Adv Ther (2011) 28(4):270-278.
DOI 10.1007/s12325-011-0004-6

REVIEW

Fingolimod: an Oral Disease-Modifying Therapy for Relapsing Multiple Sclerosis

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Received: November 30, 2010 / Published online: March 7, 2011

ABSTRACT

This paper presents a summary of the current knowledge of the mechanism of action of fingolimod (FTY720; Gilenya®; Novartis Pharma Stein AG, Stein, Switzerland) and the phase 2 and 3 studies that have been performed on the drug. This study will discuss specific safety issues that should be considered when initiating this therapy. Multiple sclerosis (MS), an inflammatory disease of the central nervous system, is considered to be a leading cause of neurologic disability in young adults, and predominantly affects young women. The past two decades have seen significant growth in therapeutic options for relapsing forms of MS, including FTY720. Fingolimod (FTY720) is a sphingosine-1-phosphate receptor modulator, and currently the approved dosage is 0.5 mg daily. Notable side effects include bradycardia in the first hours after administration and macular edema. There may be an increased risk of herpetic infections (varicella zoster virus and herpes simplex virus) associated with this medication. This oral therapy has been shown to be effective in double-blind, placebo-controlled studies, and in trials comparing it to weekly interferon beta-1a therapy. However, the long-term efficacy and safety of this oral medication in relapsing MS, including the effect on reduction of disability progression and cognitive decline, remains to be established.

Keywords: fingolimod; multiple sclerosis; sphingosine-1-phosphate receptor modulator

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INTRODUCTION

Multiple sclerosis (MS), an inflammatory disease of the central nervous system, is considered to be a leading cause of neurologic disability in young adults, and predominantly affects young women.[1] Disease onset typically occurs in the third decade of life. The majority of patients (75%-80%) are affected by a disease course characterized by intermittent relapses followed by quiescent periods (relapsing-remitting MS [RRMS]). In general, 10-15 years

after disease onset, up to 50% of MS patients undergo progressive deterioration with or without additional superimposed acute attacks (secondary progressive MS [SPMS]).[2] Up to 20% of patients are classified as having primary progressive MS (PPMS), which presents with relentless disease progression from the onset of disease.[1,2]

The past two decades have seen significant growth in the therapeutic options for relapsing forms of MS (RRMS and SPMS), including the approval of multiple disease-modifying therapies (DMT): four considered to be first-line therapies (glatiramer acetate [GA; Copaxone®; TEVA Neuroscience Inc., Kansas City, MO, USA], intramuscular [IM] interferon beta-1a [Avonex®; Biogen Idec, Cambridge, MA, USA], subcutaneous [SC] interferon beta-1a [Rebif®; EMD Serono Inc., Rockland, MA, USA], and SC interferon beta-1b [Betaseron®; Bayer Healthcare Pharmaceuticals Inc., Montville, NJ, USA]) and two second-line therapies (mitoxantrone [Novantrone®; EMD Serono Inc.] and natalizumab [Tysabri®; Biogen Idec Inc.]). In addition, therapies such as alemtuzumab (Campath®; Genzyme Corporation, Cambridge, MA, USA), rituximab (Rituxan®; Genentech Inc., South San Francisco, CA, USA), daclizumab (Zenapax®; Roche Inc., Nutley, NJ, USA), and cyclophosphamide (Cytoxan®; Bristol-Myers Squibb Co., Mead Johnson and Co., Somerville, NJ, USA) have been evaluated in phase 2 trials in adults with breakthrough disease.[3-8] However, it is widely accepted that currently approved therapies for MS are only partially effective, and some may carry significant potential side effects. Furthermore, limitations in patient comfort and medication adherence exist, as until this year, the US Food and Drug Administration (FDA)-approved first-line therapies were only available in intravenous (IV), SC, and IM formulations.

Recently, fingolimod (FTY720; Gilenya®, Novartis Pharma Stein AG, Stein, Switzerland), became the first oral medication in the United States (US) to receive FDA approval for relapsing forms of MS.[9-11] This paper will present a short summary of current knowledge about the mechanism of action of FTY720 and the phase 2 and 3 studies that have been performed on this drug. It will discuss specific safety issues that should be considered when initiating this therapy.

FINGOLIMOD: MECHANISM OF ACTION

Fingolimod (FTY720) is derived from myriocin (ISP-1), which is a substance isolated from a vegetative wasp. This was originally used in traditional Chinese medicine as an antiaging elixir.[12] It was described as an antifungal antibiotic in the 1970s.[13] Potent immunosuppressive activity was described in relation to ISP-1 in vitro two decades later, suggesting immunosuppressive activity 10 to 100 times greater than cyclosporin A.[14] In 1992, the structure of ISP-1 was altered, resulting in the development of FTY720.[12]

Fingolimod (FTY720) is structurally similar to sphingosine, a cell membrane lipid that becomes a signaling protein after it is phosphorylated by one of two kinases that have multiple splice variants in different cells. Sphingosine-1-phosphate (S1P) regulates cell growth, movement and survival, angiogenesis and vascular maturation, enhances wound healing in diabetic mice, and has pronounced effects on immune function and lymphocyte trafficking.[15-17]

Plasma levels of S1P are generally higher than that in tissues, and up to 2000 times more than in the lymph nodes.[18] S1P is released by platelets, and during inflammation increases in levels of S1P may be associated with activation

by interleukin-1, tumor necrosis factor, and vascular endothelial growth factor.[19] S1P has been shown to maintain endothelial integrity.

S1P is known to bind to five G-protein-coupled receptors (S1P1-5).[20] After the binding of S1P to one of its receptors, the receptor is endocytosed, recycled through endosomes, and reexpressed on the cell surface. FTY720-phosphate (FTY720-P) binds strongly to S1P1, S1P4, and S1P5 receptors, and binds one-tenth as strongly to S1P3. FTY720-P-receptor complex is then internalized into lysosomes and degraded in the proteasome and therefore, after its binding, the receptor is not reexpressed. The end result in target cells is loss of response to S1P ("functional antagonism").

Animal data on the use of FTY720 for immunosuppression, specifically in the area of transplantation, emerged in the 1990s. Several years later, data that FTY720 was effective in experimental autoimmune encephalomyelitis (EAE) in mice emerged, including cases of relapsing-remitting EAE, a model that closely approximates RRMS; this provided conceptual support to initiate clinical trials of FTY720 in MS.[21-23] Use of FTY720 results in lymphopenia (a 70% decrease in circulating lymphocytes), secondary to the redistribution of circulating white blood cells. Finglomod (FTY720) is concentrated in lymph nodes and primarily affects T cells (CD4+CD8+). The most affected CD4 cells are T_H17 (helper T cell subtype 17), naive T cells (T_N; CCR7+CD45RA+) and central memory T cells (T_{CM}; CCR7+CD45RA–). T_H17 cells are important effectors in EAE and possibly in MS. T_{CM}, which contain the T_H17 subpopulation, are reduced by >90%.[24] Under normal conditions, T_N and T_{CM} are activated by antigens in lymph nodes and then migrate towards the source of the antigen. However, some T cells are not retained in lymph nodes during FTY720 therapy, including effector memory T cells (T_{EM}; CCR7–CD45RA±). T_{EM} are educated and specific for invading pathogens, and continue to migrate to peripheral tissues, acting as immune sentinels against pathogens and tumors. Regulatory T cells (T_{reg}, CD4CD25+) express only low levels of S1P1 and S1P4 receptors, and are not retained. In mice[25,26] and in culture[27] FTY720 increases the amount of blood T_{reg} cells and their suppressor function. Long-term FTY720 treatment, however, may reduce T_{reg} numbers and their function in the blood.[18,28]

In the heart, FTY720 affects S1P1 and S1P3, slowing the heart rate (HR). Cardiac potassium channel (K_{Ach}) receptors are also activated, but soon compensate, and the HR rebounds back to baseline levels within 3 to 4 hours. A second dose of FTY720 has minimal or no effect on HR. Bradycardia may reappear after discontinuation of FTY720 for ≥2 weeks. In endothelial cells, FTY720 prevents S1P1 from activating endogenous nitric oxide synthase (NOS), which otherwise leads to vasodilation. For this reason, vascular tone and blood pressure increase slightly with FTY720 therapy.[29-33]

CLINICAL TRIALS

Phase 2 Data

The safety and efficacy of FTY720 was evaluated in a phase 2, 6-month proof of concept study that randomly assigned 281 patients to receive oral FTY720 at a dose of 1.25 mg or 5 mg or placebo once daily.[34] Twenty-four and 36 month extension data from this study were subsequently published.

Both magnetic resonance imaging (MRI) and clinical relapse data from this study suggested benefit with FTY720: the median total number of gadolinium-enhanced (Gd+) lesions on MRI was lower with FTY720 (one lesion

for 1.25 mg [P<0.001] and three lesions for 5 mg of FTY720 [P=0.006]), as compared with placebo (five lesions) at 6 months. At month 6, the proportion of patients who were free of Gd+ lesions was greater in both FTY720 groups than in the placebo group (P<0.001 for both comparisons), with a separation between the curves becoming evident from 2 months onward. In addition, the annualized relapse rate (ARR) was 0.77 in the placebo group, as compared with 0.35 in the group given 1.25 mg of FTY720 (P=0.009) and 0.36 in the group given 5 mg of FTY720 (P=0.010).

The 24- and 36-month extensions of this study, in which all patients that were enrolled (89% from the core study) were treated with FTY720 1.25 mg, showed that at 24 months, 79%-91% of patients were free from Gd+ lesions. At 36 months, most were free from Gd+ lesions (88%-89%) or new T2 lesions (70%-78%).[35,36] There were no significant differences seen between patients treated continuously with FTY720 1.25 mg, or who were switched from 5 mg to 1.25 mg regarding the number of Gd+ or new T2 lesions, or in the proportion of patients who were free from Gd+ lesions or new T2 lesions at months 6, 12, or 24 (P≤0.05 for all comparisons). At month 6, ARR was significantly lower in patients assigned to FTY720 than in placebo-treated patients (relative reduction of 55% for FTY720 1.25 mg and 53% for FTY720 5 mg; P≤0.01 for both comparisons), and remained low during the extension phase (ARR: 0.14 to 0.17).

In placebo to FTY720 patients, ARR decreased markedly during the first 6 months of the extension (from 0.70 [core] to 0.21 [extension] for FTY720 1.25 mg and from 0.69 to 0.10 for 5 mg during months 7 to 12), remaining low throughout the extension (ARR for months 7 to 24: 0.12 to 0.26, respectively). At month 24, most patients in the continuous FTY720 groups were relapse free (75%-77%).

Kaplan-Meier estimates of the proportion of patients relapse free at month 36 were 68% in the FTY720 1.25 mg group and 73% in the FTY720 5/1.25 mg group. Fifty-one percent of patients in the placebo to FTY720 group were relapse-free.[35]

These studies did not show any effect on disability. Kurtzke Expended Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) scores at month 12 were similar across groups and remained stable at month 24 and 36. The proportion of patients with 3-month confirmed disability progression at any time during the extension was similar in all groups: 17.1% for 1.25 mg FTY720, 24.7% for 5 mg FTY720, 18.9% for placebo to 1.25 mg FTY720, and 25.6% for placebo to 5 mg FTY720.

Phase 3 Studies

Following the above mentioned phase 2 study, two pivotal, randomized, double-blind studies on oral FTY720 were performed: FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis) and TRANSFORMS (Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis).

FREEDOMS Trial

The FREEDOMS trial was a phase 3, 24-month, double-blind, randomized study of oral FTY720 treatment (0.5 or 1.25 mg/day vs. placebo) that enrolled 1272 RRMS patients from 138 centers in 22 countries.[10] Inclusion criteria were: 18 to 55 years of age, ambulatory without assistance (EDSS score of 0-5.5), and one or more relapses in the previous year or two, or more in the previous 2 years. Endpoints included relapse rate, disability progression, and MRI changes. Clinical assessments were performed monthly

for the first 3 months and then every 3 months until the end of the 24-month study. EDSS score was determined every 3 months, and MSFC z score every 6 months.

Standardized MRI examinations were undertaken at the screening visit and at 6, 12, and 24 months. A total of 1033 of the 1272 patients (81.2%) completed the study, with 945 (74.3%) continuing to receive the assigned study drug.

All clinical and MRI-related efficacy endpoints favored both doses of FTY720 over placebo. There were no significant differences in efficacy between the two FTY720 doses. The ARR was lower with FTY720 at a dose of 0.5 mg (0.18) and FTY720 at a dose of 1.25 mg (0.16) than with placebo (0.40), representing relative reductions in the ARR of 54% and 60%, respectively (P<0.001 for either dose vs. placebo). Similar ARR was seen amongst patients naive to previous DMT, as well as among those who had been formerly treated with other DMTs (P<0.01 for all comparisons).

The time to a first relapse was longer in the FTY720 groups compared to the placebo group, the risk of relapse was reduced, and proportionately more patients remained relapse free during the 24-month period (74.7±2.2 and 70.4±2.3 in the two FTY720 groups respectively vs. 45.6±2.5 in placebo; P<0.001 for all comparisons). Time to disability progression, with confirmation either after 3 months (the key secondary endpoint) or after 6 months, was longer with both FTY720 doses than with placebo. Fingolimod (FTY720) reduced the risk of disability progression, confirmed after 3 months, over the 24-month study period (hazard ratios, 0.68 for the 1.25 mg dose and 0.70 for the 0.5 mg dose). The cumulative probability of disability progression was 17.7% for 0.5 mg FTY720, 16.6% for 1.25 mg FTY720, and 24.1% for the placebo (P=0.02 for FTY720 vs. placebo).

The risk of disability progression that was confirmed after 6 months was also reduced with FTY720 over the 24-month study period (hazard ratio, 0.60 with the 1.25 mg dose and 0.63 for the 0.5 mg dose). The cumulative probability of progression was 12.5% for 0.5 mg of FTY720, 11.5% for 1.25 mg of FTY720, and 19% for placebo. During the study period, the EDSS scores and MSFC z scores remained stable or improved slightly in the FTY720 groups, and worsened in the placebo group.

With regard to MRI measures, patients in both FTY720 groups had significantly fewer Gd+ lesions than those in the placebo group at 6, 12, and 24 months, as well as fewer new or enlarged lesions on T2-weighted MRI images at 24 months (P<0.001). Similarly, more patients in the FTY720 groups than in the placebo group were also free from Gd-enhancing or new or enlarging lesions at these time points. The median volume of lesions on T2-weighted images decreased between baseline and month 24 with FTY720, but increased with placebo (P<0.001). During the 24-month study period, changes in the volume of hypointense lesions on T1-weighted images favored both doses of FTY720 over placebo. The reduction in brain volume was also significantly smaller with FTY720.

TRANSFORMS Study

A second pivotal study, TRANSFORMS, was a 12-month, phase 3, multicenter, randomized, double-blind, parallel-group study.[37] It evaluated the efficacy and safety of FTY720 in comparison to IM interferon beta-1a. RRMS patients who had at least one documented relapse during the previous year or at least two documented relapses during the previous 2 years and an EDSS score of ≤5.5 were included. Patients were randomly assigned to 12 months of treatment with oral FTY720 (1.25 or 0.5 mg/day), or IM interferon beta-1a

(30 µg/week). Assessments were conducted during screening, at baseline, and at months 1, 2, 3, 6, 9, and 12. EDSS scores were determined every 3 months, and MSFC scores every 6 months. Standardized MRI examinations were undertaken at screening and at 12 months. Definitions of relapses and progression of disability were similar to those used in the FREEDOMS trial.

A total of 1292 patients underwent randomization at 172 clinical centers in 18 countries; 1153 patients (89%) completed the study, and 1123 (87%) continued to receive the assigned study drug. There was a significantly greater reduction in the ARR in both FTY720 groups (0.20 [in the 1.25 mg arm] and 0.16 [in the 0.5 mg arm] in the two FTY720 arms) than in the interferon group (0.33; $P<0.001$). There was no significant difference in ARR between patients who had previously undergone disease treatment (0.33 and 0.26 in FTY720 groups vs. 0.53 in interferon) and those who were naive to previous therapies (0.17 and 0.15 in FTY720 groups vs. 0.31 in the interferon group).

Other relapse-related measures also favored FTY720, including the proportion of patients who were relapse free (79.8% and 82.6% in the FTY720 groups vs. 69.3% in interferon group; $P<0.001$) and the time to the first relapse. Confirmed disability progression was infrequent in all of the study groups. There were no significant differences in the time to the progression of disability or in the proportion of patients with confirmed progression among the study groups. The change in MSFC z score in FTY720 groups reached significance versus interferon ($P<0.001$ [in the 1.25 mg arm] and $P=0.02$ [in the 0.5 mg arm] for the two FTY720 doses).

MRI outcomes also favored FTY720. Patients in the two FTY720 groups had significantly fewer new or enlarged hyperintense lesions on T2-weighted images (1.5±2.7 and 1.7±3.9 in FTY720 groups vs. 2.6±5.8 in interferon group; $P<0.001$ and $P=0.004$) and fewer Gd+ lesions (0.14±0.58 and 0.23±0.97 in FTY720 group vs. interferon 0.51±1.86; $P<0.001$) at 12 months than did those in the interferon group. The mean percent reduction in brain volume from baseline to 12 months was also significantly lower in the two FTY720 groups (–0.30±0.65 and –0.31±0.65) versus the interferon group (–0.45±0.73) ($P<0.001$). Changes in the volume of lesions on unenhanced T2- or T1-weighted images at 12 months did not differ significantly among the study groups. This study showed that oral FTY720 had superior efficacy compared with weekly interferon beta-1a based on clinical and MRI outcomes.

Side Effect Profile

In both phase 3 trials, similar rates of side effects were seen in patients on FTY720 0.5 mg (86%-94.4%), 1.25 mg (90%-94%), interferon (91.6%) and placebo (92.6%), with the majority in the mild-moderate category.[10,37] The rate of serious side effects ranged from 7% to 12% in the FTY720 groups, with greater rates in the group on FTY720 1.25 mg. The rate of serious side effects in the placebo group was 13%. As has been previously noted when FTY720 was being investigated at higher doses for renal transplant, cardiovascular side effects, including bradyarrhythmias, and first and second-degree atrioventricular block were noted at both the 1.25 and 0.5 mg dose. This reduction in HR developed within 1 hour of administration of the medication and reached maximal decreases after 4 to 5 hours. This appears to be dose dependent.

Other important potential concerns include increases in liver transaminases (7%-12.5%; in comparison to interferon [2%] and placebo [1.7%]) and macular edema. The liver abnormalities (greater than three times the upper

limit of normal) reported in the studies resolved after discontinuation of the medication.

Macular edema was noted in patients on 1.25 mg FTY720 (1%-1.6%) and at a lower rate of 0.5 mg FTY720 (0.4%). It was not reported in patients on interferon beta-1a and placebo. The macular edema was seen within 3 months of initiating therapy in the majority of patients and was reversible in all cases after discontinuation of therapy.

The risk of infection and respiratory complications may be greater with the use of FTY720: lower respiratory tract infections (pneumonia and bronchitis) were higher in treatment versus placebo. In addition, a reduction in mean forced expiratory volume in 1 second (FEV_1) was noted in FTY720 groups in the FTY720-interferon trial. Finally, the risk of serious infection in relation to FTY720 is unknown. There have been two deaths due to disseminated primary varicella zoster virus (VZV) and herpes simplex encephalitis reported with the use of 1.25 mg FTY720.[37]

CONCLUSION

Finglomod (FTY720), a S1P receptor modulator, is the first oral DMT to be approved in the US for the treatment of relapsing MS. Based on the efficacy and safety profile, the US FDA approved dose is 0.5 mg daily. Additional trials evaluating even lower FTY720 doses are being considered. Trials of FTY720 for primary progressive MS are ongoing.

A Risk Evaluation and Mitigation Strategy (REMS) program must be implemented at the time of initiation of FTY720 therapy. Based on these recommendations, all patients should be observed for signs/symptoms of bradycardia for 6 hours after administration of the initial FTY720 dose, with special attention to patients on antiarrhythmics, and those with cardiac risk factors. In addition, patients without a clinical history of chickenpox or without vaccination against VZV should be tested for antibodies to VZV. If negative, VZV vaccination should be considered prior to FTY720 initiation. Ophthalmological evaluation to monitor for possible macular edema should be performed, especially in patients with diabetes or previous history of inflammatory ocular pathology.

The efficacy of this oral therapy has been shown in double-blind, placebo-controlled studies, and in trials comparing it to weekly interferon beta-1a therapy. Further, neuroprotective effects stemming from anti-inflammatory mechanisms have been demonstrated in rat models of ischemia.[38] We would argue, however, for cautious optimism regarding this medication, as long-term efficacy and, most importantly, safety of this oral medication in relapsing MS, including the effect on reduction of disability progression and cognitive decline, remain to be established.

ACKNOWLEDGMENTS

B. W-G. has participated in speaker's bureaus and served as a consultant for Biogen Idec, Teva Neurosciences, EMD Serono, Pfizer, Novartis and Acorda. She also has received grant/research support from the agencies listed above as well as Novartis and Shire. No other industry financial relationships exist. E. A. Y. has nothing to disclose.

B. W-G. is the guarantor for this article, and takes responsibility for the integrity of the work as a whole

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