphonodes into blood	Transient reduction in the heart rate within hours after the first dose, increased mean arterial blood pressure, and airway obstruction	54%	74%	82%	30%
Teriflunomide	Blocks de novo pyrimidine synthesis by inhibiting dihydroorotate dehydrogenase	Nasopharyngitis, alopecia, nausea, alanine aminotransferase increase,paresthesia, back and limb pain, diarrhea, and arthralgia	31%	67%	80%	30%
BG-12	Switching Th1 cells into an interleukin-4-dominated Th2 phenotype; induction of the expression of phase II detoxifying enzymes; impairing cell traffic	Skin flushing, pruritis, gastrointestinal disturbance, myalgia, dizziness, headache	54%	74%	82%	30%
Laquinimod	Modulates of the balance of the Th 1 and 2 induction of transforming growth factor-β inhibit infiltration of CD4+T cells and macrophages into the CNS	Potential hepatotoxicity; possible proinflammatory effect. Reported pleuritis, Budd–Chiari syndrome, pituitary adenoma with hemorrhage and possible Crohn's Disease. Pharyngolaryngeal pain, dyspepsia	23%	30%	37%	36%

Two SAES were potentially attributable to laquinimod. A case of Budd-Chiari syndrome (thrombotic venous outflow obstruction of the liver) occurred in a patient with underlying hyper-coagulability who received 0.6 mg laquinimod. But the phase III study did not report this issue [56]. The second case was a marked elevation of liver enzymes in a patient treated with 0.3 mg laquinimod. Both doses showed an excellent safety profile consistent with previous observations. Since there was no increase in AEs with the 0.6 mg dose relative to the 0.3 mg dose, a further extended study was designed at 0.6 mg daily [54]. One SAE was of a benign pituitary tumor and hemorrhage in the 0.3 mg group which was found incidentally in an MRI scan obtained before the patient was treated with laquinimod. Infections, such as *Herpes simplex* and *Herpes zoster* were reported by 30–40% of the patients in all groups. All of these infections were localized to the skin, uncomplicated, and self-limited [56].

The three most common AEs in the laquinimod group were abdominal pain (5.8 *vs* 2.9% in the placebo group), back pain (16.4 *vs* 9.0%), and cough (7.5 *vs* 4.5%). Transient elevations in alanine aminotransferase levels to greater than three times the upper limit of the normal range occurred in 24 patients receiving laquinimod (5%) and 8 receiving placebo (2%) [56].

It is worth noting that the safety concerns previously seen with roquinimex, such as serositis, cardiovascular events, and thrombosis, did not emerge as signals in this study. Abdominal pain and appendicitis were reported more frequently in the laquinimod group than in the placebo group [56].

Summary

Distinct from its parent compound, roquinimex, the clinical development of which was halted due to serious cardiopulmonary toxicity reported during phase III trials, laquinimod significantly but modestly reduced the ARR of MS in a manner consistent with its suppression of inflammatory disease activity, and was also associated with a significant reduction in the risk of confirmed progression of disability as well as the percentage change in brain volume, as measured by MRI [57].

Conclusion

Several pivotal reports have provided promising results for new oral drugs as a potential initial treatment or as an alternative to currently available therapies for patients with RRMS. The drugs are currently in development in the clinical setting, (Table) and still focus on relapse and MRI lesion suppression. While the safety profile of new treatments is critically important for the development of new MS drugs, there is a need to balance the collection of long-term safety and efficacy data. Moreover, the post-marketing surveillance of these oral drugs needs attention.

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