Neurología. 2011;**26(2)**:111-117

NEUROLOGÍA

www.elsevier.es/neurologia

REVIEW ARTICLE

Oral laquinimod treatment in multiple sclerosis

O. Fernández

Instituto de Neurociencias Clínicas, Hospital Regional Universitario Carlos Haya, Málaga, Spain

Received on 17th July 2010; accepted on 26th July 2010

KEYWORDS
Multiple sclerosis;
Immunomodulator;
Laquinimod;
Oral Treatments

Abstract
Introduction: Multiple sclerosis (MS) is a chronic disease of the central nervous system, probably of autoimmune origin. Its early treatment with interferon beta or glatiramer acetate reduces the number of exacerbations, slows disability progression and improves the quality of life, but these treatments are only partially effective and require parenteral administration.
Aim: To review current experience with laquinimod as a novel immunomodulatory therapy for relapsing-remitting MS (RRMS).
Development: Laquinimod is a new quinolone-carboxamide that has shown efficacy in various animal models of autoimmune disease, including MS. Laquinimod shows immunomodulatory effects, probably through Th1/Th2 shift, but does not lead to immunosuppression. Laquinimod is metabolised primarily by the CYP3A4 enzyme in the liver. Phase II studies in RRMS demonstrate a dose-response effect on disease activity, measured by the number of active lesions on brain magnetic resonance imaging, and show favourable 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 RRMS. The drug was granted a fast track review by the FDA in 2009.
Conclusions: Laquinimod is a novel, orally administered immunomodulator that has advanced to phase III study, a pre-submission stage to the regulatory agencies, and may become an alternative to the current injectable first-line treatments for RRMS.

PALABRAS CLAVE
Esclerosis múltiple;
Inmunomodulador;
Laquinimod;
Tratamientos orales

Tratamiento oral con laquinimod en la esclerosis múltiple

Resumen
Introducción: La esclerosis múltiple (EM) es una enfermedad crónica del sistema nervioso central de probable origen autoinmune. Su tratamiento temprano con interferón beta o acetato de glatirámero reduce el número de brotes y la progresión de la discapacidad, y

E-mail: oscar.fernandez.sspa@juntadeandalucia.es

mejora la calidad de vida, sin embargo, estos tratamientos son efectivos sólo parcialmente y requieren administración parenteral.
Objetivo: Revisar la situación actual de laquinimod como tratamiento inmunomodulador oral para la EM recurrente-remitente (EMRR).
Desarrollo: Laquinimod es una nueva quinolonecarboxamida que ha demostrado eficacia en modelos animales de varias enfermedades autoinmunes, incluyendo la EM. Muestra efectos inmunomoduladores, probablemente a través de la alteración del balance Th1/Th2, y no conduce a la inmunosupresión. Se metaboliza en el hígado, principalmente por la vía del CYP3A4. Los estudios de fase II en EMRR han demostrado un efecto dosis-respuesta de laquinimod sobre la actividad de la enfermedad, medida por el número de lesiones activas en la resonancia magnética cerebral, y muestran una tolerabilidad y seguridad favorables, basadas en indicadores clínicos y de laboratorio. En la actualidad, se está evaluando la eficacia de laquinimod en dos estudios de fase III en la EMRR, usando la dosis de 0,6 mg/día. Se ha concedido al fármaco la categoría de revisión rápida *(fast track)* por la FDA en 2009.
Conclusiones: Laquinimod es un inmunomodulador nuevo, administrado por vía oral, que ha pasado a la etapa de estudio en fase III, previo a su evaluación por las agencias reguladoras y podría ser una alternativa a los actuales tratamientos inyectables de primera línea para la EMRR.

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by inflammation, demyelinization and axonal destruction. According to the data derived from the *Atlas of MS*, there are currently approximately 2 million people suffering from MS in the world, of whom 630,000 cases are in Europe, making it the main cause of disability in young adults.[1,2] The prevalence rate in Spain is 50 to 80 cases per 100,000 inhabitants.[3-5]

MS is a very heterogeneous disease, both in terms of its pathogenic, neuropathological and clinical aspects, as well as in the response to treatment. This is why it is very difficult to establish a prognosis for a specific patient, as well as to assess the efficacy of the drugs used in its treatment. The first clinical symptoms of MS generally appear between the second and fourth decade of life, although there are cases that fall outside this age range. The disease's inflammatory activity, represented by outbreaks, is present during about to or three decades, diminishing over time. MS is a chronic condition causing disability due to the accumulation of lesions in the central nervous system over time. The assessment of the accumulated disability is fundamental when taking decisions about treatment and attempts to avoid its accumulation justify early treatment in the natural history of the disease.

The prognosis of MS has improved significantly following the approval of the first interferon beta in 1993. The availability of animal models, such as experimental autoimmune encephalomyelitis (EAE) has made it easier to study new drugs modifying the disease's progression and aimed at diminishing the presentation of antigens, their proliferation, activation or the movement of activated T cells through the blood-brain barrier (BBB). The drugs approved for the treatment of MS are listed in table 1.

Most patients with recurrent-relapsing multiple sclerosis (RRMS) benefit from treatment with interferon beta or glatiramer acetate, by obtaining partial control over the illness's activity, as measured by the annual rate of outbreaks, the number of lesions highlighted using gadolinium in the magnetic resonance imaging (MRI) of the brain, the accumulation of lesions in the T2-weighted sequences or the reduction of lesions evolving into black holes in T1. The four injectable treatments on the market in Europe represent the first line of treatment for RRMS. Natalizumab is currently used, above all, for patients who continue to have activity in the illness despite first-line treatment. Its use is constrained by the risk of a potentially fatal adverse event, progressive multifocal leukoencephalopathy (PML). Mitoxantrone is reserved for patients with a form of RRMS that fails to respond to other treatments and in the clinical forms of secondary-progressive multiple sclerosis (SPMS), due to its accumulative toxicity, in particular cardiotoxicity and the risk of acute myeloid leukaemia,[6] for which reasons its use is gradually declining.

All therapies currently approved for the treatment of MS require parenteral administration, have side effects, or their use implies a risk of adverse events. In addition, as treatment that modify the illness, they are only partially effective in reducing the frequency of the outbreaks and delaying the progression of disability. Both clinicians and sufferers of MS are impatiently waiting for the emergence of more effective oral treatments. In Phase II and Phase III clinical trials, several oral compounds with new mechanisms of action have shown very promising results, including oral fingolimod and cladribin, fumaric acid, teriflunomide and laquinimod. This review summarizes the current knowledge about laquinimod and considers its potential for the treatment of RRMS.

Table 1 Drugs currently approved for handling MS

Drug	Dosage	Route	Manufacturer
IFN-β-1b			
Betaferon®	250 μg every other day	S.C.	Bayer HealthCare Pharmaceuticals, Inc. (Leverkusen, Germany)
Extavia®			Novartis International AG (Basle, Switzerland).
IFN-β-1a			
Avonex®	30 μg once a week	IM	Biogen Idec (Cambridge, USA)
IFN-β-1a			
Rebif®	22 or 44 μg three days a week	SC	EMD Serono, Inc. (Rockland, USA)
Glatiramer acetate Copaxone®	20 mg per day	SC	Teva Pharmaceutical Industries Ltd, (Petah Tikva, Israel)
Natalizumab Tysabri ®	300 mg every 4 weeks	IV perfusion in 1 hour	Elan Pharmaceuticals, Inc., (Dublin, Ireland)
Mitoxantrone Novantrone®	12 mg/ m^2 of body surface every 3 months	IV infusion in 5-15 minutes	EMD Serono, Inc. (Rockland, USA)

Introduction to laquinimod

The molecule of laquinimod (ABR-215062) was synthesized by Active Biotech AB (Lund, Sweden) and was licensed to Teva Pharmaceutical Industries Ltd. in 2004 as an immunomodulator for the treatment of MS. Laquinimod is a derivative of roquinimex (Linomide®), which is structurally similar to laquinimod and was previously tested in the treatment of MS.[7,8] Roquinimex showed that it effectively inhibited the animal models for acute and chronic EAE[9,10] and stimulated the *in vitro* production of anti-inflammatory cytokines[10]. In the clinical trials with MS patients, treatment with roquinimex showed a reduction in the number and volume of lesions enhanced with gadolinium in the brain MRI, a primary measure of the illness's activity used in Phase II studies. The Phase III clinical trials with roquinimex were unexpectedly suspended in 1999 due to the occurrence of serious cardiac adverse events, such as pericarditis and myocardial infarction.[11-13] During the development of laquinimod, special attention has been paid to the identification of a product with a lower probability of triggering inflammatory side effects, such as serositis and vasculitis.

The laquinimod molecule is small (N-ethyl-N-fenyl-5-chloro-1,2-dihydro-4-hydro-1-methyl-2-oxo-3-quinoline-carboxamide), with a molecular weight of 357 Da. It has been researched *in vivo* to determine the potency of its activity, as well as the compound's side effects profile and safety. Using the EAE model, more than 60 different molecules in the quinolone family have been tested, with special attention being paid to their pro-inflammatory effects, the onset of fever and the alteration of inflammation markers. These same studies have been repeated in a model using Beagle dogs.[14] From all these molecules, laquinimod was selected for subsequent development due to its very robust effect on inhibiting the development of EAE,[15] and suppressing experimental autoimmune neuritis.[16] The equivalent dose of laquinimod used in this research was 10 to 100 times more effective in controlling the activity of the illness in the EAE model than its predecessor, roquinimex[14].

Mechanism of action

Laquinimod's mechanism of action, like that of other drugs for the treatment of MS, is not unique. It has been shown to have an anti-inflammatory effect and another independent neuroprotector effect. The specific targets on which it acts are now under study.

Anti-inflammatory effect

The administration of laquinimod in EAE, as an animal model for MS, showed a reduction in the infiltration of CD4, CD5, CD8 lymphocytes and macrophages. Thus, the reduction in the spread of CD5 by laquinimod might have major therapeutic implications.[15,17] The suppression of EAE by laquinimod is explained by the modulation of the Th1/ Th2 response produced by an inhibition of pro-inflammatory cytokines (IL12, TNFα), diminishing the activity of the NK cells and increasing the anti-inflammatory cytokines IL4, IL10 and TGFβ. In addition, the use of laquinimod in this model did not lead to a reduction in the number of B and T cells, did not inhibit the proliferation of lymphocytes, nor did it cause immunosuppression.[15,18] Laquinimod also reduced the production of IFNγ, TNFα, IL6, IL13 and IL17 in the studies with animal models; *in vitro* studies in human cell lines from healthy volunteers showed a reduction in IL17.[19]

Neuroprotector effect

Laquinimod also showed that it inhibits both the development of the illness and the histopathological changes in chronic

EAE in mice. This effect has been shown to be independent of the endogenous production of IFN-β. Laquinimod increases the *in vivo* levels of the BDNF neurotrophic factor in patients with MS[20]. Furthermore, it inhibits the activity of the microglía and the macrophages, which would be beneficial for MS sufferers[21]. Finally, treatment with laquinimod is capable of reducing the degree of infiltration of macrophages and T cells, demyelinization and axonal damage. These results indicate that laquinimod might be capable of protecting the axons, as well as having an anti-inflammatory effect and, therefore, it might play a relevant role in the future treatment of RRMS and SPMS with outbreaks[22].

Pharmacodynamics, pharmacokinetics and metabolism

The pharmacokinetic properties of laquinimod have been studied in several pre-clinical models, including mice, rats, rabbits and dogs[23]. Laquinimod has a high level of oral bioavailability, a small distribution volume (10 L) and a low rate of total clearance. The maximum plasma concentration (C_{max}) of laquinimod is achieved within the first hour following its administration *per os* and in humans is less than 5 μM after administration of 0.05 to 2.4 mg of the drug. There is a small fluctuation between the minimum plasma concentration (C_{min}) and the steady state of C_{max}, once achieved. Laquinimod is metabolized through one of the CYP enzymes and is a substrate with low affinity for CYP3A4 in liver microsomes. It is mainly eliminated through urine in four hydroxylated metabolites and two metabolically inactive de-alkylated metabolites. Less than 5% of laquinimod is eliminated unaltered in urine or in faeces.

The enzymes in the CYP3A family may be involved in the metabolism of ≤ 50% of the medicines used in humans, which is always of relevance due to the potential for interactions between drugs sharing the same metabolic pathway. Inhibitors of CYP3A4, such as prednisolone, erithromycin and ketoconazole have been studied *in vitro*. It is only known that ketoconazole, in humans, might reach plasma levels that would have a metabolic effect on CYP3A4 and, as a result, might affect the elimination of laquinimod. In another sense, laquinimod's low affinity for CYP3A4 enzymes reduces the risk of competitive inhibition for other substrates. The level of laquinimod necessary to cause competitive inhibition by other drugs sharing the same metabolic pathway, such as ethinylestradiol, is 30 times higher than the C_{max} expected with the doses currently used in the clinical trials.[24]

Efficacy

Phase I studies

In the Phase I studies completed, the compound was well tolerated at doses from 0.1 mg/day up to 1.2 mg/day. After 1 to 2 weeks of treatment with 2.4 mg/day of laquinimod, elevated levels of inflammatory markers were observed.[25]

Phase II studies

Study 01506203 This was the first pilot study with laquinimod in RRMS, published in 2005.[25] It was a Phase II double blind, randomized study organized at multiple centres (20 centres in the Netherlands, Russia, Sweden and the United Kingdom), assessing the effects of laquinimod at doses of 0.1 or 0.3 mg/day versus placebo over 24 weeks. The study was monitored using brain MRI with a triple dose of gadolinium (0.3 mmol/kg) at the baseline and at weeks 4, 8 and 24 during treatment and again 8 weeks after the withdrawal of treatment. The primary endpoint of the study was the accumulated number of active lesions (sum of lesions capturing gadolinium in T1 or newly-appearing or larger-sized lesions in T2) in the brain at week 24. The study included 209 patients with RRMS or SPMS, an EDSS of not more than 5.5, and evidence of the illness's activity by MRI or the presence of a clinical outbreak in the previous 1 to 2 years. Both doses of laquinimod were well tolerated and 95% of patients completed the trial. Oral therapy with laquinimod at a dose of 0.3 mg/day during 24 weeks gave rise to a reduction of 44%($p = 0.0498$) in the mean number of accumulated active lesions compared with placebo. In a sub-group of patients with at least one active lesion on the baseline MRI, the mean reduction in the number of accumulated active lesions reached 52%($p = 0.005$). There was also a significant difference in the accumulated volume of lesions enhanced by gadolinium after 24 weeks of treatment, favourable to the group treated with laquinimod at 0.3 mg/day versus placebo. The brain MRI obtained 8 weeks after the suspension of the study medication showed an increase in the illness's activity in both treatment groups; this finding might support the biological effect of the compound or might be construed as a trend suggesting a rebound effect.

Study LAQ/5062 The effects of laquinimod on the treatment of RRMS continued to be investigated in a second international double-blind, placebo-controlled, multi-centric trial published in 2008[26]. The efficacy, tolerability and safety of laquinimod at 0.3 mg/day ($n = 98$) and laquinimod at 0.6 mg/day ($n = 106$) versus placebo ($n = 102$) were evaluated after more than 36 weeks of treatment. Patients eligible for this study had a confirmed diagnosis of RRMS applying the McDonald criteria, with an EDSS scale of no more than 5 and with at least one gadolinium-enhanced lesion the brain MRI. A brain MRI was performed with and without a standard dose of gadolinium (0.1 mmol/kg) at the baseline moment, again at week 4, and monthly between weeks 12 and 36 of treatment. The main measure for the evaluation of efficacy was the accumulated number of lesions enhanced with gadolinium in the last 4 MRIs during treatment (weeks 24, 28, 32 and 36). Compared with placebo, oral therapy with laquinimod at 0.6 mg/day resulted in a 40.4% reduction in the mean number of accumulated lesions enhanced with gadolinium in the MRI, adjusted for baseline values (mean for placebo = 4.2; SD = 9.2 versus the mean for laquinimod at 0.6 mg/day = 2.6; SD = 5.3; $p = 0.0048$).

These differences were significant in favour of the group treated with the 0.6 mg/day dose, and were also observed in almost all the study's secondary variables. The accumulated number of new lesions on T2 and the accumulated number of new hypointense lesions in T1 in the group receiving laquinimod at 0.6 mg/day were

significantly reduced by 44 and 51%, respectively, in comparison with the placebo group.

The subjects treated with laquinimod at 0.6 mg/day had an annual rate of outbreaks of 0.52 (SD = 0.92) versus 0.77(SD = 1.25) for the placebo group (NS, p = 0.0978), but studies of this size and duration (36 weeks) do not have sufficient statistical power to detect changes in the illness's activity using the outbreak rate as an outcome measure. The analysis of the primary or the secondary variables in the group receiving laquinimod at 0.3 mg/day did not reveal any significant differences with respect to the placebo. On the other hand, Polman et al.[25] found statistical significance in the results of the MRI when comparing 0.3 mg/day with the placebo group; they used a triple dose of gadolinium, which increases the sensitivity for determining the alteration of BBB patency. In the paper published by Polman, two types of lesion were also considered to assess the primary endpoint, gadolinium-enhanced lesions and new lesions or those enlarging their size in T2, therefore there may have been greater sensitivity to the change in the illness's activity based on these MRI results.

Extension of the study – LAQ/5063 The subjects included in clinical trial LAQ/5062 published by Comi et al.[26] were invited to participate in an extension study (91% were recruited) for an additional period of 36 weeks. The placebo group was re-randomized to receive laquinimod at a dose of 0.3 or 0.6 mg/day. There was a 52% reduction ($p < 0.0007$) in the average number of gadolinium-enhanced lesions in the patients who switched from placebo to active treatment with laquinimod. This reduction was significant for any of the patients, whether they switched to the high dose ($p < 0.009$) or the low dose ($p < 0.03$) of laquinimod. Of the patients who started active treatment in this extension phase, 47%($p < 0.012$) did not develop any new gadolinium-enhanced lesions. The study sponsor decided to proceed with the 0.6 mg/day dose in future Phase III trials. This research is on-going as an open-label trial 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 RRMS patients over time.[27]

The design of the Phase II studies is shown in figure 1.

Phase III studies

Study LAQ/301 – Allegro This is a double-blind trial designed to evaluate the efficacy, safety and tolerability of laquinimod at a dose of 0.6 mg/day versus placebo in the treatment of RRMS.[28] The recruitment phase was completed in November, 2008, with 1,107 patients at 152 centres in 25 countries.[29] The primary endpoint is the number of outbreaks during the double-blind period. The secondary endpoints included the sustained progression time on the EDSS scale and the results of the MRI after 12 and 24 months. The trial subjects will reach 24 months of follow-up before the end of the summer of 2010, with the possibility of an extension phase to 30 months of treatment.

Study LAQ/302 – Bravo This trial started in April, 2008, and has completed the recruitment of 1,300 patients.[30] This international, multi-centric, randomized trial attempts to compare the effect of oral treatment with a dose of 0.6 mg/day of laquinimod and two other groups: IFNβ1a or placebo in patients with RRMS. The primary endpoint of the

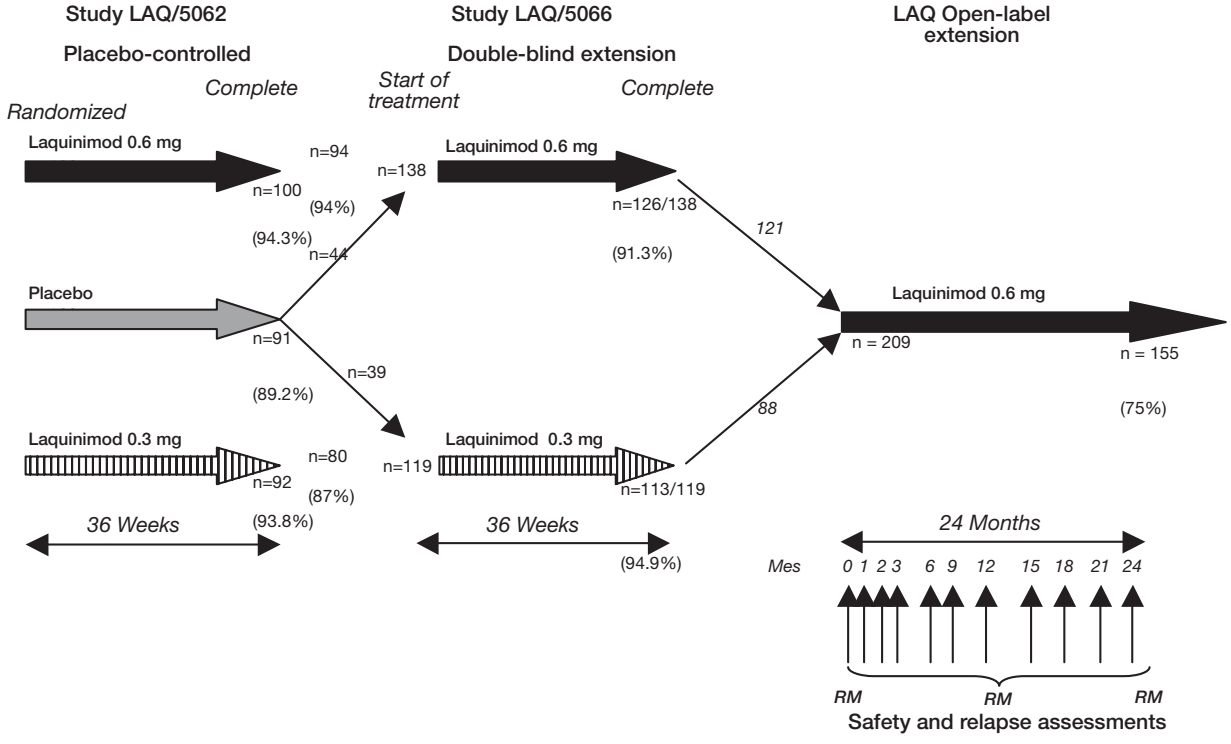

Figure 1 Design of the Phase II studies with laquinimod.
Taken from Comi G et al. (for the LAQ/5063 Study Group). ECTRIMS 2009. Poster 443.

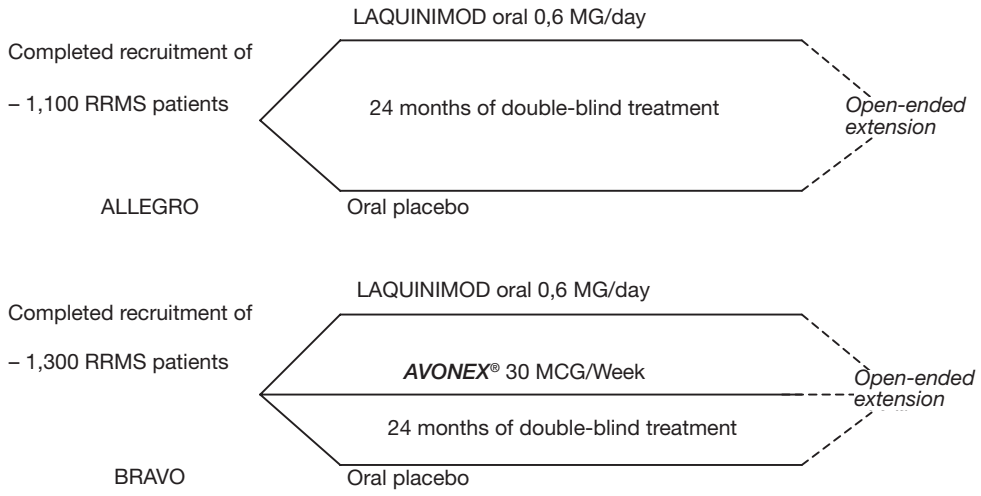

Figure 2 Design of the pivot clinical trials with laquinimod.

trial is the annual rate of outbreaks after 24 months with treatment, together with the accumulated disability and the results of the brain MRIs as secondary endpoints.

The design of the Phase II studies is shown in figure 2.

Safety and tolerability

In general, all the doses of laquinimod used in Phase II trials were well tolerated with ~ 95% of patients completing the study periods in accordance with the protocol. The main safety concerns were the elevated levels of hepatic enzymes and the possible pro-inflammatory effects. There were no clinical or laboratory signs of undesirable inflammatory events (serositis), myocardial infarction, thrombosis or pulmonary embolism. There was one case of thrombosis with obstruction of the venous flow in the liver (Budd-Chiari syndrome) which occurred after 1 month of treatment with laquinimod at a dose of 0.6 mg/day in a patient with a prior history of hypercoagulability (heterozygotic for the mutation of Leyden factor V). The increases in liver enzymes were dose-dependent and reversible. There was no evidence of severe cardiac adverse events, nor any electrocardiographic alterations[26].

Regulatory status

A submission has been made to the FDA for a new investigative drug. The FDA awarded laquinimod the status of fast track review in February, 2009, for the treatment of RRMS.[29] Clinical trials are under way to prove laquinimod's efficacy in the treatment of Crohn's disease.

Conclusions

Laquinimod is a derivative of a synthetic 3-carboxamide quinolein with immunomodulating properties. Treatment with laquinimod is effective in the reduction of the severity of the illness, reducing inflammation, demyelinization and axonal damage in the EAE animal model for MS.[15,22] Laquinimod is administered orally once a day. Phase III trials have begun and it might become an alternative to the current first-line injectable treatments to alter the progression of RRMS. Knowing how it will be positioned among the existing and future therapies will depend on a balance that must be struck between considerations of the safety, efficacy and tolerability of laquinimod versus other drugs. On the basis of the available data, its excellent tolerability, with a single daily dose, gives laquinimod an advantage among future oral drugs. Safety was very good in Phase II trials. There are no signs of irreversible side effects with a dose of 0.6 mg/day.

Conflict of interest

The author has received professional fees as a consultant, moderator and speaker at meetings and has participated, and continues to participate, in clinical trials and other research projects sponsored by Teva, Bayer-Schering; Merck-Serono, Biogen-Idec and Novartis. He is currently taking part in a Phase III clinical trial of laquinimod as the principal investigator at his centre.

References

1. National Multiple Sclerosis Society. Who gets MS? [Accessed 15/3/2009]. Available at: http://www.nationalmssociety.org/about-multiple-sclerosis/who-gets-ms/index.aspx.
2. Atlas of Multiple Sclerosis database. [Accessed 15/3/2009]. Available at: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx.
3. Modrego PJ, Pina M.A. Trends in prevalence and incidence of multiple sclerosis in Bajo Aragón, Spain. J Neurol Sci. 2003;216:89-93.
4. Aladro Y, Alemany MJ, Pérez-Vieitez MC, Amela R, Conde M, Reyes MP, et al. Prevalence and incidence of multiple sclerosis in Las Palmas, Canary Islands, Spain. Neuroepidemiology. 2005;24:70-5.
5. Ares B, Prieto JM, Lema M, Dapena D, Arias M, Noya M. Prevalence of multiple sclerosis in Santiago de Compostela (Galicia, Spain). Mult Scler. 2007;13:262-4.

6. Pascual AM, Téllez N, Boscá I, Mallada J, Belenguer A, Abellán I, et al. Revision of the risk of secondary leukaemia after mitoxantrone in multiple sclerosis populations is required. Mult Scler. 2009;15:1303-10.
7. Wolinsky JS, Narayana PA, Noseworthy JH, Lublin FD, Whitaker JN, Linde A, et al. MRI analysis center of the University of Texas–Houston, health science center, and the North American Linomide investigators. Linomide in relapsing and secondary progressive MS. Part II: MRI results. Neurology. 2000;54:1734-41.
8. 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.
9. Karussis DM, Lehmann D, Slavin S, Vourka-Karussis U, Mizrachi-Koll R, Ovadia H, et al. Inhibition of acute experimental autoimmune encephalomyelitis by the synthetic immunomodulator Linomide. Ann Neurol. 1993;34:654-60.
10. Karussis DM, Lehmann D, Slavin S, Vourka-Karussis U, Mizrachi-Koll R, Ovadia H, et al. Treatment of chronic-relapsing experimental autoimmune encephalomyelitis with the synthetic immunomodulator linomide (quinoline-3-carboxamide). Proc Natl Acad Sci U S A. 1993;90:6400-4.
11. Andersen O, Lycke J, Tollesson PO, Svenningsson A, Runmarker B, Linde AS, et al. Linomide reduces the rate of active lesions in relapsing-remitting multiple sclerosis. Neurology. 1996;47:895-900.
12. Karussis DM, Meiner Z, Lehmann D, Gomori JM, Schwarz A, Linde A, et al. Treatment of secondary progressive multiple sclerosis with the immunomodulator linomide: a double-blind, placebo-controlled pilot study with monthly magnetic resonance imaging evaluation. Neurology. 1996;47:341-6.
13. Wiendl H, Hohlfeld R. Therapeutic approaches in multiple sclerosis: lessons from failed and interrupted treatment trials. BioDrugs. 2002;16:183-200.
14. Yang JS, Xu LY, Xiao BG, Hedlund G, Link H. Laquinimod (ABR-215062) suppresses the development of experimental autoimmune encephalomyelitis, modulates the Th1/Th2 balance and induces the Th3 cytokine TGF-beta in Lewis rats. J Neuroimmunol. 2004;156:3-9.
15. Brunmark C, Runström A, Ohlsson L, Sparre B, Brodin T, Aström M, et al. The new orally active immunoregulator laquinimod (ABR-215062) effectively inhibits development and relapses of experimental autoimmune encephalomyelitis. J Neuroimmunol. 2002;130:163-72.
16. Zou LP, Abbas N, Volkmann I, Nennesmo I, Levi M, Wahren B, 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;42:731-9.
17. Nussbaum S, Snir A, Hayardeny L, Melamed D, Miller A, Toubi E. The immunoregulatory properties of laquinimod on human b cells Neurology 2010;74(9 Suppl 2):P05.503.
18. Gurevich M, Timan B, Hayardeny L, Achiron A. Anti-inflammatory pathways activated by laquinimod in CD4+, CD8+, CD14+, CD19+ and NK peripheral blood cells subtypes of relapsing-remitting multiple sclerosis patients. Multiple Sclerosis. 2009;15(Suppl 9):S31-S150. P264
19. Achiron A. Laquinimod reduces level of Il-7 in cultured splenocytes from treated MOG induced EAE and in cultured PBMCs from healthy human donors. Annual Meeting of the American Academy of Neurology. Chicago, IL. Neurology. 2008;70:A374.
20. Thöne J, Seubert S, Conrad R, Comi G, Wiese S, Hayardeny L, et al. Laquinimod Induces Up-Regulation of BDNF in Serum of Patients with Relapsing-Remitting Multiple Sclerosis. Neurology.2010;74 Suppl 2: PD5.004.
21. Wang J, Silva C, Sloka S, Yong VW. The activation of microglia and macrophages is attenuated by laquinimod. Neurology. 2010;74 Suppl 2: P04.222.
22. Wegner C, Stadelmann C, Brück W. Reduced inflammation, demyelination and axonal damage after therapeutic laquinimod treatment in experimental autoimmune encephalomyelitis. Multiple Sclerosis. 2009;15(Suppl 9):S31-S150. P441
23. Tuvesson H, Hallin I, Persson R, Sparre B, Gunnarsson PO, Seidegård J. Cytochrome P450 3A4 is the major enzyme responsible for the metabolism of laquinimod, a novel immunomodulator. Drug Metab Dispos. 2005;33:866-72.
24. Preiningerova J. Oral laquinimod therapy in relapsing multiple sclerosis. Expert Opin Investig Drugs. 2009;18:985-9.
25. Polman C, Barkhof F, Sandberg-Wollheim M, Linde A, Nordle O, Nederman T, et al. Treatment with laquinimod reduces development of active MRI lesions in relapsing MS. Neurology. 2005;64:987-91.
26. Comi G, Pulizzi A, Rovaris M, Abramsky O, Arbizu T, Boiko A, et al. Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008;371:2085-92.
27. Comi G, Abramsky O, Arbizu T, Boyko A, Gold R, Havrdová E, et al. Oral laquinimod in patients with relapsing-remitting multiple sclerosis: 9-month double-blind active extension of the multicenter, randomized, double-blind, parallel-group placebo-controlled study. Multiple Sclerosis. 2008;14(Suppl 1):S37.
28. Comi G. Safety and efficacy of orally administered laquinimod for treatment of relapsing remitting multiple sclerosis (RRMS) (ALLEGRO). 2008. [Accessed 15/3/2009]. Available at: http://www.clinicaltrial.gov/ct2/show/NCT00509145?term=ALLEGRO&rank=11.
29. Comi G, Jeffery D, Kappos L, Montalban L, Boyko AN, Filippi M. Baseline demographics of a placebo-controlled, double-blind, randomised study of oral laquinimod 0.6mg in treating relapsing-remitting multiple sclerosis: the ALLEGRO study. Multiple Sclerosis. 2009;15(Suppl 9):S127.
30. Vollmer DL, Sorensen PS. BRAVO study: Laquinimod double blind placebo controlled study in RRMS patients with a rater blinded reference arm of interferon B-1a (Avonex). 2009. [Accessed 15/3/2009] Available at: http://www.clinicaltrial.gov/ct2/show/NCT00605215?term=bravo&rank=3.