Profile of oral laquinimod and its potential in the treatment of multiple sclerosis

Matthew S West
Augusto Miravalle

Department of Neurology,
University of Colorado,
Denver, CO, USA

Abstract: The medications available to treat relapsing-remitting multiple sclerosis (RRMS) are expanding as newer, and more potent, disease-modifying treatments become available. In particular, there is an impetus for safe and effective oral options. Laquinimod is a novel oral immunomodulator currently under investigation for the treatment of RRMS. Although the exact mechanism of action is not known, laquinimod is not an immunosuppressant. Rather, it appears to have multiple effects on the immune system, including a shift to an anti-inflammatory cytokine state, reduction in antigen presentation, and effect on migration of T cells. In addition, laquinimod may have a neuroprotective effect. Phase II trials of RRMS patients showed a statistically significant reduction in magnetic resonance imaging (MRI) outcomes, such as decrease in gadolinium-enhancing lesions, and initial Phase III data have now shown a reduction in relapse rate, reduction in sustained disability, and a decrease in atrophy on brain MRI. In all trials, laquinimod has shown a favorable tolerability and safety profile. Laquinimod has been granted fast-track status by the US Food and Drug Administration, and may become an approved treatment for RRMS.

Keywords: laquinimod, multiple sclerosis, mechanism of action, efficacy

Introduction

Multiple sclerosis is a chronic inflammatory autoimmune disease affecting the central nervous system, and characterized by demyelination and axonal damage. It is estimated that there are over 400,000 Americans with multiple sclerosis, with approximately 2.5 million cases worldwide,¹ and the disease is the second most common cause of neurological disability in young adults.² Multiple sclerosis typically affects individuals in their 20 s to 40 s. The most common form, relapsing-remitting (RRMS), involves exacerbations that can affect vision, strength, sensation, ambulation, and cognition. If untreated, multiple sclerosis typically leads to substantial accumulation of both physical and cognitive disability over time. For that reason, early use of disease-modifying medications has become the cornerstone of treatment over the past two decades.

There are currently eight drugs approved by the US Food and Drug Administration for treatment of RRMS. These include two forms of interferon β -1a (intramuscular Avonex[®] and subcutaneous Rebif[®]), subcutaneous interferon β -1b (Betaseron[®] and Extavia[®]), glatiramer acetate (Copaxone[®]), intravenous mitoxantrone, intravenous natalizumab (Tysabri[®]) and oral fingolimod (Gilenya[®]). All of these medications have shown benefit in trials, ie, reduction of relapses, diminished disease activity on magnetic resonance imaging (MRI), and decreased disability over time.

Correspondence: Matthew West
12631 East 17th Ave, B185,
Aurora, CO 80045, USA
Tel +1 303 724 2187
Fax +1 303 724 0985
Email matthew.west@ucdenver.edu

However, in clinical practice, it is not uncommon to have a suboptimal clinical response, side effects that limit use and patient compliance, or increased risk of more severe complications, such as progressive multifocal leukoencephalopathy, with natalizumab, or acute leukemia and cardiac toxicity with mitoxantrone.³ Furthermore, prior to October 2010, these therapies were only available as injections or infusions. The recent approval and release of Gilenya, the first oral medication approved to treat multiple sclerosis in the US, may signal a shift in prescribing practice and demand remains high from both patients and clinicians for novel oral agents with low-risk profiles.

Laquinimod is a promising new immunomodulator that has shown benefit in mouse models with experimental autoimmune encephalomyelitis (EAE) and initial studies in humans with RRMS. This article will review the currently available literature for laquinimod.

Background

Laquinimod (ABR-215062) is a novel synthetic chemical compound that is structurally related to its predecessor compound, roquinimex (Linomide®), but with important pharmacological and chemical differences. Roquinimex is an orally active quinoline-3-carboxamide immunomodulator that had previously shown ability to inhibit disease in acute EAE and chronic EAE mice⁴ and to suppress manifestations of acute EAE in Lewis rats.⁵ Based on these results, roquinimex was entered into Phase II trials that demonstrated decreased active lesions on MRI vs placebo in relapsing-remitting patients⁶ and secondary progressive patients.⁷ These findings led to Phase III trials in both relapsing-remitting and secondary progressive multiple sclerosis. However, the Phase III trials were prematurely terminated due to unexpected serious adverse events, including multiple cases of pericarditis, pleuritis, pancreatitis, and myocardial infarction.^{8,9} Two deaths also occurred in patients on study medication, one secondary to myocardial infarction, another presumed secondary to a pulmonary embolism.

Laquinimod was then discovered in an in vivo structure-activity relationship screening program aiming to define compounds effective in autoimmune disease such as multiple sclerosis, that were lacking the side effects of known immunomodulators, such as fevers and myalgias.¹⁰ Among 60 compounds that were synthesized and screened, laquinimod was chosen for further clinical study after showing increased potency in animal models and a good safety profile. The laquinimod compound was originally synthesized by Active Biotech with the chemical structure N-ethyl-N-phenyl-5-

chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinoline-carboxamide (Figure 1). During synthesis, chemical modifications were performed on the roquinimex structure, involving both the quinoline ring and elongation of the amidic methyl group.¹⁰ These modifications led laquinimod to have an encouraging side effect profile in Beagle dogs and an approximately 20-fold increase in potency compared with roquinimex in animal models of EAE.¹¹ Brunmark et al further suggest that when taking into account the exposure of free drug at equal doses, laquinimod may be greater than 100 times more potent at inhibiting disease in an EAE mouse model than roquinimex.¹⁰

Laquinimod went on to show effects in treating both acute and chronic EAE,¹³ as well as multiple preclinical animal models, including rheumatoid arthritis, inflammatory bowel disease, insulin-dependent diabetes, and Guillain-Barré syndrome.¹⁴ In addition to multiple sclerosis trials, other current studies involving laquinimod consist of Phase II trials in lupus nephritis¹⁵ and patients with moderate-to-severe Crohn's disease.¹⁶

Mechanism of action

The exact mechanism of action of laquinimod is not currently known. Studies in both mice and humans have demonstrated that laquinimod does not suppress the immune system;¹⁷ rather, it appears to act as an immunoregulator. Multiple studies have suggested that laquinimod alters the balance between inflammatory Th1-mediated cytokines in favor of a more Th2-mediated anti-inflammatory cytokine profile.

Initial work with the compound in experimental autoimmune neuritis first demonstrated this proposed shift. In an EAN mouse model, Zou et al¹⁸ demonstrated suppression of T cell proliferation with a significant decrease in cells

Figure 1 Laquinimod chemical structure, N-ethyl-N-phenyl-5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinoline-carboxamide.

Reprinted from Runstrom A, Leanderson T, Ohlsson L, et al. Inhibition of the development of chronic experimental autoimmune encephalomyelitis by laquinimod in IFN- β k.o. and wild type mice. *J Neuroimmunol*. 173:69–78.

Copyright © 2006, with permission from Elsevier.

expressing interferon-gamma (IFN- γ) and tissue necrosis factor- α (TNF- α) in sciatic nerves, with an increase in cells expressing interleukin (IL)-4. They concluded that the drug may shift the cytokine profile from inflammatory to anti-inflammatory and affect T cell differentiation.

Similar results have been found in EAE models. In Lewis rats with EAE, there was a downregulation of cells expressing TNF- α and IL-12, with upregulation of cells expressing IL-4, transforming growth factor-beta (TGF- β), and IL-10 mRNA.¹² Both TNF- α and IL-12 are cytokines involved in inflammation, with IL-12 playing a key role in induction of the Th1 immune response and increased production of other inflammatory cytokines, such as IFN- γ and TNF- α .¹⁹ IL-4 is an important anti-inflammatory cytokine that induces differentiation of naïve helper T cells to Th2 cells and suppresses IFN- γ and TNF- α ,²⁰ while TGF- β and IL-10 affect activation of lymphocytes and monocytes and downregulate expression of Th1 cytokines, with spinal cord sections also demonstrating decreased infiltrates of CD4+ T cells and macrophages.

Further work in myelin oligodendrocyte-induced EAE mice treated with laquinimod not only showed dose-dependent suppression of EAE signs, but also a decrease in proinflammatory cytokines.²¹ Analysis of splenic cells demonstrated significantly decreased levels of IFN- γ , TNF- α , IL-13, IL-5, and IL-17. IL-17 is of particular interest because it is secreted by Th17 cells, a subset of CD4+ cells involved in the pathogenesis of EAE and likely multiple sclerosis.²² Furthermore, it was found that laquinimod impaired very late antigen (VLA)-4 activation in lymphocytes by a reduction in ability of VLA-4 to integrate chemokine signals on T cells. VLA-4 binds to the integrin receptor, VCAM-1, which is an important step in cell adhesion and transendothelial migration. By affecting VLA-4, laquinimod may impair the migratory capability of effector T cells into an inflamed central nervous system.

In human studies, treatment with laquinimod has resulted in underexpression of major histocompatibility complex class II genes and suppression of toll-like receptor-6, suggesting downregulation of antigen-presenting pathways.²³ In vitro study of peripheral blood cell subtypes in RRMS patients has also shown activation of the anti-inflammatory IL-4 pathway in CD4+ cells, a decrease in genes involved in CD8+ proliferation, including the critical E2F3-transcription factor, and suppression of metabolic activity of CD14+ and natural killer cells. Additionally, laquinimod may reduce the accumulation of monocytoid cells in the human central nervous system through reduced levels of cytokines, matrix

metalloproteinase-9, and beta2-integrins.²⁴ Another possible target of laquinimod in humans is the S100A9 protein. Quinoline-3-carboxamide compounds, such as laquinimod, have been shown to target human S100A9, inhibiting its interaction with toll-like receptor-4. The S100A9 protein, when complexed with S100A8 in the extracellular space, promotes inflammatory responses when bound to toll-like receptor-4 on monocytes, resulting in extravasation of leukocytes into inflamed tissue.²⁵ This complex leads to activation of innate immunity and downstream release of inflammatory cytokines, including TNF- α and IL-1, and it has been speculated that preventing the formation of this complex may suppress reactivation of autoimmune T cells.²⁶

Preclinical data suggest that laquinimod may have neuroprotective properties as well. Laquinimod is known to cross the blood-brain barrier, and studies in EAE mice have indicated that the drug may work via a brain-derived neurotrophic factor-dependent pathway.²⁷ In a study of RRMS patients treated with laquinimod, there was a significant 11-fold increase in serum brain-derived neurotrophic factor levels after 3 months of therapy.²⁸

Although the exact mechanism of action of laquinimod is not completely understood, current work has demonstrated that its effects likely include shifting to an anti-inflammatory Th2-mediated cytokine profile. Other possible mechanisms of action include suppression of antigen presentation, reduction of migration of autoreactive T cells, and neuroprotective effects via brain-derived neurotrophic factor and reduction of axonal loss.

Metabolism and pharmacokinetics

Laquinimod has high oral bioavailability and is rapidly absorbed after ingestion, with a peak plasma concentration within 1 hour. There is a relatively small volume of distribution of approximately 10 L in the circulation, and the drug is predominantly protein-bound in serum.²⁹

Laquinimod is metabolized in the liver as a low-affinity substrate of the cytochrome P450 (CYP) pathway, specifically the CYP3A4 isozyme.³⁰ The drug is broken down into at least six primary metabolites. The major pathway involves hydroxylation of different sites on the quinoline moiety, resulting in 66% of total metabolism, followed by N-demethylation (19%). The metabolites are inactive and cleared predominantly through the urine.³¹ Supporting evidence of this route of metabolism is the formation of metabolites being significantly inhibited by ketoconazole and troleandomycin, known inhibitors of CYP3A4 metabolism. The exact drug-drug interaction profile with other medications that affect

CYP3A4 metabolism is not yet known, but the relatively low affinity of laquinimod and CYP3A4 is important to consider because this may decrease the risk of competitive inhibition of the metabolism of other CYP3A4 substrates.

Clinical trials in RRMS

Phase II clinical trials

The first Phase II trial was a 24-week proof-of-concept study sponsored by Active Biotech to determine the safety, tolerability, and efficacy of laquinimod on MRI brain lesions.³² The trial was a multicenter, double-blind, randomized study comparing two doses of laquinimod (0.1 mg/day and 0.3 mg/day) with placebo in 209 RRMS and secondary progressive multiple sclerosis patients. Inclusion criteria were patients aged 18–65 years, with an Expanded Disability Status Score of 0–5.5, and evidence of active disease with at least one documented clinical or subclinical (based on MRI) exacerbation in the last year, two exacerbations in the last 2 years (one of which could be subclinical), or presence of gadolinium-enhancing lesions on a screening MRI. The primary outcome was the cumulative number of active lesions on brain MRI (defined as the sum of new gadolinium-enhancing lesions, new T2-weighted lesions, and new enlargement of T2 lesions) after 24 weeks of treatment. Brain MRI scans with triple-dose gadolinium were followed every 8 weeks, along with Expanded Disability Status Score, Multiple Sclerosis Functional Composite, Quality of Life-36, and safety evaluations. Subjects were treated for 24 weeks, at which point treatment was discontinued. After being monitored for 8 more weeks, a repeat brain MRI was performed. Only the per-protocol population was used for primary outcome analysis, while an intention-to-treat population that included all randomized patients was used to assess safety.

Overall, both doses of laquinimod were well tolerated, with 198 (95%) of the randomized patients completing the study and 187 (89%) used for the primary outcome analysis. Treatment with laquinimod 0.3 mg/day resulted in a 44% reduction ($P = 0.0498$) in mean active lesions on MRI at 24 weeks, with no significant difference in the 0.1 mg/day group. Greater effect was seen in patients with at least one gadolinium-enhancing lesion on baseline MRI, with a reduction of 52% ($P = 0.005$) in active lesions. The authors reported that the total number of exacerbations, Expanded Disability Status Score, and Multiple Sclerosis Functional Composite were all stable over the treatment time with no significant differences, although values were not published. After discontinuing the study medication, there was a trend of increased disease activity in both groups, which either

supported evidence of laquinimod's treatment effect or suggested a rebound phenomenon.

A second Phase II trial, sponsored by Teva Pharmaceutical Industries, was a 36-week double-blind, placebo-controlled study assessing the effect of oral laquinimod at two doses, ie, 0.3 mg/day and 0.6 mg/day.³³ This study was also a multicenter and multinational trial, and enrolled 306 eligible patients with RRMS, aged 18–50 years, with an Expanded Disability Status Score of 1–5. The main inclusion criteria were different from those of the previous study in that patients were required to have one or more relapses in the preceding year and at least one gadolinium-enhancing lesion on screening MRI, thus selecting for patients with more active disease. Brain MRI with single-dose gadolinium scans were performed at week 0 and then every 4 weeks starting in week 12 until week 36. The primary efficacy outcome was defined as the cumulative number of gadolinium-enhancing lesions in the last four scans (ie, weeks 24, 28, 32, and 36). Secondary outcomes included cumulative number of gadolinium-positive lesions on MRI from weeks 12 to 36, cumulative number of new T2 lesions from weeks 24 to 36, and total number of confirmed relapses during treatment.

The group treated with laquinimod 0.6 mg/day had a 40.4% ($P = 0.0048$) reduction in adjusted mean cumulative gadolinium-enhancing lesions on the last four scans vs placebo (Figure 2). When the median, rather than the mean, number of gadolinium-enhancing lesions was used for analysis, there was a 55% reduction, although no P values were given for this outcome. Benefit was also observed in the 0.6 mg/day group compared with placebo in secondary outcomes, including a

Figure 2 Cumulative number of gadolinium enhancing lesions in the last four scans. Reprinted from Comi G, Pulizzi A, Rovaris M, et al. Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: a multicentre, randomized, double-blind, placebo-controlled phase IIb study. *The Lancet*. 371:2085–2092.

Copyright © 2008, with permission from Elsevier.

44% ($P = 0.0013$) reduction in cumulative number of new T2 lesions, 51% ($P < 0.0001$) reduction in the mean cumulative number of gadolinium-enhancing lesions per scan from weeks 12 to 36, and a 51% ($P = 0.0064$) reduction in cumulative number of new T1-hypointense lesions. The data demonstrated that the effect for laquinimod on MRI can be as early as 12 weeks of treatment. Annual relapse rates in the 0.6 mg/day group were 0.52 ± 0.92 vs 0.77 ± 1.25 for placebo, or a 32% reduction, but this was not statistically significant ($P = 0.0978$). This outcome may not have reached statistical significance due to the short duration of the trial, and could not accurately assess clinical outcomes and lack of power due to the sample size.

There was no statistically significant effect on primary or secondary outcomes in the laquinimod 0.3 mg/day group vs placebo, which was surprising given the previous positive study by Polman et al.³² The authors hypothesized that this discrepancy may have been due to the previous study using triple-dose gadolinium vs the standard dose used by Comi et al, with triple dosing increasing sensitivity for active multiple sclerosis lesions and consequently the statistical power in an MRI-based trial.

Upon completion of the trial, subjects were given the chance to enroll in a double-blind active extension for another 36 weeks to evaluate whether there was a sustained and reproducible treatment effect with laquinimod.³⁴ In the extension phase, placebo patients were randomized to either 0.3 mg/day or 0.6 mg/day doses, while actively treated patients remained in their original treatment groups. In total, 257 (91%) of patients from the original study were enrolled in the extension. After rerandomization of the placebo group, there were 138 patients in the laquinimod 0.6 mg/day group and 119 in the 0.3 mg/day group, with a total of 239/257 (93%) completing the additional 36 weeks. A total of 222 (87%) patients had a study termination MRI and were used in the analysis. Brain MRIs were performed at baseline and at 36 weeks. Primary efficacy outcomes included number of gadolinium-enhancing lesions, number of new T2 lesions, volume of T2 lesions, and number of new hypointense T1 lesions.

Patients who were switched from placebo to either dose of laquinimod had a 52% reduction ($P = 0.0006$) in mean number of gadolinium-enhancing lesions, which was significant for both doses, although a greater effect was observed at the 0.6 mg/day dose (Figure 3). Patients initially randomized to laquinimod 0.6 mg/day continued to show a statistically significant reduction in gadolinium-enhancing lesions over time, while those who continued the 0.3 mg dose also demonstrated a significant decrease in mean number of

Figure 3 Mean number of Gd-enhanced T1 lesions at the beginning and at the end of laquinimod extension study.

Reprinted from Comi G, Abramsky O, Arbizu T, et al. Oral laquinimod in patients with relapsing-remitting multiple sclerosis: 36-week double-blind active extension of the multi-centre, randomized, double-blind, parallel-group placebo-controlled study. *Multiple Sclerosis*. 16(11):1360–1366. Copyright © 2010, with permission from SAGE.

gadolinium-enhancing lesions in contrast with the core study. At 36 weeks, 50% of the 0.6 mg laquinimod arm and 47% (compared with 31% at baseline) of patients rerandomized from placebo to an active treatment arm were gadolinium-lesion free. Once again, the relapse rates did not show a statistically significant difference.

Both Phase II trials and the extension found statistically significant effects on MRI-based outcomes for laquinimod, including reduction in enhancing lesions, new T2 lesions, and T1-hypointense lesions, and were shown to be safe. Based on these positive results, the laquinimod 0.6 mg daily dose was chosen for further study in two 24-month Phase III trials, ie, ALLEGRO (Assessment of oraL Laquinimod in prEventing proGReSSION of multiple sclerOsis) and BRAVO (Benefit-Risk assessment of AVOnex and laquinimod), to assess clinical and imaging outcomes further.

Phase III trials

ALLEGRO was a double-blind, randomized, placebo-controlled Phase III trial in RRMS patients. This was a 2-year, multinational, multicenter trial that enrolled 1106 patients who were randomized to receive oral laquinimod 0.6 mg daily or placebo. Inclusion criteria required patients to have RRMS, be aged 18–55 years with an Expanded Disability Status Score 0–5.5, and to have experienced at least one relapse in the previous 12 months, two relapses in the last 24 months, or one relapse between months 12 and 24 prior to screening, with at least one gadolinium-enhancing lesion on MRI within the year prior to screening. The primary outcome was relapse rate during the 24-month treatment period, and secondary outcomes included disability

progression, measured by confirmed progression of the Expanded Disability Status Score, and MRI outcomes at 12 and 24 months, such as gadolinium-enhancing lesions, new T2 lesions, and brain atrophy.

Results for this study have only recently become available. The primary outcome showed a 23% ($P = 0.0024$) reduction in relapse rate compared with placebo.³⁵ Secondary outcomes were also positive, including a 36% ($P = 0.0122$) reduction in sustained disability progression on Expanded Disability Status Score, 37% ($P = 0.0003$) reduction in gadolinium-enhancing lesions, and 33% ($P < 0.0001$) reduction in brain atrophy on MRI. This reduction in brain atrophy could further support the notion that laquinimod has a clinically relevant neuroprotective effect.

The BRAVO trial is ongoing at the time of this review. This Phase III trial is a multinational, randomized, parallel-group, placebo-controlled study comparing the effect of oral laquinimod 0.6 mg/day with that of intramuscular interferon β -1a 30 μ g once weekly and placebo over 24 months in RRMS patients. Over 1300 patients have been enrolled. Laquinimod will be compared with placebo in a double-blind design, while comparison with the interferon β -1a arm will be rater-blinded. Inclusion criteria are similar to those for the ALLEGRO trial. The primary outcome measure is relapse rate over the treatment period, with secondary outcomes including accumulation of sustained disability on the Expanded Disability Status Score and MRI outcomes, specifically brain atrophy. Results are expected in the third quarter of 2011.

Safety

Safety and tolerability of laquinimod in the clinical trials has been excellent. In both Phase II trials, and in the extension, over 90% of patients completed the studies. In the initial Phase II trial, the most common findings were elevation of liver function tests and proinflammatory markers. Erythrocyte sedimentation rate was elevated on at least one assessment in 17.6% of patients on 0.3 mg/day dosing vs 6% on placebo, while occurrences of elevated C-reactive protein were similar between both treatment and placebo groups at 34%. Liver function enzymes were elevated at least once in 34% of placebo patients and 47% in those on laquinimod 0.3 mg/day, but all were considered mild, transient, and not of clinical significance.

The subsequent Phase II study also reported an increase in liver enzymes that occurred in a dose-dependent manner. Levels of alanine transaminase in the blood were elevated in

33% of subjects in the 0.6 mg/day group, with 13% having values exceeding normal by two times or more, compared with 23% in the 0.3 mg/day group and 10% receiving placebo. All abnormalities were reversible. There was one occurrence of Budd–Chiari syndrome in a patient taking laquinimod 0.6 mg/day at 1 month of treatment. This patient was heterozygous for Factor V Leiden mutation, likely causing an underlying hypercoagulable state. In this trial, C-reactive protein was actually elevated to a greater extent in the placebo group compared with either laquinimod dose. The rates of infections were similar amongst the groups, with the exception of herpes simplex and herpes zoster infections that were more frequent in the laquinimod 0.3 mg group. Both Phase II trials had no deaths and no cases of pericarditis, pleuritis, myocardial infarction, thrombophlebitis, or pulmonary embolism.

The Phase III ALLEGRO trial further supported the safety of laquinimod. There was a discontinuation rate secondary to adverse events of 7.6% in the laquinimod 0.6 mg/day group and 5% in those on placebo. Herpetic infections occurred at similar rates between the groups, with 3.5% on active treatment and 3.6% on placebo, and the overall incidence of all infections was similar. Reversible elevation in liver enzymes continued to occur at a higher rate in the laquinimod group, with elevation of alanine transaminase in 6.9% of laquinimod patients vs 2.7% on placebo. Treatment was discontinued in 13 of the laquinimod patients with elevated alanine transaminase. There were no deaths, no cases of pericarditis/pleuritis, and similar rates of neoplasm.³⁶

All available trials at this time have shown laquinimod to have an acceptable safety profile without serious toxicity. The most common adverse event is an elevation in liver enzymes that is typically mild and reversible, while the proinflammatory effects appear to be modest, with no cases of serositis.

The future

The Food and Drug Administration granted laquinimod 0.6 mg oral daily fast-track review status for treatment of RRMS in February 2009, awaiting results from the Phase III clinical trials. Laquinimod has shown beneficial effect on MRI outcomes in two Phase II trials and now a statistically significant reduction in relapse rate, reduction of sustained disability, and decrease in MRI outcomes, including brain atrophy, in the Phase III ALLEGRO trial. The BRAVO trial hopefully will provide further information about its efficacy compared with that of intramuscular

interferon β -1a. Laquinimod has also proven to have excellent tolerability and a favorable side effect profile. If positive results continue, laquinimod could realistically add a novel and safe oral medication to the growing armamentarium of disease-modifying medications to treat multiple sclerosis.

Disclosure

MSW received a Neuroimmunology Fellowship grant sponsored by Biogen Idec. AM has received honoraria and grant support from Teva Pharmaceutical Industries, Biogen Idec, EMD Serono, and Bayer AG.

References

- National Multiple Sclerosis Society. FAQs. Available from: <http://www.nationalmssociety.org>. Accessed March 23, 2011.
- Patwardhan MB, Matchar DB, Samsa GP, et al. Cost of multiple sclerosis by level of disability: a review of the literature. *Mult Scler*. 2005; 11:232–239.
- Marriott JJ, Miyasaki JM, Gronseth G, et al. Evidence report: the efficacy and safety of mitoxantrone in the treatment of multiple sclerosis: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology*. 2010;74: 1463–1470.
- Karussis DM, Lehmann D, Slavin S, et al. Treatment of chronic-relapsing EAE with the synthetic immunomodulator linomide. *Proc Natl Acad Sci U S A*. 1993;90:6400–6404.
- Diab A, Levi M, Wahren B, et al. Linomide suppresses acute experimental autoimmune encephalomyelitis in Lewis rats. *J Neuroimmunol*. 1998;85:146–154.
- Andersen O, Lycke J, Tolleson P, et al. Linomide reduces the rate of active lesions in relapsing-remitting multiple sclerosis. *Neurology*. 1996;47:895–900.
- Karussis DM, Meiner Z, Lehmann D, et al. Treatment of secondary progressive multiple sclerosis with the immunomodulator linomide. *Neurology*. 1996;47:341–346.
- Tan IL, Lycklama à Nijeholt GJ, Polman CH, Adèr HJ, Barkhof F. Linomide in the treatment of multiple sclerosis: MRI results from prematurely terminated Phase-III trials. *Mult Scler*. 2000;6: 99–104.
- Noseworthy JH, Wolinsky JR, Lublin FD, et al. Linomide in relapsing and secondary progressive MS. Part 1: trial design and clinical results. *Neurology*. 2000;54:1726–1733.
- Brunmark C, Runstrom A, Ohlsson L, et al. The new orally active immunoregulator laquinimod effectively inhibits development and relapses of experimental autoimmune encephalomyelitis. *J Neuroimmunol*. 2002;130:163–172.
- Jönsson S, Andersson G, Fex T, et al. Synthesis and biological evaluation of new 1,2-dihydro-4-hydroxy-2-oxo-3-quinolinecarboxamides for treatment of autoimmune disorders. *J Med Chem*. 2004;47: 2075–2088.
- Yang JS, Xu LY, Xiao BG, Hedlund G, Link H. Laquinimod suppresses the development of experimental autoimmune encephalomyelitis, modulates the Th1/Th2 balance and induces the Th3 cytokine TGF- β in Lewis rats. *J Neuroimmunol*. 2004;156:3–9.
- Runstrom A, Leanderson T, Ohlsson L, et al. Inhibition of the development of chronic experimental autoimmune encephalomyelitis by laquinimod in IFN- β k.o. and wild type mice. *J Neuroimmunol*. 2006;173:69–78.
- Teva Pharmaceutical Industries. Innovative R & D products. Available from: <http://www.tevapharm.com>. Accessed May 20, 2011.
- Teva Pharmaceutical Industries. Laquinimod study in systemic lupus erythematosus patients with active lupus nephritis. In: ClinicalTrials.gov. NLM identifier: NCT01085097. Bethesda, MD, National Library of Medicine, US. Available from: <http://clinicaltrials.gov/ct2/show/NCT01085097>. Accessed May 20, 2011.
- Teva Pharmaceutical Industries. Laquinimod Phase IIa study in active Crohn's disease. In: ClinicalTrials.gov. NLM identifier: NCT00737932. Bethesda, MD, National Library of Medicine, US. Available from: <http://clinicaltrials.gov/ct2/show/NCT00737932>. Accessed May 20, 2011.
- Birnberg T, Nisimov L, Spiegelstein O, et al. The effect of laquinimod on immune cell compartment. *Neurology*. 2011;76(Suppl 4): A139–P02.196.
- Zou LP, Abbas N, Volkmann J, et al. Suppression of experimental autoimmune neuritis by ABR-215062 is associated with altered Th1/Th2 balance and inhibited migration of inflammatory cells into the peripheral nerve tissue. *Neuropharmacology*. 2002;42:731–739.
- Kaliński P, Hilkens CM, Snijders A, et al. IL-12-deficient dendritic cells, generated in the presence of prostaglandin E2, promote type 2 cytokine production in maturing human naive T helper cells. *J Immunol*. 1997; 159:28–35.
- Hart PH, Vitti GF, Burgess DR, et al. Potential antiinflammatory effects of interleukin 4: suppression of human monocyte tumor necrosis factor alpha, interleukin 1, and prostaglandin E2. *Proc Natl Acad Sci U S A*. 1989;86:3803–3807.
- Wegner C, Stadelmann C, Pfortner R, et al. Laquinimod interferes with migratory capacity of T cells and reduces IL-17 levels, inflammatory demyelination and acute axonal damage in mice with experimental autoimmune encephalomyelitis. *J Neuroimmunol*. 2010;227: 133–143.
- Fletcher JM, Lalor SJ, Sweeney CM, Tubridy N, Mills KH. T-cells in multiple sclerosis and experimental autoimmune encephalomyelitis. *Clin Exp Immunol*. 2010;162:1–11.
- Gurevich M, Gritzman T, Orbach R, et al. Laquinimod suppress antigen presentation in relapsing remitting MS: in-vitro high-throughput gene expression study. *J Neuroimmunol*. 2010;221:87–94.
- Yong W, Mishra M, Wang J, et al. Mechanisms of laquinimod in reducing the accumulation of monocytoic cells in the CNS. *Neurology*. 2011;76(Suppl 4):A136–P02.184.
- Ehrchen JM, Sunderkutter C, Foell D, Vogl T, Roth J. The endogenous toll-like receptor 4 agonist S100A8/S100A9. *J Leukoc Biol*. 2009;86: 557–566.
- Bjork P, Bjork A, Vogl T, et al. Identification of human S100A9 as a novel target for treatment of autoimmune disease via binding to quinoline-3-carboxamides. *PLoS Biol*. 2009;7:e1000097.
- Thone J, Lee DH, Ellrichmann G, et al. Laquinimod skews monocytes to a regulatory phenotype and modulates autoimmune demyelination via a brain derived neurotrophic factor. *Neurology*. 2011;76(Suppl 4): A132–P02.170.
- Linker R, Thone J, Comi G, Gold R. Laquinimod induces up-regulation of neurotrophins in serum of patients with RRMS. *Mult Scler*. 2009; 15:P783.
- Jeffery DR, Pharr E, Zeid NA. Laquinimod in relapsing remitting MS. *US Neurology*. 2010;6:70–75.
- Turesson H, Hallin I, Persson R, et al. Cytochrome P450 3A4 is the major enzyme responsible for the metabolism of laquinimod, a novel immunomodulator. *Drug Metab Dispos*. 2005;33:866–872.
- Preiningerova J. Oral laquinimod therapy in relapsing multiple sclerosis. *Expert Opin Investig Drugs*. 2009;18:985–989.
- Polman C, Barkhof F, Sandberg-Wollheim M, et al. Treatment with laquinimod reduces development of active MRI lesions in relapsing MS. *Neurology*. 2005;64:987–991.
- Comi G, Pulizzi A, Rovaris M, et al. Effect of laquinimod on MRI-monitored disease activity in patients with relapsing remitting MS: a multicentre, randomized, double-blind, placebo-controlled Phase IIb study. *Lancet*. 2008;371:2085–2092.

34. Comi G, Abramsky O, Arbizu T, et al. Oral laquinimod in patients with relapsing remitting MS: 36-week double-blind active extension of the multi-centre, randomized, double-blind, parallel-group placebo-controlled study. *Mult Scler*. 2010;16:1360–1366.
35. Teva Pharmaceutical Industries. Oral laquinimod for multiple sclerosis treatment significantly reduced disease activity and disability progression while providing good safety and tolerability. Available from: http://www.tevapharm.com/pr/2011/pr_1004.asp. Accessed April 17, 2011.
36. Comi G. Oral laquinimod reduced relapse rate and delayed progression of disability in ALLEGRO, a placebo-controlled Phase III trial for RRMS. Presented at the annual meeting of the American Academy of Neurology, April 9–16, 2011, Honolulu, HI.

Degenerative Neurological and Neuromuscular Disease

Dovepress

Publish your work in this journal

Degenerative Neurological and Neuromuscular Disease is an international, peer-reviewed, open access journal focusing on research into degenerative neurological and neuromuscular disease, identification of therapeutic targets and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced

survival and quality of life for the patient. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/degenerative-neurological-and-neuromuscular-disease-journal>