Central effects of fingolimod

Vítor T. Cruz, Joaquim Fonseca

Introduction. Fingolimod, a sphingosine-1-phosphate receptor modulator, was the first oral therapy approved for relapsing-remitting multiple sclerosis, and shows a novel mechanism of action. Upon binding to S1P1 receptors in lymphocytes, the selective retention of naïve and central memory T cells in secondary lymphoid tissues is promoted, preventing their egress to the central nervous system (CNS). In addition, fingolimod readily crosses the blood brain barrier, and several reports suggest a direct neuroprotective effect in the CNS.

Aim. To review the available data on the central effects of fingolimod.

Development. Imbalances between damage and repair processes are a reflection of chronic demyelination, axonal degeneration and gliosis, and seem to contribute to multiple sclerosis associated disability. Given fingolimod readily crosses the blood brain barrier, it can exert its action directly on S1P receptors present in CNS cells. Fingolimod occupies S1P receptors in oligodendrocytes, oligodendrocyte precursor cells, astrocytes, microglial cells and neurons, promoting remyelination, neuroprotection, and endogenous regeneration processes. Efficacy results from clinical trials are consistent with a mechanism of action that includes direct effects in CNS cells.

Conclusions. Current evidence suggests that the efficacy of fingolimod in the treatment of Multiple Sclerosis is due to its dual action as an immunomodulatory molecule and as a direct modulator of S1PRs in the CNS. In fact, recent reports propose that fingolimod has neuroprotective effects in several models, and open new avenues of potential therapeutic applications, such as Alzheimer's disease, cerebral malaria, neuroblastoma and neuroprotection in cranial irradiation.

Key words. Astrocytes. Central effects. Fingolimod. Multiple sclerosis. Neurons. Oligodendrocytes.

Neurology Department; Centro Hospitalar de Entre o Douro e Vouga, EPE; Santa Maria da Feira (V.T. Cruz). Clinical Research Office; Health Sciences Department; University of Aveiro (V.T. Cruz). Novartis Farma SA (J. Fonseca). Portugal.

Corresponding author:
Vítor Tedim Cruz, MD. Neurology Department. Centro Hospitalar de Entre o Douro e Vouga, EPE. Rua Dr. Cândido de Pinho. 4520-211 Santa Maria da Feira (Portugal).

Fax:
+351 256 373 867.

E-mail:
vitor.cruz@chedv.min-saude.pt

Conflict of interest:
V.T.C has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Allergan, Bayer (Schering), Biogen-Idec, Merck (Serono), Novartis, Sanofi Aventis, TEVA. His institution has received financial support by unrestricted research grants (Biogen-Idec, Novartis). J.F. is an employee of Novartis Farma S.A.

Accepted:
14.03.14.

How to cite this paper:
Cruz VT, Fonseca J. Central effects of fingolimod. Rev Neurol 2014; 59: 121-8.

Versión española disponible en www.neurologia.com

Introduction

Fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator, was the first oral therapy approved for relapsing-remitting multiple sclerosis (RRMS), showing very promising efficacy and safety results [1-10]. Moreover, given its more convenient administration route, patients initiating fingolimod are more compliant, less likely to discontinue treatment, and discontinue later than patients initiating injectable disease-modifying therapies (DMTs) [11]. *In vivo*, fingolimod is rapidly metabolized by sphingosine kinase (SphK) to its active form, fingolimod-1-phosphate [12], a structural analogue of S1P. Upon receptor binding, the selective retention of naïve and central memory T cells in secondary lymphoid tissues is promoted, therefore preventing their egress to the central nervous system (CNS), where they would cause the inflammatory injuries characteristic of multiple sclerosis (MS) [13,14]. Although this lymphocyte redistribution will cause a reversible lymphopenia, this does not seem to be associated with higher risk of opportunistic and non-opportunistic infections. The two reported cases of severe herpetic infections while using fingolimod need to be confirmed by further studies [15]. Fingolimod is a lipophilic compound that readily crosses the blood-brain barrier (BBB), and several reports suggest a direct neuroprotective effect in the CNS [14,16-22]. This dual action of fingolimod seems relevant in light of recent reports suggesting that MS is as much neurodegenerative as inflammatory, and therapeutic strategies should focus on the protection and repair of the nervous system and not only on the control of inflammation [23]. This paper reviews the available data on the central effects of fingolimod.

Neurodegeneration and disability in multiple sclerosis

Multiple sclerosis is a chronic inflammatory and neurodegenerative pathology, characterized by progressive demyelination resulting from imbalances between damage and repair processes, axonal de-

generation and gliosis [24]. RRMS is a stage of the disease characterized by recurring episodes of neurological deficits or exacerbations of existing deficits (relapses), followed by partial or full recovery (remission), due to the remyelination that still occurs [25]. However, as the disease progresses, this repair ability is lost, leading to the accumulation of injuries and irreversible neurologic deficits, axonal loss, and the consequent loss of brain volume, all contributing to an increased degree of disability [23,26].

Although the pathophysiology of MS remains unclear, it has been proposed that the underlying cause of RRMS is inflammation, whereas the progressive phase is dominated by neurodegeneration, which is at least in part independent from inflammation. Also, in the progressive stage of MS, the inflammatory reaction becomes enclosed within the CNS, protected by an intact BBB, and thus no longer under the control of the peripheral immune system [26]. This may explain the ineffectiveness of immunotherapies at this stage of the disease.

Given the neurodegeneration in MS is directly related to the loss of remyelination ability, protection of cells involved in the remyelination process, such as oligodendrocytes [18], oligodendrocyte precursor cells (OPC) [22], astrocytes [27] and microglial cells [28], as well as neurogenesis promotion [29], should be advantageous.

S1P and S1P receptors

S1P, a zwitterionic endogenous lysophospholipid implicated in several physiological processes, exerts its actions through 5 S1P receptors (S1PR1-5), having affinity for all of them [30]. These receptors are present in several cells, including various CNS cells, and its activation results in different functions, depending both on receptor and cell type [31]. The active form of fingolimod, fingolimod-1-phosphate, is an agonist of S1PR1 and S1PR3-5, having different affinities for these 4 receptors [32], and no affinity for S1PR2 [31]. Fingolimod's anti-inflammatory effect is mediated by S1PR1 in lymphocytes, where binding triggers receptor internalization and is thought to result in functional antagonism [14,30]. The central effects of fingolimod are discussed in the next sections.

S1PRs in the CNS

All S1PRs are present in the CNS, with the exception of S1PR4. However, the type of S1PRs present on different CNS cells is still controversial, given it varies with the cell differentiation stage and activation status. Oligodendrocytes express S1PR1 and S1PR5 and may also express S1PR3, neurons express S1PR1-3 and may also express S1PR5, and astrocytes and microglial cells express all S1P1Rs except S1PR4 [33]. S1PR1 and S1PR3 have been found to be upregulated in MS lesions [34] and one report suggests a disturbance in sphingolipid metabolism in MS patients [35].

Blood-brain barrier

Fingolimod seems to have a direct action on the BBB itself. It has been proposed that, by functionally antagonizing S1P1 and S1P3 receptors in astrocytes, fingolimod could reduce the deleterious effects of increased S1P levels and astrocytes on gap junctions between neural cells, thus helping to restore the gap-junctional communication between astrocytes, neurons and endothelial cells of the BBB [32,36]. Fingolimod activation of S1P1 receptors enhances adherens junction assembly and endothelial barrier integrity [12]. BBB permeability can also be altered by S1PR1 and S1PR3 expressed in cerebral capillaries [37]. However, in an *in vitro* model of human pulmonary endothelial cells, fingolimod's enhancement of barrier function seemed to be independent of both S1P1R and phosphorylation of fingolimod [38]. This apparent variability and heterogeneity of vascular beds raises the question of whether fingolimod actually alters the BBB function.

Oligodendrocytes and OPCs

Oligodendrocyte is the major cell type involved in the remyelination process. Fingolimod exerts direct protective effects on oligodendrocytes [39], promoting their survival including in situations of serum and glucose deprivation [17,18]. Fingolimod promotes remyelination via direct interaction with S1PRs on oligodendrocytes [29,40], an effect also observed in organotypic cell cultures [20]. In cultures of human mature oligodendrocytes, low concentrations of fingolimod promote myelin production, stimulate membrane formation and enhance process extension, while high concentrations have the opposite effect [17,18].

It is thought that the loss of OPCs within MS lesions plays an important role in remyelination failure [41,42]. Fingolimod protects OPCs from apoptosis induced by growth factor deprivation, inflam-

matory chemokines and microglial activation [19,22], promotes remyelination via direct interaction with S1PRs in OPCs [40], regulates OPC differentiation into oligodendrocytes [17] and inhibits OPC migration [18,43], although the latter effect can be prevented if platelet-derived growth factor is used as a chemoattractant [17]. However, the remyelination process may fail at several stages of oligodendrocyte development, and may be associated to a slow response of astrocytes and/or microglial cells to demyelination, regardless of its association to OPC response failure [44].

Astrocytes

Astrocytes are the most abundant cells both in the CNS and in MS lesions [45,46]. Astrocytes promote neuron and oligodendrocyte protection [47], axonal regeneration [45] and myelination [48]. It is thought that astrocytes contribute to MS pathophysiological processes through the secretion of matrix metalloproteinases (MMP) and BBB disruption, secretion of adhesion molecules and chemokines, facilitation of inflammatory cells invasion, and secretion of tumor necrosis factor-alpha (TNFα) and lymphotoxin-α, causing oligodendrocytes death and axonal injury. Also, astrogliosis and glial scar formation, a feature of chronic MS lesions, may interfere with the migration of precursor cells, remyelination and axonal regeneration [49].

Activation of S1PRs leads to astrocyte proliferation, inhibition of inflammatory chemokines release [34,50,51] and increase in the unphosphorylated form of connexin 43, an important protein for neuron survival [52]. In astrocytes, fingolimod decreases the production of the inflammatory chemokine Monocyte Chemotactic Protein-1 (MCP-1) [34], mediates neuroinflammation relevant effects [53], promotes migration [54] and reduces astrogliosis [32,40]. In an adult rat model of lithium-pilocarpine induced epilepsy, fingolimod decreased activation of astrocytes in the hippocampus [55]. These effects seem to be mediated by S1PR1, and suggest a beneficial neurobiological effect of fingolimod, independent of its immunomodulatory mechanism [56].

Microglial cells

The primary function of microglia is the maintenance of tissue homeostasis and the support of regeneration from the earliest stages in the development of demyelinating lesions. Microglia supports remyelination and produces several cytokines and chemokines involved in the activation and recruitment of endogenous OPCs to the lesion site, also providing trophic support during remyelination [28].

Microglial activation is involved in the neurodegeneration of MS progressive types [25], and fingolimod inhibits persistent activation of microglial cells after a demyelinating event, thus promoting remyelination [57]. Moreover, activated microglial cells release proinflammatory cytokines known to be involved in neuroinflammation [28], and fingolimod, via S1PR1, downregulates the production of interleukin-6 (IL-6), interleukin-1beta (IL-1β) and TNFα, while upregulating microglial production of brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GCDNF) [58], thus suggesting a direct effect in microglia's neuroprotective actions [14].

Administration of fingolimod to spinal cord injury models reduces T-lymphocyte infiltration without affecting neutrophil infiltration and microglia activation [59], and in an adult rat model of lithium-pilocarpine induced epilepsy, fingolimod reduced microglial activation in the hippocampus [55].

Taken together, these data suggest a positive role of fingolimod in microglia and consequently in microglia's functions.

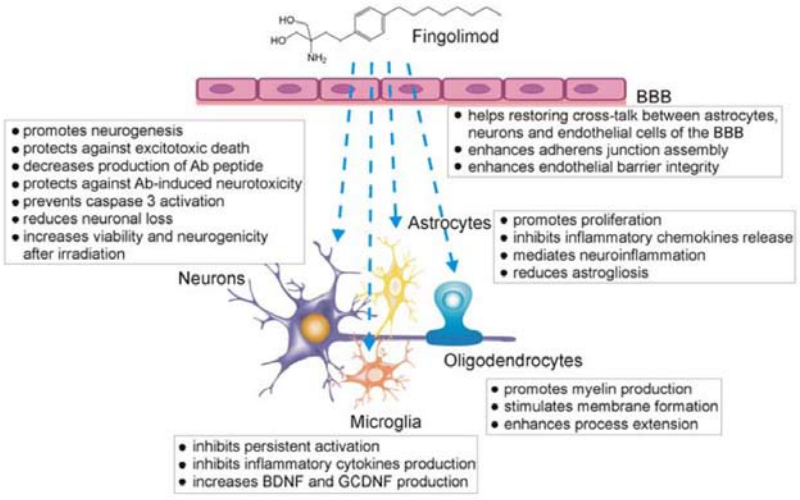
Neuroprotection

The S1P signaling pathway has neuroprotective and pro-cell survival effects during the development phase. S1PRs play a role in neurogenesis and induce proliferation of neuronal progenitor cells in cultures from rat embryonic hippocampus [60], and S1PR1-*knockout* mice show defects in neurogenesis, while the double SphK1/2 *knockout* increases apoptosis in the developing nervous system, disrupts neurogenesis and increases embryonic mortality [61]. S1PR1 enhances neurite extension, while S1PR2 inhibits it [62]. Given fingolimod only occupies S1PR1, having no affinity for S1PR2, it may be speculated that it promotes endogenous repair processes mediated by S1PR1 while inhibiting the detrimental effects mediated by S1PR2 activation.

Within the last few years, both *in vitro* and *in vivo* models have provided evidence in favor of fingolimod's neuroprotection ability.

Fingolimod may have a neuroprotective action, having a positive role in neurite outgrowth and neurogenesis [29]. In vitro, fingolimod protects cortical neurons against excitotoxic death [16] and against oligomeric amyloid beta-induced neurotoxicity, be-

Figure 1. Summary of fingolimod's most relevant effects on the main cell types of the central nervous system. Ab: amyloid-beta; BBB: blood brain barrier; BDNF: brain-derived neurotrophic factor; GCDNF: glial cell-derived neurotrophic factor.



ing the latter mediated by upregulation of neuronal BDNF levels [63]. Fingolimod also decreases production of amyloid-beta peptide by neuronal cells [64]. In a rat model of Alzheimer's disease, fingolimod significantly attenuated the $A\beta_{42}$-induced learning and memory impairment, and prevented hippocampus neuronal damage and caspase-3 activation [65].

Fingolimod has been studied in several variants of experimental autoimmune encephalomyelitis (EAE), preventing the development of clinical and histological disease when used prophylactically, and reversing its manifestations when administered therapeutically after disease onset. Clinical benefits include decreased inflammation [14,66,67], electrophysiological anomalies [68], demyelination and axonal loss [66,67,69-72], synaptic dysfunction [73] and dendritic injury [29], while improving axial and radial diffusivity, which correlate with clinical scores in EAE mice [71]. Genetic knockdown of astrocyte S1PR1 reduces EAE values and prevents the development of astrogliosis, inflammation, demyelination and neuronal loss in the MOG-EAE model [56]. Taken together, these results suggest that fingolimod's functional antagonism of S1PR1 is effective in EAE.

In an adult rat model of lithium-pilocarpine induced epilepsy, fingolimod has been shown to be neuroprotective by reducing neuronal loss, increasing neuronal nuclei positive cells and decreasing fluoro-jade B positive cells in the hippocampus [55].

Administration of fingolimod to spinal cord injury models shortly after injury, significantly increases motor function recovery without affecting the mRNA expression of inflammatory cytokines, reduces vascular permeability and astrogliosis, having similar effects in severely immuno-compromised spinal cord injury model mice [59].

In a Lewis mice model of delayed type hypersensitivity, whose later stages resemble MS in that there is damage to CNS components behind an intact BBB, fingolimod has been shown to reduce the CNS inflammatory response, decreasing demyelination and inhibiting microglial activity [74].

In a model of experimental cerebral malaria, fingolimod inhibited vascular leakage and neurological signs and prolonged survival [75].

Fingolimod has shown preclinical anti-cancer activity in neuroblastoma, acting sinergistically with topotecan [76], and increases viability and neurogenicity of hippocampal neural stem cells after irradiation [77].

However, there is one report in which fingolimod did not promote remyelination in cuprizone and lysolecithin models of demyelination [78], suggesting that fingolimod's remyelination ability depends on the mechanisms leading to demyelination.

Taken together, these results suggest that fingolimod has direct neuroprotective effects in several disease models, and not only in MS.

Figure 1 summarizes fingolimod's most relevant effects on the main cell types of the CNS.

Clinical trials

The central effects of fingolimod have also been supported by the efficacy results demonstrated by clinical trials, showing a significant efficacy in reducing relapse rate, disability progression and disease activity as assessed by MRI [1-7]. The confirmed 37% decrease in disability progression at 6 months, reported by the FREEDOMS study [1], and the significant reduction in inflammatory activity as early as at the second month of treatment [3] are consistent with a mechanism of action that includes direct effects in CNS cells. However, the most relevant data from clinical trials that confirms this possibility is the reduction of brain atrophy rate, already demonstrated in 3 large studies. In fact, the TRANSFORMS [7], FREEDOMS [1] and FREEDOMS II [5] studies, involving a total of 3,647 pa-

tients, have shown that fingolimod reduced the rate of cerebral atrophy by 32% ($p < 0.001$), 35% ($p < 0.001$) and 33% ($p < 0.05$), respectively. The fingolimod-induced reduction of cerebral atrophy was shown to be independent of the presence of inflammatory lesions at baseline (Fig. 2).

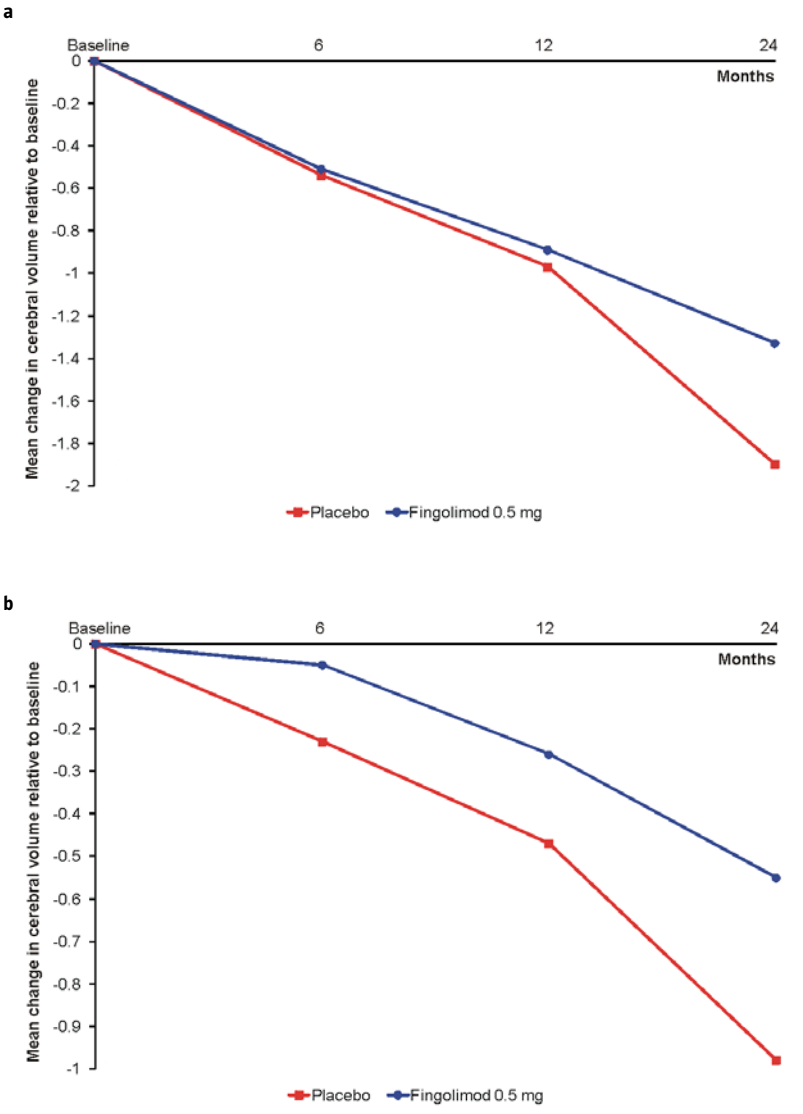
Results from the extension of these studies [8-10], and results of seven years from the phase II study [6], have shown that fingolimod provides a sustained treatment effect, with improved clinical and MRI outcomes, and a tendency of brain atrophy curves from patients treated with fingolimod to resemble the ones from healthy individuals.

Despite its side effects, fingolimod shows efficacy, real-world adherence and tolerability, and some authors have suggested that it is precisely the differential modulation of S1PRs in different cells of the immune, cardiovascular and central nervous systems that may be responsible for fingolimod's efficacy and side effects [30,79], thus supporting the central effects of fingolimod. Nevertheless, continuous research is warranted, not only to unravel fingolimod's underlying mechanisms of action but also to determine its long-term effects. One useful approach that is currently underway in Spain is the establishment of an electronic register of patients with multiple sclerosis who began treatment with fingolimod, which will provide information, in the shortest possible time, concerning the most suitable management of these patients, in order to be able to make the best and most efficient use of fingolimod [80].

Conclusion

The effectiveness of fingolimod in the treatment of MSs seems to go beyond its immunomodulatory effects. Studies in several *in vitro* and *in vivo* models have shown evidence in favor of a direct neuroprotective function of fingolimod, and results from clinical trials are consistent with a mechanism of action that includes direct effects in CNS cells. Moreover, recent reports in different pathologies suggest that fingolimod has neuroprotective effects in several models, and open new avenues of potential therapeutic applications, such as Alzheimer's disease, cerebral malaria, neuroblastoma and neuroprotection in cranial irradiation.

Figure 2. Effects of fingolimod on cerebral volume in patients with (a) and without (b) inflammatory injuries at the beginning of the FREEDOMS study.



References

1. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362: 387-401.
2. Radue EW, O'Connor P, Polman CH, Hohlfeld R, Calabresi P, Selmaj K, et al. Impact of fingolimod therapy on magnetic resonance imaging outcomes in patients with multiple sclerosis. Arch Neurol 2012; 69: 1259-69.
3. Radue EW, Barkhof F, Cohen J, Holdbrook F, Francis G, Kappos L. MRI analyses in RRMS patients with highly active disease: results from FREEDOMS and TRANSFORMS phase 3 studies. Neurology 2012; 78 (Meeting Abstracts 1): P01.134.
4. Cohen JA, Barkhof F, Comi G, Izquierdo G, Khatri B, Montalban X, et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol 2013; 260: 2023-32.

5. Calabresi PA, Radue EW, Goodin D, Jeffery D, Reder AT, Vollmer T, et al. Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis (RRMS): results from an additional 24-month double-blind, placebo-controlled study (FREEDOMS II Study). Presented at the 65th AAN annual meeting Emerging Science Session, 25th April 2012.
6. Antel J, Montalban X, O'Connor P, De Vera A, Cremer M, Sfikas N, et al. Long-term (7-year) data from a phase 2 extension study of fingolimod in relapsing multiple sclerosis. Neurology 2012; 78 (Meeting Abstracts 1): P01.129.
7. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010; 362: 402-15.
8. Khatri B, Barkhof F, Comi G, Hartung HP, Kappos L, Montalban X, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. Lancet Neurol 2011; 10: 520-9.
9. Montalban X, Barkhof F, Comi G, Hartung H, Kappos L, Khatri B, et al. Long-term comparison of fingolimod with interferon-beta-1a: results of 4.5-year follow-up from the extension phase III TRANSFORMS study. Presented at the 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 11th October 2012, Lyon, France (Poster P517). 2012.
10. O'Connor P, Polman C, Hohlfeld R, Selmaj K, Olsson T, Agoropoulou C, et al. Phase III FREEDOMS study extension: long-term safety of fingolimod (FTY720) in relapsing-remitting multiple sclerosis. Presented at the 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 11th October 2012, Lyon, France (Poster P523). 2012.
11. Agashivala N, Wu N, Abouzaid S, Wu Y, Kim E, Boulanger L, et al. Compliance to fingolimod and other disease modifying treatments in multiple sclerosis patients, a retrospective cohort study. BMC Neurol 2013; 13: 138.
12. Brinkmann V, Cyster JG, Hla T. FTY720: sphingosine 1-phosphate receptor-1 in the control of lymphocyte egress and endothelial barrier function. Am J Transplant 2004; 4: 1019-25.
13. Chun J, Hartung H-P. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. Clin Neuropharmacol 2010; 33: 91-101.
14. García-Merino JA, Sánchez AJ. Mecanismos básicos de acción del fingolimod en relación con la esclerosis múltiple. Rev Neurol 2012; 55: 31-7.
15. Cervera C. Infections y fingolimod. Rev Neurol 2012; 55: 227-37.
16. Di Menna L, Molinaro G, Di Nuzzo L, Riozzi B, Zappulla C, Pozzilli C, et al. Fingolimod protects cultured cortical neurons against excitotoxic death. Pharmacol Res 2013; 67: 1-9.
17. Jung CG, Kim HJ, Miron VE, Cook S, Kennedy TE, Foster CA, et al. Functional consequences of S1P receptor modulation in rat oligodendroglial lineage cells. Glia 2007; 55: 1656-67.
18. Miron VE, Hall JA, Kennedy TE, Soliven B, Antel JP. Cyclical and dose-dependent responses of adult human mature oligodendrocytes to fingolimod. Am J Pathol 2008; 173: 1143-52.
19. Miron VE, Jung CG, Kim HJ, Kennedy TE, Soliven B, Antel JP. FTY720 modulates human oligodendrocyte progenitor process extension and survival. Ann Neurol 2008; 63: 61-71.
20. Miron VE, Ludwin SK, Darlington PJ, Jarjour A, Soliven B, Kennedy TE, et al. Fingolimod (FTY720) enhances remyelination following demyelination of organotypic cerebellar slices. Am J Pathol 2010; 176: 2682-94.
21. Miron VE, Schubart A, Antel JP. Central nervous system-directed effects of FTY720 (fingolimod). J Neurol Sci 2008; 274: 13-7.
22. Coelho RP, Payne SG, Bittman R, Spiegel S, Sato-Bigbee C. The immunomodulator FTY720 has a direct cytoprotective effect in oligodendrocyte progenitors. J Pharmacol Exp Ther 2007; 323: 626-35.
23. Confavreux C, Vukusic S. Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment. Clin Neurol Neurosurg 2006; 108: 327-32.
24. McQualter JL, Bernard CC. Multiple sclerosis: a battle between destruction and repair. J Neurochem 2007; 100: 295-306.
25. Compston A, Coles A. Multiple sclerosis. Lancet 2008; 372: 1502-17.
26. Lassmann H, Bruck W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. Brain Pathol 2007; 17: 210-8.
27. Kipp M, Gingele S, Pott F, Clarner T, Van der Valk P, Denecke B, et al. BLBP-expression in astrocytes during experimental demyelination and in human multiple sclerosis lesions. Brain Behav Immun 2011; 25: 1554-68.
28. Olah M, Amor S, Brouwer N, Vinet J, Eggen B, Biber K, et al. Identification of a microglia phenotype supportive of remyelination. Glia 2012; 60: 306-21.
29. Dev KK, Mullershausen F, Mattes H, Kuhn RR, Bilbe G, Hoyer D, et al. Brain sphingosine-1-phosphate receptors: implication for FTY720 in the treatment of multiple sclerosis. Pharmacol Ther 2008; 117: 77-93.
30. O'Sullivan C, Dev KK. The structure and function of the S1P1 receptor. Trends Pharmacol Sci 2013; 34: 401-12.
31. Gasperini C, Ruggieri S, Mancinelli CR, Pozzilli C. Advances in the treatment of relapsing-remitting multiple sclerosis –critical appraisal of fingolimod. Ther Clin Risk Manag 2013; 9: 73-85.
32. Fazekas F, Bajenaru O, Berger T, Fabjan TH, Ledinek AH, Jakab G, et al. How does fingolimod (Gilenya ®) fit in the treatment algorithm for highly active relapsing-remitting multiple sclerosis? Front Neurol 2013; 4: 10.
33. Groves A, Kihara Y, Chun J. Fingolimod: direct CNS effects of sphingosine 1-phosphate (S1P) receptor modulation and implications in multiple sclerosis therapy. J Neurol Sci 2013; 328: 9-18.
34. Van Doorn R, Van Horssen J, Verzijl D, Witte M, Ronken E, Van Het Hof B, et al. Sphingosine 1-phosphate receptor 1 and 3 are upregulated in multiple sclerosis lesions. Glia 2010; 58: 1465-76.
35. Wheeler D, Bandaru VV, Calabresi PA, Nath A, Haughey NJ. A defect of sphingolipid metabolism modifies the properties of normal appearing white matter in multiple sclerosis. Brain 2008; 131: 3092-102.
36. Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. Br J Pharmacol 2009; 158: 1173-82.
37. Pilorget A, Demeule M, Barakat S, Marvaldi J, Luis J, Béliveau R. Modulation of P-glycoprotein function by sphingosine kinase-1 in brain endothelial cells. J Neurochem 2007; 100: 1203-10.
38. Dudek SM, Camp SM, Chiang ET, Singleton PA, Usatyuk PV, Zhao Y, et al. Pulmonary endothelial cell barrier enhancement by FTY720 does not require the S1P1 receptor. Cell Signal 2007; 19: 1754-64.
39. Melzer N, Meuth SG. Disease-modifying therapy in multiple sclerosis and chronic inflammatory demyelinating polyradiculoneuropathy: common and divergent current and future strategies. Clin Exp Immunol 2014; 175: 359-72.
40. Thone J, Ellrichmann G. Oral available agents in the treatment of relapsing remitting multiple sclerosis: an overview of merits and culprits. Drug Health Patient Saf 2013; 5: 37-47.
41. Prineas JW, Barnard RO, Kwon EE, Sharer LR, Cho ES. Multiple sclerosis: remyelination of nascent lesions. Ann Neurol 1993; 33: 137-51.
42. Prineas JW, Barnard RO, Revesz T, Kwon EE, Sharer L, Cho ES. Multiple sclerosis. Pathology of recurrent lesions. Brain 1993; 116: 681-93.
43. Novgorodov AS, El-Alwani M, Bielawski J, Obeid LM, Gudz TI. Activation of sphingosine-1-phosphate receptor S1P5 inhibits oligodendrocyte progenitor migration. FASEB J 2007; 21: 1503-14.
44. Kipp M, Amor S. FTY720 on the way from the base camp to the summit of the mountain: relevance for remyelination. Mult Scler 2012; 18: 258-63.
45. Nair A, Frederick TJ, Miller SD. Astrocytes in multiple sclerosis:

a product of their environment. Cell Mol Life Sci 2008; 65: 2702-20.
46. Williams A, Piaton G, Lubetzki C. Astrocytes –friends or foes in multiple sclerosis? Glia 2007; 55: 1300-12.
47. Sofroniew MV. Reactive astrocytes in neural repair and protection. Neuroscientist 2005; 11: 400-7.
48. Ishibashi T, Dakin KA, Stevens B, Lee PR, Kozlov SV, Stewart CL, et al. Astrocytes promote myelination in response to electrical impulses. Neuron 2006; 49: 823-32.
49. Cohen JA, Chun J. Mechanisms of fingolimod's efficacy and adverse effects in multiple sclerosis. Ann Neurol 2011; 69: 759-77.
50. Bassi R, Anelli V, Giussani P, Tettamanti G, Viani P, Riboni L. Sphingosine-1-phosphate is released by cerebellar astrocytes in response to bFGF and induces astrocyte proliferation through Gi-protein-coupled receptors. Glia 2006; 53: 621-30.
51. Sheridan GK, Dev KK. S1P1 receptor subtype inhibits demyelination and regulates chemokine release in cerebellar slice cultures. Glia 2012; 60: 382-92.
52. Rouach N, Pébay A, Même W, Cordier J, Ezan P, Etienne E, et al. S1P inhibits gap junctions in astrocytes: involvement of G and Rho GTPase/ROCK. Eur J Neurosci 2006; 23: 1453-64.
53. Wu C, Leong SY, Moore CS, Cui QL, Gris P, Bernier LP, et al. Dual effects of daily FTY720 on human astrocytes in vitro: relevance for neuroinflammation. J Neuroinflammation 2013; 10: 41.
54. Mullershausen F, Craveiro LM, Shin Y, Cortes-Cros M, Bassilana F, Osinde M, et al. Phosphorylated FTY720 promotes astrocyte migration through sphingosine-1-phosphate receptors. J Neurochem 2007; 102: 1151-61.
55. Gao F, Liu Y, Li X, Wang Y, Wei D, Jiang W. Fingolimod (FTY720) inhibits neuroinflammation and attenuates spontaneous convulsions in lithium-pilocarpine induced status epilepticus in rat model. Pharmacol Biochem Behav 2012; 103: 187-96.
56. Choi JW, Gardell SE, Herr DR, Rivera R, Lee CW, Noguchi K, et al. FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. Proc Natl Acad Sci U S A 2011; 108: 751-6.
57. Jackson SJ, Giovannoni G, Baker D. Fingolimod modulates microglial activation to augment markers of remyelination. J Neuroinflammation 2011; 8: 76.
58. Noda H, Takeuchi H, Mizuno T, Suzumura A. Fingolimod phosphate promotes the neuroprotective effects of microglia. J Neuroimmunol 2013; 256: 13-8.
59. Norimatsu Y, Ohmori T, Kimura A, Madoiwa S, Mimuro J, Seichi A, et al. FTY720 improves functional recovery after spinal cord injury by primarily nonimmunomodulatory mechanisms. Am J Pathol 2012; 180: 1625-35.
60. Harada J, Foley M, Moskowitz MA, Waeber C. Sphingosine-1-phosphate induces proliferation and morphological changes of neural progenitor cells. J Neurochem 2004; 88: 1026-39.
61. Mizugishi K, Yamashita T, Olivera A, Miller GF, Spiegel S, Proia RL. Essential role for sphingosine kinases in neural and vascular development. Mol Cell Biol 2005; 25: 11113-21.
62. Toman RE, Payne SG, Watterson KR, Maceyka M, Lee NH, Milstien S, et al. Differential transactivation of sphingosine-1-phosphate receptors modulates NGF-induced neurite extension. J Cell Biol 2004; 166: 381-92.
63. Doi Y, Takeuchi H, Horiuchi H, Hanyu T, Kawanokuchi J, Jin S, et al. Fingolimod phosphate attenuates oligomeric amyloid beta-induced neurotoxicity via increased brain-derived neurotrophic factor expression in neurons. PLoS One 2013; 8: e61988.
64. Takasugi N, Sasaki T, Ebinuma I, Osawa S, Isshiki H, Takeo K, et al. FTY720/fingolimod, a sphingosine analogue, reduces amyloid-beta production in neurons. PLoS One 2013; 8: e64050.
65. Asle-Rousta M, Kolahdooz Z, Oryan S, Ahmadiani A, Dargahi L. FTY720 (fingolimod) attenuates beta-amyloid peptide (Abeta42)-induced impairment of spatial learning and memory in rats. J Mol Neurosci 2013; 50: 524-32.
66. Foster CA, Howard LM, Schweitzer A, Persohn E, Hiestand PC, Reuschel R, et al. Brain penetration of the oral immunomodulatory drug FTY720 and its phosphorylation in the central nervous system during experimental autoimmune encephalomyelitis: consequences for mode of action in multiple sclerosis. J Pharmacol Exp Ther 2007; 323: 469-76.
67. Foster CA, Mechtcheriakova D, Storch MK, Balatoni B, Howard LM, Bornancin F, et al. FTY720 rescue therapy in the dark agouti rat model of experimental autoimmune encephalomyelitis: expression of central nervous system genes and reversal of blood-brain-barrier damage. Brain Pathol 2009; 19: 254-66.
68. Balatoni B, Storch MK, Swoboda EM, Schönborn V, Koziel A, Lambrou GN, et al. FTY720 sustains and restores neuronal function in the DA rat model of MOG-induced experimental autoimmune encephalomyelitis. Brain Res Bull 2007; 74: 307-16.
69. Papadopoulos D, Rundle J, Patel R, Marshall I, Stretton J, Eaton R, et al. FTY720 ameliorates MOG-induced experimental autoimmune encephalomyelitis by suppressing both cellular and humoral immune responses. J Neurosci Res 2010; 88: 346-59.
70. Schubart AS, Howard L, Seabrook T. FTY720 suppresses ongoing EAE and promotes a remyelinating environment preventing axonal degeneration within the CNS. Neurology 2008; 70 (Suppl 1): A339.
71. Wang X, Brieland JK, Kim JH, Chen YJ, O'Neal J, O'Neil SP, et al. Diffusion tensor imaging detects treatment effects of FTY720 in experimental autoimmune encephalomyelitis mice. NMR Biomed 2013; 26: 1742-50.
72. Schubart A, Seabrook T, Rausch M. CNS mediated effects of FTY720 (fingolimod). Neurology 2007; 68 (Suppl 1): S315.
73. Rossi S, Giudice TL, De Chiara V, Musella A, Studer V, Centonze D. Oral fingolimod rescues the functional deficits of synapses in experimental autoimmune encephalomyelitis. Br J Pharmacol 2012; 165: 861-9.
74. Anthony DC, Sibson NR, Leppert D, Piani-Meier D. Fingolimod (FTY720) therapy reduces demyelination and microglial activation in a focal delayed-type hypersensitivity model of multiple sclerosis during the remission phase. Mult Scler 2010; 16 (Suppl 10): S283-4.
75. Nacer A, Movila A, Baer K, Mikolajczak SA, Kappe SH, Frevert U. Neuroimmunological blood brain barrier opening in experimental cerebral malaria. PLoS Pathog 2012; 8: e1002982.
76. Li MH, Hla T, Ferrer F. FTY720 inhibits tumor growth and enhances the tumor-suppressive effect of topotecan in neuroblastoma by interfering with the sphingolipid signaling pathway. Pediatr Blood Cancer 2013; 60: 1418-23.
77. Stessin AM, Gursel DB, Schwartz A, Parashar B, Kulidzhanov FG, Sabbas AM, et al. FTY720, sphingosine 1-phosphate receptor modulator, selectively radioprotects hippocampal neural stem cells. Neurosci Lett 2012; 516: 253-8.
78. Hu Y, Lee X, Ji B, Guckian K, Apicco D, Pepinsky RB, et al. Sphingosine 1-phosphate receptor modulator fingolimod (FTY720) does not promote remyelination in vivo. Mol Cell Neurosci 2011; 48: 72-81.
79. Soliven B, Miron VE, Chun J. The neurobiology of sphingosine 1-phosphate signaling and sphingosine 1-phosphate receptor modulators. Neurology 2011; 76 (Suppl 3): S9-14.
80. Fernández O, Rodríguez-Antigüedad A, Oreja-Guevara C, García-García M, Montalban X. Utilidad de los registros electrónicos de medicamentos: registro español de pacientes tratados con fingolimod (Gilenya®). Rev Neurol 2014; 58: 77-83.

Efectos del fingolimod en el sistema nervioso central

Introducción. El fingolimod, un modulador del receptor de la esfingosina-1-fosfato (S1P) dotado de un mecanismo de acción novedoso, fue el primer tratamiento oral aprobado para la esclerosis múltiple remitente recurrente. Su unión a los receptores S1P1 de los linfocitos promueve la retención selectiva de los linfocitos T vírgenes y de memoria central en los tejidos linfoides secundarios, lo que impide su salida hacia el sistema nervioso central (SNC). Asimismo, el fingolimod atraviesa con facilidad la barrera hematoencefálica, y diversos estudios le atribuyen un efecto neuroprotector directo en el SNC.

Objetivo. Revisar la información disponible acerca de los efectos centrales del fingolimod.

Desarrollo. El desequilibrio entre los procesos lesivos y reparadores constituye un reflejo de la desmielinización crónica, la degeneración axonal y la gliosis, y parece contribuir a la discapacidad que la esclerosis múltiple acarrea. La facilidad con la que el fingolimod atraviesa la barrera hematoencefálica le permite actuar directamente sobre los receptores S1P localizados en las células del SNC. Una vez en el interior del SNC, ocupa los receptores S1P de los oligodendrocitos y de sus células precursoras, de los astrocitos, los microgliocitos y las neuronas, fomentando la remielinización, la neuroprotección y los procesos endógenos de regeneración. La eficacia evidenciada en los ensayos clínicos concuerda con un mecanismo de acción que incluiría efectos directos sobre las células del SNC.

Conclusiones. Los datos disponibles indican que la eficacia del fingolimod en el tratamiento de la esclerosis múltiple se debe a su ambivalencia como molécula inmunomoduladora y moduladora directa de los receptores S1P del SNC. Tanto es así que estudios recientes le atribuyen efectos neuroprotectores en varios modelos que suscitan expectativas en torno a su posible aplicación terapéutica en la enfermedad de Alzheimer, el paludismo cerebral y el neuroblastoma, así como en la neuroprotección frente a la radioterapia craneal.

Palabras clave. Astrocitos. Efectos centrales. Esclerosis múltiple. Fingolimod. Neuronas. Oligodendrocitos.