Oral laquinimod therapy in relapsing multiple sclerosis

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Background: Multiple sclerosis (MS) is a chronic autoimmune disease of the CNS. Early treatment reduces the number of relapses, limits progression of disability, and improves quality of life; however, existing therapies are only partially effective and require parenteral administration. Objective: To review current experience with laquinimod as a novel immunomodulatory therapy for MS. Results: Laquinimod is a new quinolonecarboxamide that has demonstrated efficacy in animal models of several autoimmune diseases, including MS. It shows immunomodulatory effects, likely through Th1/Th2 shift, but does not lead to immunosuppression. Laquinimod is metabolized in the liver, primarily by the CYP3A4 enzyme. Phase II studies in relapsing MS demonstrate a dose-response effect on disease activity, measured by number of active lesions on brain magnetic resonance imaging, and show favorable tolerability and safety based on clinical and laboratory indicators. Two Phase III studies currently in progress are evaluating the efficacy of laquinimod 0.6 mg/day in relapsing MS. The drug was granted a fast track review by the FDA in 2009. Conclusion: Laquinimod is a novel, orally administered immunomodulator that has advanced to the pre-submission stage and may become an alternative to the current injectable first-line treatments for relapsing MS.

Keywords: ABR-215062, EAE, immunomodulator, laquinimod, multiple sclerosis, quinolone

1. Introduction and overview of the market

Multiple sclerosis (MS) is a chronic disease of the CNS characterized by inflammation, demyelination and axonal injury. There are an estimated 2 – 2.5 million people with MS worldwide, with 350,000 – 400,000 cases in the US alone [1,2]. The challenges of treating MS, evaluating the efficacy of disease-modifying drugs and formulating a prognosis of the disease in individual patients lies in the histopathological heterogeneity of the disease and its unpredictable disease course. The first clinical symptoms of MS typically occur between the second and fourth decade of life although it is not unusual to diagnose MS outside of this range. The inflammatory activity of the disease, represented by relapses, remains active for about two – three decades. Multiple sclerosis is a chronic disease that causes disability through the accumulation of damage to the nervous system over time. Therefore, it is critical to diagnose MS and institute disease-modifying therapy early in the course of the disease.

The prognosis of MS improved significantly with the approval of the first interferon in 1993. Availability of experimental autoimmune encephalomyelitis (EAE) as an animal model of MS facilitated the development of several disease-modifying therapies targeting proliferation, activation or trafficking of activated T cells across the BBB. Three interferons have been approved by US and European regulatory agencies for the treatment of MS, including two formulations each of interferon beta-1a (Avonex®, Biogen Idec [Cambridge, USA] and Rebif®, EMD Serono, Inc. [Rockland, USA]) and interferon beta-1b (Betaseron®, Bayer HealthCare...
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Pharmaceuticals, Inc. [Leverkusen, Germany] and Extavia®,
Novartis International AG (Basel, Switzerland)). Glatiramer
acetate (Copaxone®, Teva Pharmaceutical Industries Ltd,
Petach Tikva, Israel) is a random polymer of four amino acids
prevalent in myelin basic protein that seems to affect Th1/Th2
balance. The next generation of therapies includes monoclonal
antibodies that target specific receptors or key molecules of the
immune system. Natalizumab (Tysabri®), developed by Elan
Pharmaceuticals, Inc. [Dublin, Ireland] owned by Biogen
Idec) is a humanized monoclonal antibody that binds to
the alpha 4 integrins on the surface of leukocytes and effect-
ively limits the trafficking of lymphocytes across the BBB.
Mitoxantrone (Novantrone®, EMD Serono, Inc.) is the only
FDA-approved drug among several strong immunosuppressants
used in the treatment of MS.

Most patients with relapsing forms of MS benefit from
interferon beta or glatiramer acetate injections by gaining
partial control over the disease activity as measured by
relapse rate, number of gadolinium (Gd) enhancing lesions
on brain magnetic resonance imaging (MRI) and accumula-
tion of lesions on T2-weighted sequences. These four inject-
able therapies represent the first line of treatment in relapsing
MS. Natalizumab is currently used mostly in patients who
are unable to tolerate injectable therapies or continue to
experience disease activity despite treatment. Its use is lim-
ited by the risk of the rare, but potentially fatal adverse
event of progressive multifocal leukoencephalopathy.
Mitoxantrone is reserved for patients with secondary pro-
gressive MS and patients failing other therapies owing to
its cumulative toxicity, in particular cardiotoxicity and risk
of acute myelogenous leukemia.

All existing therapies for MS require parenteral adminis-
tration, have significant side effects or carry risk of serious
adverse events and are only partially effective in decreasing
the frequency of relapses and slowing the progression of dis-
ability. More effective therapies with oral administration and
improved tolerability are much desired by both clinicians
and MS patients. Several oral compounds with novel mecha-
nisms of action have shown promising results in Phase II
clinical studies, including fingolimod, fumaric acid, oral
cladribine, teriflunomide and laquinimod. This review will
summarize current experience with laquinimod and discuss
its potential for the treatment of MS.

2. Introduction of the compound

The laquinimod (ABR-215062) molecule was synthesized
by Active Biotech AB (Lund, Sweden) and was licensed to
Teva Pharmaceutical Industries Ltd in 2004 as an immuno-
modulatory agent for the treatment of MS. Laquinimod is a
derivative of roquinimex (linomide), which is structurally
similar to laquinimod and has previously been applied to
MS. Roquinimex has been found to effectively inhibit
experimental autoimmune encephalomyelitis and favorably
affect production of anti-inflammatory cytokines in vivo. In
clinical trials in patient with MS, treatment with roquinimex
demonstrated a reduction in the number and volume of Gd
enhancing lesions on brain MRI, a primary measure of
disease activity used in Phase II studies. Phase III clinical
investigations with roquinimex were unexpectedly discontin-
ued in 1999, owing to the occurrence of severe cardiac
adverse events, such as pericarditis and myocardial infarc-
tion. During the development of laquinimod, special atten-
tion has been paid to the identification of a product with a
lower likelihood of inflammatory side effects, such as serositis
and vasculitis [3-5].

The laquinimod molecule is a product of an in vivo struc-
ture–activity relationship screening used to determine the
potency as well as the side effect profile and safety of the
compound. More then 60 different molecules from the qui-
nolinone family were tested for effects in EAE and induc-
tion of proinflammatory effects, such as fever and other
inflammatory markers in Beagle dogs. Of these, laquinimod
was selected for further development owing to its robust
effect on amelioration of EAE, as well as the low levels of
inflammatory markers it induced. The equivalent dose of
laquinimod used in this investigation was 10 – 100 times
more effective in controlling the disease activity in the acute
EAE model than its predecessor, roquinimex [6].

3. Chemistry and mechanism of action

Laquinimod is a small molecule (N-ethyl-N-phenyl-5-chloro-
1,2-dihydro-4-hydro-1-methyl-2-oxo-3-quinoline-carboxamide)
with a molecular weight of 357 Da. It has demonstrated a
potent therapeutic efficacy in animal models of several auto-
immune diseases, such as rheumatoid arthritis, insulin-de-
pendent diabetes, Guillain Barré syndrome, lupus,
inflammatory bowel disease and MS. The efficacy of laquin-
imod in a broad spectrum of animal models of inflamma-
tory diseases suggests that laquinimod affects a critical
pathway of inflammation and autoimmunity; however, the
precise mechanism of action is currently being explored.

Administration of laquinimod in the EAE model as an
animal model of MS resulted in reduced infiltration of CD4,
CD8 and macrophages [7]. It did not lead to a reduction in B
or T cell numbers [8], inhibit proliferation of lymphocytes, nor
lead to immunosuppression. Laquinimod also reduced the
production of IL-1 and IL-17 cytokines in animal studies [9].
In addition to inhibiting disease activity in acute EAE [8],
laquinimod was also shown to inhibit both disease develop-
ment and histopathological changes in chronic EAE in mice.
This mechanism was shown to be independent of endogenous
production of interferon beta.

4. Pharmacodynamics, pharmacokinetics
and metabolism

The pharmacokinetic properties of laquinimod have been
studied in several pre-clinical species, including mice, rats,
rabbits and dogs [10]. Laquinimod has high oral bioavailability, small volume of distribution (10 L) and a low total clearance rate. The peak plasma concentration is reached within 1 h of oral administration. The maximum serum level (Cmax) of laquinimod in humans is below 5 µM after administration of 0.05 – 2.4 mg of the drug. There is little fluctuation between the minimum serum level (Cmin) and Cmax once steady state is reached. Laquinimod is metabolized by one of the CYP enzymes as a low affinity substrate for CYP3A4 in liver microsomes. Four hydroxylated and two dealkylated products are cleared primarily through the urine and are not metabolically active. Less than 5% of laquinimod is eliminated unchanged in urine or feces.

Enzymes from the CYP3A family may be involved in the metabolism of ≤ 50% of the drugs used in humans, which raises a concern for drug-to-drug interactions. Strong specific inhibitors of the CYP3A4 enzyme such as ketoconazole can slow the elimination of laquinimod. Other inhibitors of CYP3A4, such as prednisolone and erythromycin, have been studied in vitro; only ketoconazole is known to reach plasma levels in humans that would have a metabolic effect on CYP3A4. Laquinimod has low affinity to the CYP3A4 enzyme, which reduces the risk for competitive inhibition of other substrates. The level of laquinimod needed to cause competitive inhibition of another common drug metabolized by CYP3A4, ethinyl estradiol, is 30 times above the expected Cmax with current dosing protocols of laquinimod.

5. Clinical efficacy: pre-clinical, Phase II and Phase III studies

5.1 Pre-clinical and Phase I studies
A total of eight Phase I studies in normal volunteers and MS patients using laquinimod have been completed so far. The compound was well tolerated in doses of 0.1 mg/day, up to 1.2 mg/day. Elevation of inflammatory laboratory markers was observed in human subjects after 1 – 2 weeks of treatment with 2.4 mg/day.

5.2 Phase II studies
The first proof-of-concept study of laquinimod in relapsing MS was funded by Active Biotech AB [11]. This multicenter (20 centers from the Netherlands, Russia, Sweden and the UK), double-blind, randomized, placebo-controlled, parallel group, Phase II study examined the effects of laquinimod at dosages of 0.1 or 0.3 mg/day versus placebo over 24 weeks. Brain MRIs with triple doses of Gd contrast were obtained at baseline and at week 4, 8 and 24 of treatment and 8 weeks after discontinuation of therapy. The primary outcome measure was the cumulative number of active lesions (sum of new or enlarging lesions on T2-weighted images, plus new enhancing lesions) in the brain at week 24. The study included 209 patients with relapsing remitting MS (RRMS) or secondary MS, with EDSS (Expanded Disability Status Scale) scores of 0 – 5.5, evidence of disease activity on brain MRI or a clinical relapse in the previous 1 – 2 years. Both doses of laquinimod were well tolerated and 95% of patients completed the study. Treatment with oral laquinimod 0.3 mg/day for 24 weeks led to a 44% reduction (p = 0.0498) in mean cumulative number of active lesions compared to placebo. In a subgroup of patients with at least one active lesion on baseline MRI scans, the reduction in mean cumulative number of active lesions reached 52% (p = 0.005).

There was also a significant difference in the cumulative volumes of Gd enhancing lesions over the 24 weeks of treatment between the laquinimod 0.3 mg/day dose and placebo groups (p-values not provided). Other secondary outcome measures, including number and volume of enhancing lesions and number of relapses, failed to reach statistical significance compared to placebo for either dose of laquinimod. Brain MRI obtained 8 weeks after discontinuation of the study medication revealed an increase in disease activity in both treatment groups, which further supported the biological activity of the compound, but may be interpreted as a trend suggestive of a rebound effect.

The effects of laquinimod in the treatment of relapsing remitting MS were further investigated in a multicenter, international, double-blind, placebo-controlled, parallel group study funded by Teva Pharmaceutical Industries Ltd [12]. The efficacy, tolerability and safety of laquinimod 0.3 mg/day (n = 98) and laquinimod 0.6 mg/day (n = 106) versus placebo (n = 102) was evaluated over 36 weeks of treatment. Patients eligible for this study were 18 – 50 years old, diagnosed with relapsing remitting MS by the McDonald criteria, with EDSS scores between 1 and 5.0 (ambulatory) and with at least one Gd enhancing lesion on a screening brain MRI. Brain MRI with and without a standard dose of Gd (0.1 mmol/kg) was obtained at week 4, baseline and monthly between weeks 12 and 36 of treatment. The primary outcome measure was the cumulative number of Gd enhancing lesions in the last 4 scans during treatment (weeks 24, 28, 32 and 36). Compared to placebo, treatment with oral laquinimod 0.6 mg/day resulted in a 40.4% reduction in mean cumulative number of Gd enhancing lesions per scan, adjusted to baseline (placebo mean = 4.2, SD = 9.2 versus laquinimod 0.6 mg/day mean = 2.6, SD = 5.3; p = 0.0048). Significant differences in favor of the 0.6 mg/day group were also observed for almost all secondary and exploratory outcome measures. The cumulative number of new lesions on T2-weighted images and the cumulative number of new T1 hypointense lesions in the laquinimod 0.6 mg/day group were significantly reduced by 44 and 51%, respectively, versus placebo.

Subjects treated with 0.6 mg/day of laquinimod had an annualized relapse rate of 0.52 (SD = 0.92) versus 0.77 (SD = 1.25) for the placebo group (NS; p = 0.0978); however, studies of this size and duration (36 weeks) do not have sufficient power to detect changes in activity of the disease using relapse rate as the outcome measure. Primary or secondary outcome variables in the 0.3 mg/day treatment group were not significantly different from that of the
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placebo group. While Polman and colleagues [11] did report statistical significance in MRI outcomes when comparing the 0.3 mg/day group to placebo, they used a triple dose of Gd, which increases sensitivity to impairment of the BBB. In the case of the Polman study, the primary outcome measure also captured both enhancing lesions and new or enlarged T2 lesions and, therefore, may have had increased sensitivity to change in disease activity based on MRI outcomes.

Subjects in the aforementioned study by Comi and colleagues [12] were offered the opportunity to participate in an extension to the study (91% enrolled) for an extra 36 weeks. The placebo group was re-randomized to receive laquinimod at a dosage of 0.3 or 0.6 mg/day. There was a 52% reduction (p < 0.0007) in the mean number of Gd enhancing lesions in patients who switched from placebo to active treatment with laquinimod. The reduction was significant for patients switching to either the high dose (p < 0.009) or low dose (p < 0.03) of laquinimod. Of the patients who started active therapy, 47% (p < 0.012) in the extension study did not develop new Gd enhancing lesions. The sponsor made the decision to pursue the 0.6 mg/day dosing in future studies.

The investigation is continuing as an open label study with the same patients who completed the extension phase and will provide important safety data on the use of laquinimod at a dose of 0.6 mg/day in relapsing remitting patients over time.

5.3 Phase III studies

Two pivotal Phase III studies examining the use of laquinimod in the treatment of MS are continuing. The ALLEGRO study (Assessment of oral laquinimod in preventing progression of MS) is a double-blind Phase III study designed to evaluate the efficacy, safety and tolerability of laquinimod at 0.6 mg/day versus placebo in the treatment of RRMS [13]. Enrollment was completed in November 2008, with < 1,000 patients from 152 sites in 25 countries [14]. The primary outcome measure is the number of confirmed relapses during the double-blind study period. The secondary outcome measures include time to sustained progression on the EDSS scale and MRI outcomes measured at 12 and 24 months. Study subjects will reach the 24-month time point by the end of summer 2010, with the possibility of an extension to 30 months of treatment.

A second pivotal Phase III study, BRAVO (benefit–risk assessment of Avonex and laquinimod), was initiated in April 2008, and is currently open for enrollment of ≤ 1200 subjects [15]. This international, multicenter, randomized study aims to compare the effect of oral treatment with 0.6 mg/day of laquinimod to that of a placebo and with effects of placebo or interferon β-1a in patients with RRMS. Laquinimod is compared to placebo in a double-blind design, while the interferon β-1a arm is assessed in a rater blinded design, serving as a calibrator arm. The primary outcome measure is relapse rate over 24 months of treatment with accumulation of disability and brain MRI measures being secondary outcome measures.

6. Safety and tolerability

Overall, all doses of laquinimod used in Phase II studies were well tolerated with ~ 95% of patients completing the study periods. The primary safety concerns with laquinimod included elevation of liver enzymes and proinflammatory effects. There were no clinical or laboratory indications of undesired inflammatory manifestation (serositis), myocardial infarction, thrombophlebitis or pulmonary embolism as with the predecessor compound, roquinimex. There was one case of thrombotic venous outflow obstruction of the liver (Budd–Chiari syndrome) that occurred after 1 month of treatment with laquinimod at 0.6 mg/day in a patient with underlying hypercoagulability (heterozygosis for Factor V Leiden mutation). Increases in liver enzymes were dose dependent and reversible. There was no evidence of laquinimod-related effects on electrocardiogram.

7. Regulatory affairs

An investigational new drug application has been submitted to the FDA. The FDA granted fast track review status for laquinimod in February 2009 for the treatment of RRMS [14].

8. Conclusion

Laquinimod is a synthetic quinoline 3-carboxamide derivative with immunomodulatory properties. Treatment with laquinimod is effective in ameliorating disease severity, extent of inflammation, demyelination and axonal damage in the EAE animal model of MS. Laquinimod is orally administered once daily. It has advanced to the stage of Phase III studies and may become an alternative to the current injectable first-line treatments for relapsing forms of MS.

9. Expert opinion

The availability of an oral disease-modifying therapy in relapsing MS is very desirable. Laquinimod has the potential to become an alternative to the current injectable first-line treatments for relapsing MS. Ascertaining how laquinimod will be positioned among existing and future therapies will be a balancing act in which the safety, efficacy and tolerability of laquinimod must be considered. Data remains limited on most of those parameters for laquinimod, as well as on its alternatives. Once daily dosing with excellent tolerability puts laquinimod at an advantage among future oral drugs.

The safety of laquinimod in Phase II studies was very good. No signs of irreversible side effects at 0.6 mg/day dosing were evident. Phase II studies in relapsing MS do not have sufficient power to evaluate the effects of disease-modifying drugs on clinical outcomes (such as relapse rate and change in disability) and must use surrogate outcomes (MRI) to determine the therapeutic potential of new drugs. It can be misleading to predict the clinical efficacy of new
drugs based on MRI outcomes, such as number or Gd enhancing lesions [16], if the mechanism of action does not target the BBB. The pivotal Phase III ALLEGRO study comparing 0.6 mg/day of laquinimod with placebo has met the enrollment target. Therefore, the effects of laquinimod at this dosage on relapse rate may be known in early 2011.

All current Phase II – III clinical drug trials in relapsing MS have a similar challenge: demonstrating a drug effect over a relatively short study period in a highly variable disease. If the cohort of patients enrolled in a study does not show sufficient disease activity, the power of the study is lowered and it becomes very difficult to demonstrate a significant decrease in drug-related disease activity. If this situation were to apply to a Phase III investigation for a new oral medication, an additional large, costly and time-consuming study would be needed to establish the value of the drug.

On the basis of data from Phase II studies, laquinimod at 0.6 mg/day may offer efficacy similar to existing injectable therapies. The BRAVO study will provide data on the efficacy of laquinimod at 0.6 mg/day p.o. versus weekly injection of interferon beta-1a. Comparisons with other disease-modifying drugs will also remain in the sphere of speculation until well-powered comparison studies with other drugs are completed.

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Declaration of interest

J Preiningerova receives honoraria for consulting from Teva Neuroscience (developer of laquinimod). She also receives honoraria for consulting and/or speaking fees from other pharmaceutical companies making disease-modifying treatments for MS. She conducts or has conducted clinical trials and research projects sponsored by Teva Neuroscience and other companies that compete with each other in the MS disease-modifying drug market. Specifically, she is currently participating in a Phase III clinical trial of laquinimod as the principal investigator at the Yale MS Center study site.

Bibliography


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