Canadian Agency for Drugs and Technologies in Health

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Laquinimod for Relapsing-Remitting Multiple Sclerosis

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Summary

- ✓ **Laquinimod is a once daily, synthetic, oral immunomodulator currently under development for the treatment of relapsing-remitting multiple sclerosis (RRMS).**
- ✓ **Evidence of laquinimod's efficacy in decreasing the rate of relapse in RRMS is inconsistent.**
- ✓ **Initial phase II and III placebo-controlled trials favoured laquinimod, but in a later phase III trial (the BRAVO study) laquinimod was not shown to be more effective than placebo in reducing the annualized relapse rate.**
- ✓ **The CONCERTO study is currently recruiting patients and will assess time to confirmed disease progression and change in brain volume as its primary and secondary outcomes, respectively. Results are not expected until June of 2018.**
- ✓ **Laquinimod was generally well-tolerated in placebo-controlled studies. It was, however, associated with an elevation in liver enzymes. While this was mainly mild and transient, ongoing monitoring of liver function tests (LFTs) may be required for those taking laquinimod. Further, laquinimod is metabolized via cytochrome P450 (CYP450) enzymes, which increases the potential for drug interactions.**
- ✓ **Longer-term extension trials of laquinimod suggest it was well-tolerated.**
- ✓ **Given the number of oral treatments for RRMS that are under development or that have recently became available, laquinimod's place in therapy, alone or in combination, is uncertain.**

Background

Multiple sclerosis is a chronic, progressive, incurable disease of the central nervous system associated with inflammatory demyelination (damage to the protective layer around the nerves).[1] This results in neurological dysfunction and other symptoms including fatigue, pain, depression, anxiety, spasticity, ataxia, tremor, double vision, bowel or bladder problems, dizziness, numbness, and tingling.[2] Genetic, geographic, and environmental factors have a role in the development of MS, and it is diagnosed through clinical assessment, imaging, and other tests.[2,3] Multiple sclerosis is usually diagnosed between the ages of 20 and 40[4] and has a peak onset of around 29 years of age.[3] Multiple sclerosis is categorized based on its clinical course, with RRMS, a subtype characterized by episodes of dysfunction and periods of stability, being the most common and accounting for 85% to 90% of cases. In most patients, the initial clinical course is relapsing-remitting, but over time most will develop secondary-progressive disease.[2] While MS causes significant disability and is the most frequent cause of non-traumatic disability in young adults,[1] life expectancy is generally unaffected.[2]

The Technology

Laquinimod (Teva Pharmaceutical Industries, Israel) is a once daily, oral drug currently under development for the treatment of RRMS and other autoimmune disorders. Until recently, most drugs available in Canada for the treatment of RRMS required parenteral administration. Oral MS treatments are expected to simplify administration and reduce other barriers associated with the parenteral route, such as pain and inconvenience. Active Biotech AB (Lund, Sweden) sponsored the initial phase I and phase II studies of laquinimod; however, Teva Pharmaceutical Industries is currently the manufacturer of the drug.[5] Laquinimod is derived from roquinimex, a drug previously under development for the treatment of MS,[5] whose phase III trials were stopped due to cardiopulmonary toxicity.[6] An extensive study of structure activity relationships of roquinimex was then undertaken to identify related compounds that had the potential for use in autoimmune disorders but would not produce the same adverse effects. From 60 compounds identified, laquinimod was selected for further development. The precise mechanism of action of laquinimod in MS is not fully understood, but it appears to have central and peripheral immunomodulary effects.[6,7] In animal models, laquinimod reduces the influx of lymphocytes into the central nervous system (CNS), reduces the concentration of macrophages and T cells in the spinal cord, protects against axonal loss, and causes a shift from the proinflammatory state to the antiinflammatory state.[5] As well, laquinimod may have a neuroprotective

effect by increasing brain-derived neurotrophic factor. Laquinimod does not appear to be immunosuppressive or reduce the ability to mount immune responses.[6]

Regulatory Status

Currently laquinimod is not approved for use in Canada, the United States, United Kingdom, or European Union countries.[8] A marketing authorization application for laquinimod for the treatment of RRMS was submitted to the European Medicines Agency (EMA) in July of 2012;[9] however, it was refused in January of 2014. The manufacturer requested a re-review in February of 2014.[10] The manufacturer of laquinimod decided to delay application for approval from the FDA after failure to meet the primary end point in the BRAVO trial.[8]

Patient Group

Canada has one of the highest prevalence rates of MS worldwide.[11] The nationwide prevalence of MS in Canada is estimated to be approximately 240 per 100, 000 and varies across the provinces, with the highest rates observed in the Atlantic and Prairie regions.

Current Practice

In patients with RRMS, treatment goals include improvement in quality of life and reduction in the number and severity of relapses, burden of disease on magnetic resonance imaging (MRI), and disability progression. Initial therapies for RRMS identified in the 2013 recommendations from the Canadian MS Working Group include interferon beta-1a, interferon beta-1b, and glatiramer acetate, all of which are administered by injection and are considered to be equally efficacious.[12] As such, other factors may guide the choice among initial therapies including adverse effect profile, administration schedule, ease of use, reimbursement, and patient preference. Dimethyl fumarate (oral), fingolimod (oral), natalizumab (injection), mitoxantrone, alemtuzumab, cladribine, and cyclophosphamide (all injections) are alternatives for those who fail to respond to the initial therapies. They are generally reserved for patients with highly active disease or those with breakthrough disease activity on one of the initial therapies. While two oral agents for MS have recently entered the market in Canada (teriflunomide and dimethyl fumarate), they were not available at the time of guideline development, but are not considered initial therapies.[13] Indirect evidence suggests fingolimod and dimethyl fumarate may be more efficacious than laquinimod.[14]

Methods

Literature Search

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and The Cochrane Library (2013, Issue 11). Grey literature was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between January 1, 2008 and November 29, 2013. Regular alerts were established to update the search until March 6, 2014.

Study Selection

Phase II or III randomized, controlled clinical trials, published in full or as conference abstracts, that compared orally administered laquinimod to placebo or an active comparator in adults with MS were selected for inclusion. Open-label extension trials of laquinimod in adults with MS were also included.

The Evidence

Two phase II studies,[15,16] two phase III studies (ALLEGRO[17] and BRAVO[18]), and three extension studies[16,19,20] of laquinimod in RRMS were identified from the literature. One additional phase III study is currently recruiting patients (CONCERTO), with results expected in 2018.[21]

Polman et al. was a 24-week, phase IIa randomized, double-blind, placebo-controlled, multicentre study that compared two doses of laquinimod (0.1 mg and 0.3 mg) to placebo in 209 adults aged 18 to 65 with RRMS (85% of participants) or secondary-progressive MS (15% of participants).[15] Patients with active disease (defined as one exacerbation in the past year or two exacerbations in the last two years) and Expanded Disability Status Scale (EDSS) scores between 0 to 5.5 were enrolled. The average age of participants was 40 years (range 19 to 62) and 74% were female. The average duration of MS was 5.5 years (range 0.1 to 32.0). Baseline characteristics were similar across groups. The primary outcome was the mean cumulative number of active lesions at 24 weeks (Table 1). Only the 0.3 mg dose showed a statistically significant reduction in the mean cumulative number of active lesions (41% compared with placebo).

No statistically significant differences were observed for the secondary outcomes of total number of exacerbations, function, and health-related quality of life (Table 1); however, the data were not reported. Four serious adverse events occurred in the three study arms (Table 1). Elevated liver function tests (LFTs) and abnormal erythrocyte sedimentation rates (ESRs) were noted.

Comi et al.[19] reported results from a 24-month, open-label extension study of Polman et al.[15] Limited data were available from this study, as it was only published as a conference abstract. All 209 participants (those originally treated with laquinimod 0.1 mg, 0.3 mg or placebo) entered open-label treatment with laquinimod 0.6 mg; 159 (76%) completed the 24 month follow-up. The mean annualized relapse rate was 0.46 over the entire 42-month study period and 10.5% of patients had confirmed disability progression on the EDSS. The most commonly observed adverse effects were nasopharyngitis (25.8%), back pain (12.4%), and headache (8.1%).

Comi et al.[16] was a 36-week, phase IIb, randomized, double-blind, placebo-controlled, multicentre study that compared two doses of laquinimod (0.3 mg and 0.6 mg) to placebo in a total of 306 participants with RRMS (Table 1). Adults (aged 18 to 50 years) with EDSS scores between 1 and 5 and at least one gadolinium-enhancing lesion (GdE lesion) were enrolled. Steroid use or relapse in the 30 days prior to enrollment were not permitted, nor were immunosuppressive or cytotoxic agents or immunomodulators (interferon, glatiramer acetate, laquinimod, intravenous immunoglobulins) in the previous two months. Those who had used cladribine in the previous two years; had taken warfarin, theophylline, erythromycin, or ketoconazole in the previous two weeks; or had ever taken amiodarone were also excluded. Treatment with intravenous (IV) methylprednisolone was permitted for on-study relapse. The primary outcome measure was the cumulative number of GdE lesions at the last four scans (weeks 24, 28, 32, and 36). Demographic characteristics (average age, sex, duration of MS) were not reported, but baseline EDSS scores ranged from an average of 2.3 to 2.5 across groups, and the baseline number of GdE lesions ranged from 4.2 to 5.6. The mean ± SD cumulative number of GdE lesions at the last four scans was lower in both laquinimod groups, but was only statistically significant for the comparison of laquinimod 0.6 mg and placebo (2.6 ± 5.3 versus 4.2 ± 9.2; P = 0.0048).

From Comi et al.,[16] 257 patients entered a 36-week, double-blind extension trial in which patients originally randomized to laquinimod 0.3 mg or 0.6 mg maintained treatment, and those from the placebo group were re-randomized to active treatment with laquinimod 0.3 mg or 0.6 mg. Approximately 93% of patients completed the follow-up and 86.3% had a final scan. An average reduction of 52% from baseline in mean number of GdE lesions was seen for those who switched from placebo to laquinimod, with a greater reduction for the 0.6 mg dose. For those maintained on the 0.3 mg and 0.6 mg dosages from the original study, further reductions in the mean number of GdE lesions were observed (from 3.9 at entry to 2.2 at the end of the extension, P = 0.0062 for the 0.6 mg dosage; and from 4.6 at entry to 2.5 at the end of the extension, P = 0.0013 for the 0.3mg dosage). At the end of the extension trial, 50%, 44%, and 47% of patients were lesion-free in the original 0.6 mg, 0.3 mg, and placebo groups, respectively. The incidence of serious adverse events was 3.8% in the original 0.3 mg group, 3.2% in the original 0.6 mg group, 5.1% in the placebo-switched-to-0.3 mg group, and 6.8% in the placebo-switched-to-0.6 mg group. The incidence of adverse effects was similar across groups.

Comi et al.[22] was a 24-month, phase III, randomized, double-blind, placebo-controlled multicentre study (ALLEGRO) that compared laquinimod 0.6 mg to placebo in a total of 1,106 participants with RRMS (Table 1). Enrolled were adults (aged 18 to 55 years) with EDSS scores less than 5.5, a disease duration of at least six months, and at least one relapse in the previous 12 months or two relapses in the previous 24 months. Participants who received disease-modifying therapy prior to enrollment were eligible for inclusion, but immunosuppressive agents in the previous six months were not permitted; nor were interferon, glatiramer acetate, laquinimod, or intravenous immunoglobulins in the previous two months. Those participants with a history of cladribine, natalizumab, or laquininmod, or inhibitors of CYP3A4 in the previous two weeks were also excluded. Treatment with IV methylprednisolone was permitted for relapse during the study. The primary outcome measure was annualized relapse rate. Overall, 69% of study participants were female, with an average age of about 39 years, EDSS scores of about 2.6, and disease duration of 8.7 years. Patients treated with laquinimod had reductions in relapse of about 23% relative to placebo (95% confidence interval [CI]: 9% to 35%), with an adjusted annualized relapse rate of 0.30 in the laquinimod and 0.39 in the placebo groups (P =

0.002), respectively. Secondary outcomes (disability progression, mean number of cumulative GdE lesions, and mean number of new or enlarged lesions on T2-weighted MRI) also favoured laquinimod over placebo (Table 1). Immune function of those who were treated with laquinimod in the ALLEGRO study was reported in a separate publication.[23] This study demonstrated that patients treated for two years maintained their immune function.[23] A further exploratory analysis of MRI markers of tissue damage associated with RRMS suggested that laquinimod may reduce some of the destructive pathological processes of the disease in the initial phase of treatment.[24] In a subsequent publication of patient-reported outcomes from the ALLEGRO study, laquinimod had a favourable effect on fatigue, functional status, the mental composite score of the SF-36 (MCS-36) health survey; and the vitality, social functioning, role emotional, physical functioning, and role physical subscales of the SF-36 relative to placebo.[14] One-year results of an ongoing, open-label extension trial of 839 patients who were enrolled in the ALLEGRO study suggest that disability progression was reduced in those who were treated early with laquinimod compared with those who started late (11.8% versus 16.7%, hazard ratio [HR]: 0.62; P = 0.0038).[20] Results of the extension study of ALLEGRO have not yet been published in full.

Vollmer et al.[18] was a second phase III trial (BRAVO) that compared laquinimod 0.6 mg daily with interferon beta-1a 30 mcg intramuscular weekly and to placebo in RRMS (Table 1). BRAVO was a randomized, placebo-controlled, active comparator, multinational, multicentre study. The study included patients with RRMS and EDSS scores between 0 and 5.5 with one relapse in the previous 12 months, two relapses in the previous 24 months, or one relapse in the previous 12 to 24 months, with one GdE lesion in the year prior to screening.[18] Excluded from the study were patients with progressive forms of MS, or who had used corticosteroid for relapses in the previous 30 days; patients who had used experimental drugs, investigational drugs, or immunosuppressive therapy in the previous six months; glatiramer acetate in the previous two months; or any previous use of natalizumab, laquinimod, cladribine, or interferon-beta. The primary outcome measure was the annualized relapse rate, and secondary outcomes included EDSS progression and MRI measures.

Overall, 68% of study participants were female, with an average age ranging from 36.7 to 38.5 years across groups. The average disease duration was between 4.7 to 5.3 years across groups. No statistical comparisons were made between laquinimod and interferon beta-1a.The adjusted annualized relapse rate did not demonstrate superiority of laquinimod over placebo and, as such, all analyses on the secondary end points were considered exploratory (Table 1). Exploratory analyses of secondary end points showed statistically significant differences, favouring laquinimod over placebo, for EDSS progression (HR: 0.61, 95% CI: 0.38 to 0.68; P = 0.042) and percent brain volume change, which showed a smaller reduction with laquinimod than with placebo over the 24-month study.

Adverse Effects

In a pooled analysis based upon the ALLEGRO and BRAVO studies (983 patients treated with laquinimod 0.6 mg daily and 1,005 treated with placebo), 81.8% of laquinimod patients and 76.2% of placebo patients experienced an adverse effect, the most common of which (laquinimod versus placebo) were headache (18.2% versus 15.1%), back pain (13.6% versus 8.2%), arthralgia (7.2% versus 6.0%), and increased alanine aminotransferase (5.0% versus 2.6%). The serious adverse effect (SAE) rate was about 9% in both groups, with appendicitis being the most frequently reported SAE in laquinimod patients (n = 6 compared with n = 1 placebo patient).[25] In the individual phase II and phase III studies, over 30% of patients had increased LFTs, which were generally described as mild and transient; however, in the ALLEGRO study, 5% of patients had increases that were more than three times the upper limit of normal. No cases of hepatic failure were observed.[22]

Administration and Cost

Laquinimod was taken orally, once daily, at a dose of 0.6 mg in the BRAVO and ALLEGRO studies; however, the CONCERTO study, which is currently recruiting patients, will evaluate dosages of 0.6 mg and 1.2 mg.[21] No information on drug cost is available at this point. One advantage of orally administered medications for MS is that there are no additional administration costs as with some injectable medications; however, additional costs with laquinimod could potentially be required for ongoing monitoring of liver enzymes.

Table 1: Summary and Critical Appraisal of Randomized Controlled Trials of Laquinimod in Multiple Sclerosis			
Study and Design	**Intervention and Comparator**	**Outcomes**	**Critical Appraisal**
Polman et al., 2005[15] Phase IIa 32 weeks total (24 weeks active treatment and 8 weeks of additional follow-up) Randomized, double-blind, placebo-controlled Multicentre	LAQ 0.1 mg once daily (n = 68) LAQ 0.3 mg once daily (n = 74) Placebo once daily (n = 67)	**Mean (SD) cumulative number of active lesions (24 weeks):** Placebo 9.3 (17.2) LAQ 0. 1 mg 6.7 (9.7); 28% reduction *P* = 0.172[a] LAQ 0.3 mg 5.5 (9.7); 41% reduction relative to placebo; *P* = 0.0498 [a] No significant differences in total number of exacerbations, EDSS, MSFC or SF-36 (data not shown) **SAEs** Placebo − 1 UTI LAQ 0.1 mg − 1 brain contusion LAQ 0.3 mg − 1 case of iritis 1 case of burning sensation **AEs** Abnormal ESR Placebo – 6.0% LAQ 0.1 mg – 13.2% LAQ 0.3 mg – 17.6% Elevated LFTs [b] Placebo – 34% LAQ 0.1 mg – 34% LAQ 0.3 mg – 47%	Selection bias: Patient selection, enrollment, randomization, and allocation concealment appeared to be appropriate. Performance bias: No information on co-interventions or patient compliance was provided. Detection bias: Blinding appeared to be appropriate. Outcomes independently interpreted. Attrition bias: ITT analysis performed, and 95% of those randomized completed the study Generalizability: Patients who used interferon or glatiramer acetate for more than 12 months or in the previous 6 months were excluded. Study locations were not reported. The dosages of LAQ were lower than those used in subsequent phase III trials.
Comi et al., 2008[16] 36 weeks Randomized, double-blind, placebo-controlled 51 centres in nine European countries	LAQ 0.3 mg once daily (n = 98) LAQ 0.6 mg once daily (n = 106) Placebo once daily (n=102)	**Mean (SD) cumulative number of GdE lesions at the last four scans:** Placebo: 4.2 (9.2) LAQ 0.3 mg: 3.9 (5.5) *P* > 0.1[a] LAQ 0.6 mg: 2.6 (5.3); 40.4% reduction relative to placebo; *P* = 0.0048 [a] **Annual relapse rate (SD)** Placebo: 0.77 (1.25) LAQ 0.3 mg: 0.76 (1.02) *P* > 0.1 [a] LAQ 0.6 mg: 0.52 (0.92) *P* = 0.0978 [a]	Selection bias: Patient selection, enrollment, and randomization appeared to be appropriate, but allocation concealment was not reported. Performance bias: No information on patient compliance was provided. Detection bias: Blinding appeared to be appropriate. Outcomes independently interpreted. Attrition bias: ITT analysis performed. Attrition was greater in the placebo group, with 89% (placebo) to 94% (LAQ 0.6mg) of those randomized completing the study. Generalizability: There were a number of exclusions based on medication use. Safety when co-administered with key

Table 1: Summary and Critical Appraisal of Randomized Controlled Trials of Laquinimod in Multiple Sclerosis			
Study and Design	**Intervention and Comparator**	**Outcomes**	**Critical Appraisal**
		% Patients relapse free Placebo: 62.7% LAQ 0.3 mg: 59.2% *P* > 0.1 [a] LAQ 0.6 mg: 70.8% *P* > 0.1 [a] **SAE event rate** Placebo – 4.9% LAQ 0.3 mg – 5.1% LAQ 0.6 mg – 2.8% **AE event rate** Placebo – 82.4% LAQ 0.3 mg – 84.7% LAQ 0.6 mg – 77.4% **Elevated LFTs**[b] Placebo – 10.8% LAQ 0.3 mg – 23.4% LAQ 0.6 mg – 33.07%	drugs that inhibit CYP3A4 remains unknown. There were no North American study sites. Demographic characteristics were not reported. The 0.3mg dosage of LAQ was lower than those used in subsequent phase III trials.
Comi et al., 2012[22] ALLEGRO study 24 months Randomized, placebo-controlled 139 centres in 24 countries (including Canada and the United States)	LAQ 0.6 mg once daily (n = 550) Placebo once daily (n = 556)	**Annualized relapse rate (SE)** LAQ 0.6 mg – 0.30 ± 0.02 Placebo – 0.39 ± 0.03 Risk ratio 0.77 (95% CI: 0.65 to 0.91) *P* = 0.002 **Disability progression at 3 months**[c] HR: 0.64 (95% CI: 0.45 to 0.91) *P* = 0.01 **Disability progression at 6 months**[c] HR: 0.51 (95% CI: 0.34 to 0.79) *P* = 0.002 **Mean number (SD) of cumulative GdE lesions at 12 and 24 months** Placebo – 2.12 (0.22) LAQ 0.6 mg – 1.33 (0.14); *P* < 0.001 Rate ratio: 0.63 (95% CI: 0.49 to 0.81) **Mean (SE) New or enlarged lesions on T2 weighted MRI** Placebo – 7.14 (0.07) LAQ 0.6 mg – 5.03 (0.08); *P* < 0.001	Selection bias: Patient selection, enrollment, and randomization appeared to be appropriate, but allocation concealment was not reported. Performance bias: No information on patient compliance was provided. Detection bias: Blinding appeared to be appropriate. Outcomes independently interpreted. Attrition bias: ITT analysis performed, but the attrition rate was more than 20% in both groups, with 79.5% of the laquinimod group and 76.8% of the placebo group completing the study. Generalizability: There were a number of exclusions based on previous medication use. Safety when co-administered with drugs that inhibit CYP3A4 is unknown. The average disease duration was almost 9 years.

Table 1: Summary and Critical Appraisal of Randomized Controlled Trials of Laquinimod in Multiple Sclerosis			
Study and Design	**Intervention and Comparator**	**Outcomes**	**Critical Appraisal**
		Rate ratio 0.70 (95% CI: 0.58 to 0.85) **SAE Event Rate** Placebo – 9.5% LAQ 0.6 mg – 11.1% **AE Event Rate** Placebo – 81% LAQ 0.6 mg – 87% **Elevated LFTs** 1 to 3 times ULN Placebo – 17.7% LAQ 0.6 mg – 30% > 3 times ULN Placebo – 1.6% LAQ 0.6 mg – 4.8%	
Vollmer et al., 2014[18] BRAVO study 24 months Randomized, double-blind, placebo-controlled, active comparator 155 centres in 18 countries (including Canada and the United States)	LAQ 0.6 mg once daily (n = 434) Interferon beta-la 30 mcg IM once weekly (n = 447) Oral placebo (n = 450)	**Annualized relapse rate[d] (SE)** LAQ 0.6 mg – 0.28 ± 0.03 Placebo – 0.34 ± 0.03 Risk ratio 0.82 (95% CI: 0.66 to 1.02) *P* = 0.075 Interferon beta-1a – 0.26 ± 0.02 Placebo – 0.34 ± 0.03 Risk ratio 0.74 (95% CI: 0.60 to 0.92) *P* = 0.023 **Adjusted risk of EDSS progression[d] at 6 months** LAQ 0.6mg HR[e]: 0.61 (95% CI: 0.38 to 0.98); *P* = 0.042 Interferon beta-1a HR[e]: 0.73 (95% CI: 0.47 to 1.14); *P* = 0.042 **Mean number (SD) of cumulative GdE lesions at 12 and 24 months** LAQ 0.6 mg – 1.84 (0.19) Placebo – 2.34 (0.25); *P* = 0.069 Rate ratio: 0.79 (95% CI: 0.66 to 1.02) Interferon beta-1a – 0.90 (0.10) Placebo – 2.34 (0.25); *P* < 0.001 Rate ratio: 0.39 (95% CI: 0.40 to 60)	Selection bias: Patient selection, enrollment, and randomization appeared to be appropriate, but allocation concealment was not reported. Performance bias: No information on patient compliance was provided. Detection bias: Patients and treating neurologists were blinded to LAQ treatment status, but not to interferon beta-1a. The examining neurologist was blinded to all treatments, and an effort was made to conceal injection sites. Outcomes were independently interpreted. Attrition bias: Did not state that ITT analysis was performed, but appeared to be based upon sample sizes reported in outcome tables. Attrition rates were higher in the placebo (20.2%) and LAQ (18.7%) groups than in the interferon beta-1a group. Generalizability: There were a number of exclusions based on previous medication use.

Table 1: Summary and Critical Appraisal of Randomized Controlled Trials of Laquinimod in Multiple Sclerosis			
Study and Design	**Intervention and Comparator**	**Outcomes**	**Critical Appraisal**
		Mean (SE) new or enlarged lesions on T2-weighted MRI LAQ 0.6 mg – 10.88 (0.85) Placebo – 13.03 (1.1) *P* = 0.078 Rate ratio 0.84 (95% CI: 0.68 to 1.02) Interferon beta-1a – 6.37 (0.51) Placebo – 13.03 (1.1) *P* < 0.001 Rate ratio 0.49 (95% CI: 0.40 to 0.56) **Percent brain volume change from baseline to 24 months (treatment effect vs placebo)** LAQ 0.6mg – +0.28% (*P* < 0.001) Interferon beta-1a – −0.11% (*P* = 0.14) **SAE event rate** Placebo – 8.0% LAQ 0.6 mg – 7.2% Interferon beta-1a – 5.7% **AE event rate** Placebo – 70% LAQ 0.6 mg – 75% Interferon beta-1a – 82% **Elevated LFTs** Placebo –17.8% LAQ 0.6 mg – 28.9% Interferon beta-1a – 29.1%	

AE = adverse event; CI = confidence interval; CYP = cytochrome P; EDSS = expanded disability status scale; ESR = erythrocyte sedimentation rate; GdE = gadolinium enhancing; HR = hazard ratio; ITT = intention to treat; LAQ = laquinimod; LFT = liver function test; MRI = magnetic resonance imaging; MSFC = multiple sclerosis functional composite; SAE = serious adverse event; SD = standard deviation; SE = standard error; ULN = upper limit of normal; UTI = urinary tract infection.

[a] *P* = value compared to placebo

[b] Mild and transient

[c] Defined as a sustained increase in EDSS for at least 3 months of 1.0 points or more if baseline was between 0 and 5.0 or 0.5 points if baseline was 5.5.

[d] Adjusted for baseline EDSS score, number of relapses in previous two years and geographical region.

[e] Laquinimod versus placebo.

Concurrent Development

In 2011, fingolimid was the first oral agent for the treatment of RRMS to enter the Canadian market. Other oral agents have recently been approved for use in Canada, including dimethyl fumarate (April 2013) and teriflunomide (November 2013). Alemtuzumab (an IV agent) was approved for use in Canada in December 2013. Cladribine is an oral agent approved for use in Australia and Russia for MS, but it was not approved in the EU or US due to safety concerns related to malignancies.[26] While phase III trials of cladribine in MS will be completed, it is not clear whether development of this drug for MS will continue. Cladribine is available in Canada as an IV antineoplastic agent and is considered a third-line treatment option using this formulation.[12] Several monoclonal antibodies are also in development for the treatment of RRMS, including rituximab (available in Canada but not approved for use in MS), ocrelizumab, ofatumumab, secukinumab, and daclizumab, and are in phase II or III trials.[8] A phase IIa trial (the TERMS trial) of tovaxin, a subcutaneously administered autologous T cell immunotherapeutic agent, has been completed, but the extension of the trial was terminated due to financial constraints. Other drugs in phase II trials include ibudilast (an oral phosphodiesterase inhibitor), estrogen compounds (oral), firategrast (oral agent that reduces trafficking of leukocytes across the blood brain barrier), ONO-4641 and BAF312 (oral sphingosine-1 phosphate receptor agonists).[8]

Given laquinimod's unique mechanism of action, it has been suggested that it could potentially be used in combination with glatiramer acetate or interferon for the treatment of RRMS; however, there are no studies to support this at present. Laquinimod is also under evaluation for the treatment of Crohn's disease (phase II) and systemic lupus erythematosus patients with active nephritis and active lupus arthritis (phase II studies).

Rate of Technology Diffusion

After failing to meet the primary outcome in the BRAVO study, the manufacturer of laquinimod opted to delay application for FDA approval[8] until additional efficacy data was made available.[27] Currently, the CONCERTO study is in progress and will compare laquinimod 0.6 mg, laquinimod 1.2 mg, and placebo in approximately 1,800 patients with RRMS.[27] At the time of the writing of the Canadian MS Working Group 2013 guidelines, teriflunomide, dimethyl fumarate (BG-12), and laquinimod were not on the Canadian market, but it was stated that they are expected to become initial therapies agents for the treatment of RRMS based upon their efficacy and adverse effect profiles. Additional safety and efficacy data from the CONCERTO study should help to better define laquinimod's place in therapy for RRMS. The oral route of administration and the favourable adverse effects profile are likely to encourage the use of laquinimod; however, other oral medications for MS are likely to be alternatives. Laquinimod has an advantage in that it does not appear to be immunosuppressive and could potentially slow disease progression.[6] Despite the availability of other oral agents for RRMS, some have immunosuppressive effects that have been associated with opportunistic infections and malignancies, which could deter their use. Indirect comparison from a network meta-analysis suggested that alemtuzumab, natalizumab, fingolimod, and dimethyl fumarate were more efficacious than other agents, including laquinimod.[14] Recommendations from a CADTH review of drugs for RRMS suggest dimethyl fumarate, fingolimod, or natalizumab as alternatives in those who do not respond to or are unable to take both glatiramer acetate or interferon beta-1b.[13] There is a potential for off-label use of laquinimod in the other indications for which the drug is currently in clinical trials, including Crohn disease and systemic lupus erythematosus, and in types of MS other than RRMS.

Implementation Issues

A number of oral agents for the treatment of MS have recently been approved; however, the place in therapy of these agents has yet to be clearly established. There is currently a lack of guidance or knowledge of which patients are appropriate candidates for the new and emerging treatment alternatives.[28] Development of biomarkers that reliably predict response could aid in these decisions, but at present such biomarkers are lacking.[28] There is a paucity of direct evidence for the comparative efficacy of laquinimod with other oral agents and evidence is limited comparing laquinimod with drugs administered via injection.[29] The efficacy of agents for the treatment of MS in combination remains unknown. In addition, questions remain about when to initiate, switch, or escalate treatment, and the sequencing of agents has yet to be established.[30] Further, laquinimod is metabolized via CYP450 enzymes, which increases the potential for drug interactions[6] and studies of laquinimod have excluded patients taking inhibitors of CYP3A4. Thus, safety in this population remains unknown. It has been suggested that since laquinimod

provides immunomodulation without immunosuppression in the peripheral nervous system, may be neuroprotective in the CNS, has a clinical effect on brain atrophy and disability progression, and has a favourable adverse effects profile, it is differentiated from other oral and IV treatments for MS.[6] The place in therapy for laquinimod as an alternative for monotherapy or combination therapy with peripherally acting immunomodulary drugs, remains to be defined.[6]

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