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REVIEW

Safety and Efficacy of Fingolimod in Treatment-Naïve Multiple Sclerosis Patients

James J. Marriott

Section of Neurology, University of Manitoba, Health Sciences Centre, GF543-820 Sherbrook Street, Winnipeg, MB, Canada. Corresponding author email: jmarriott@hsc.mb.ca

Abstract: Fingolimod was recently approved for use in the United States after two phase III trials confirmed its effectiveness in reducing disease activity in relapsing-remitting multiple sclerosis. These positive results, coupled with the important fact that this is the first oral disease-modifying therapy, has lead to considerable enthusiasm amongst physicians and patients. However, fingolimod is associated with rare but serious adverse events. In addition, unlike conventional disease-modifying therapies, cardiopulmonary, ophthalmological and dermatological safety monitoring unfamiliar to both neurologists and patients is required before and during treatment. This paper will discuss these issues from the perspective of using fingolimod as a first-line disease-modifying therapy in treatment-naïve relapsing-remitting multiple sclerosis patients.

Keywords: fingolimod, multiple sclerosis, disease-modifying therapy, treatment-naïve

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Introduction

The development of interferon (IFN)-β1a/b and glatiramer acetate (GA) in the 1990s was an unprecedented advance in the therapy of multiple sclerosis (MS).[1–4] For the first time, there were disease-modifying therapies (DMTs) available for relapsing remitting MS (RRMS). While IFN and GA are now well-established first-line therapies, they are far from ideal medications. Firstly, as subcutaneous/intramuscular agents they are all associated with various injection-related side effects including the nuisance and psychological issues inherent with injected medications. Furthermore, their effectiveness is still limited to an approximate 30% reduction in relapse rate with variable reductions in magnetic resonance imaging (MRI) T2-weighted and gadolinium-enhancing (Gd+) lesion burden over time (Table 1). It also remains unproven that long-term disability outcomes are improved with early treatment initiation.[5] Finally, these first-line DMTs are not effective in either secondary progressive MS (SPMS) or primary progressive MS (PPMS).[6–8] Natalizumab (NZ) reduces relapse rates by approximately 70% and MRI activity by approximately 80%–90%.[9] While still parenteral, NZ has the advantage over IFN/GA of being only a single monthly intravenous infusion. Acknowledging the lack of comparative data evaluating NZ head-to-head with either IFN or GA, this agent is typically used as a second-line therapy given the risk of progressive multifocal leukoencephalopathy (PML).[10]

Against this backdrop of the established DMTs, a large number of other therapies are under development in MS. One oral therapy, fingolimod (also called FTY720), is the subject of this review. Fingolimod was recently approved for use by the Food and Drug Administration (FDA) in the United States[11] for all patients with relapsing MS and is under regulatory review elsewhere.

The recent approval of fingolimod obviously represents an advance with respect to the ease of medication administration. In comparison to the established first-line DMTs, compliance/adherence and patient satisfaction could be higher with an oral medication. Importantly, this DMT is also the first for which there is phase III, randomized controlled trial (RCT) comparative efficacy data to support its evidence-based use as a second-line therapy in patients with a sub-optimal response to IFN-β.

This review will focus on the evidence, and corresponding areas of uncertainty, supporting the use of fingolimod as a first-line DMT in treatment-naïve MS patients. This requires a more nuanced risk/benefit calculation as the potential advantages of fingolimod need to be weighted against the requirement for more extensive patient monitoring and the risk of serious adverse events. When considering fingolimod treatment, clinicians and patients must also take

Table 1. Key clinical and MRI endpoints in pivotal RRMS trials.

DMT	Route/dose frequency	Relapse rate reduction	MRI T2-lesion reduction	Side effect profile
IFN-β1b (Betaseron®)[1]	SC/qod	34%	83%	Flu-like symptoms, injection-site reactions, rare lymphopenia and transaminitis
IFN-β1a (Avonex®)[3,34]	IM/qw	18%	36%*	Flu-like symptoms, injection-site reactions, rare lymphopenia and transaminitis
IFN-β1a (Rebif®)[4]	SC/tiw	33%	78%	Flu-like symptoms, injection-site reactions, rare lymphopenia and transaminitis
GA (Copaxone®)[2,35]	SC/qd	29%	38%*	Lipoatrophy, rare self-limiting systemic reaction (chest tightness, palpitations)
NZ (Tysabri®)[9]	IV/q4w	68%	83%	Rare infusion reactions (anaphylaxis/anaphylactoid), PML

Note: *Key MRI outcomes reported in separate publications from original pivotal trial.
Abbreviations: DMT, disease modifying therapy; GA, glatiramer acetate; IFN, interferon; IM, intramuscular; NZ, natalizumab; PML, progressive multifocal encephalopathy; q4w, every 4 weeks; qd, daily; qod, every other day; SC, subcutaneous; tiw, three times weekly.

into account the excellent overall long-term safety profile of the established first-line therapies IFN-β and GA. Finally our current inability to accurately predict, on an individual level, which "treatment-naïve" patients are most at risk for developing significant MS-related disability further complicates any discussion of how to best treat such patients.

Pharmacokinetic Profile, Metabolism and Mechanism of Action

Fingolimod (2-amino-2-(2-[4-octylphenyl]ethyl)-1,3-propanediol hydrochloride) was initially studied as a potential post-renal transplant immunosuppressant (Fig. 1). Early pharmacokinetic studies in that patient population indicated that fingolimod has a large volume of distribution and a mean half-life of 200 hours.[12] Steady state blood levels are attained 1–2 months after treatment initiation and are approximately 10-fold higher than the initial dose.[11,12] Fingolimod is phosphorylated in the liver by the enzyme sphingosine kinase 2 into the biologically active molecule fingolimod-phosphate. The majority of the parent compound however is metabolized through the hepatic cytochrome P450 4F2 isoenzymatic pathway into inactive metabolites which are predominantly excreted through the kidney.[11]

Fingolimod-phosphate is structurally homologous to the endogenous lysophospholipid sphingosine-1-phosphate (S1P) and binds to 4 of the 5 known S1P receptors ($S1P_1$, $S1P_3$, $S1P_4$ and $S1P_5$ but not $S1P_2$). The S1P receptors are G-protein coupled receptors that are widely distributed on various leukocyte subtypes, and on neurons and glial cells in addition to a range of other systemic tissues.[13–15] S1P binding to the S1P-receptor activates the associated membrane-bound G-protein. This in turn activates a number of different second-messenger pathways which, depending on the precise S1P-receptor, G-protein and cell involved, include phospolipase C, RAS, phosphatidylinositol 3-kinase and adenylyl cyclase.[14]

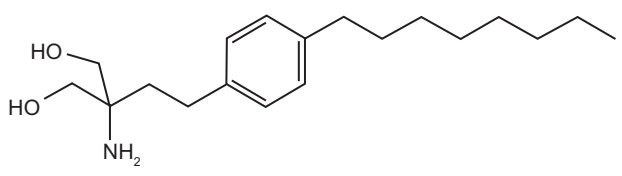

Figure 1. The structure of fingolimod.

Following antigen recognition in lymphoid organs through interactions with antigen-presenting dendritic cells, activated T-cells upregulate the $S1P_1$ receptor. Binding of endogenous S1P to these receptors is a necessary step in T-cell migration from the lymph node to the systemic circulation.[13–15] The main immunomodulatory effect of fingolimod in MS is felt to be via binding to $S1P_1$ receptors, preventing S1P binding and blocking the egress of autoreactive T-cells from lymph tissues. While fingolimod-phosphate initially has an agonistic action on the receptor, binding is felt to subsequently trigger endocytic receptor internalization and loss of surface $S1P_1$ receptors through subsequent gene down-regulation.[15,16] Without surface $S1P_1$ receptor expression, autoreactive T-cells are unable to leave the lymph nodes and migrate to the central nervous system (CNS). This process has been demonstrated in murine experimental autoimmune encephalitis (EAE) models of MS where fingolimod prevents T-cell migration from lymph nodes.[17] Fingolimod can also cross the blood-brain-barrier (BBB) and there is hope that this treatment will enhance endogenous neuroprotective mechanisms through interactions with the wide range of S1P receptor subtypes present on neurons, oligodendrocytes and other CNS glial cells.[17,18]

Clinical Trials

Efficacy

The original fingolimod phase II double-blind, randomized controlled trial (RCT) consisted of a 6-month long "core" study that compared two doses of fingolimod, 5.0 mg and 1.25 mg once daily, with placebo administration.[19] In the double-blind extension phase, placebo-treated patients were re-randomized to either low or high dose fingolimod and followed for an additional 6 months. The primary endpoint was the cumulative mean number of Gd^+-lesions detected on 6 monthly MRI scans performed during the "core" study. The double-blind extension phase was used to monitor longer-term safety and assess secondary efficacy endpoints. Of the 281 randomized patients, 255 completed the "core" study and formed the cohort used for a per-protocol analysis of the primary endpoint. While the inclusion criteria focused on RRMS, approximately 10% of randomized patients had SPMS. The number of treatment-naïve subjects was not reported.

There was a significant reduction in MRI activity over the "core" study period, with a mean of 14.8 Gd^+-lesions seen in the placebo arm in contrast to 8.4 in the 1.25 mg arm ($P < 0.001$ relative to placebo) and 5.7 in the 5.0 mg arm ($P = 0.006$ relative to placebo).[19] The trial was not powered to appropriately examine clinical endpoints. Nevertheless, the annualized relapse rate (ARR) was also significantly lower in fingolimod-treated patients; 0.35 in the 1.25 mg arm (55% reduction, $P = 0.009$) and 0.36 in the 5.0 mg arm (53% reduction, $P = 0.01$) in comparison to 0.77 in the placebo-arm.

In the 6-month double-blind extension phase, patients re-randomized to fingolimod from placebo had statistically significant declines in Gd^+-lesion activity relative to the core phase.[19] Interestingly, the ARRs also declined from 0.70 to 0.21 and from 0.69 to 0.10 between the core and extension treatment periods after placebo subjects were re-randomized to 0.5 mg and 1.25 mg, respectively. Significance testing was not reported for the ARR changes.

The results of open-label extension studies of the phase II trial subjects performed at both 24- and 36-months have also been published.[20,21] 189 and 173 of the total 255 subjects from the initial 6-month core study per-protocol MRI analysis completed follow-up at 24- and 36-months, respectively. These reports both showed sustained reductions in Gd^+-lesion burden and ARR in the patients who remained on fingolimod. As the authors note,[21] the inherent biases in uncontrolled, unblinded open-label extension studies due to the self-selection of treatment-responders who are tolerating therapy prevent efficacy conclusions from being made with such trials.[22]

In the phase II trials, adverse events were more common in the 5.0 mg arm so doses of 0.5 mg and 1.25 mg were chosen for the phase III trials. The first two phase III trials of fingolimod in RRMS, FREEDOMS and TRANSFORMS, were published simultaneously in 2010.[23,24] Both trials enrolled treatment-naïve RRMS patients in addition to those who had previously been on DMT.

FREEDOMS was a placebo-controlled, double-blind RCT that compared two doses of fingolimod, 0.5 mg and 1.25 mg once daily, to placebo over a period of 2 years.[23] 1272 patients were enrolled, 59% of whom had never previously been on any form of DMT. The primary endpoint was the ARR over the full 2-year study period with other clinical and radiological outcomes examined as secondary endpoints.[23] The ARR was 0.40 in the placebo arm, 0.18 in the low dose and 0.16 in the high dose fingolimod arms, corresponding to relative risk reductions (RRR) of 54% and 60%, respectively ($P < 0.001$ for both comparisons relative to placebo). The risk of Expanded Disability Status Scale (EDSS) progression sustained over 3-months was lower in both of the fingolimod arms with hazard ratios of 0.70 in the low-dose 0.5 mg group ($P = 0.026$) and 0.68 in the high-dose 1.25 mg group ($P = 0.012$) relative to placebo. The mean EDSS and Multiple Sclerosis Functional Composite (MSFC) scores also either remained stable or improved slightly with fingolimod treatment in contrast to statistically significant worsening in the placebo arm. The absolute magnitude of the EDSS and MSFC changes however were negligible and not clinically significant. All of the reported MRI endpoints, including Gd^+-lesion number, new/enlarged T2-lesion number and volume, T1-hypointense lesion volume and whole brain volume, measured at various timepoints up to 2-years were also statistically significant when comparing both the 0.5 mg and 1.25 mg doses with placebo. No strong dose-dependent trends on either the primary or secondary endpoints were consistently observed between the 0.5 mg and 1.25 mg treatment arms.

Results in the treatment-naïve population were reported in a subsequent poster presentation of subgroup analyses of the FREEDOMS trial.[25] The ARRs over the 2-year treatment trial were 0.46 in the placebo arm and 0.17 in both the 0.5 mg and 1.25 mg fingolimod arms (RRR 62%–64% versus placebo, $P < 0.001$ for both comparisons). Other clinical and MRI secondary endpoints in the treatment-naïve FREEDOMS participants have not been reported.

In contrast to FREEDOMS, TRANSFORMS was a 1-year long, double-blind, double-dummy RCT using an established DMT, weekly intramuscular IFNβ1a (Avonex®), as an active-comparator.[24] A total of 1292 patients (45% treatment-naïve), were randomized in a 1:1:1 treatment allocation. As with FREEDOMS, the primary endpoint was the ARR and similar secondary MRI and clinical endpoints were assessed. The ARRs were 0.16 in the 0.5 mg arm and 0.20 in the 1.25 mg

arm in contrast to 0.33 in the IFNβ1a-treated subjects, corresponding to RRRs of 52% and 38% respectively ($P < 0.001$ for both comparisons). The authors also reported the primary endpoint separately in the two subgroups of treatment-naïve and DMT-exposed subjects: while the latter had significantly lower ARRs on fingolimod, only a trend in favor of either fingolimod dose over IFNβ1a was seen in the DMT-naïve subgroup. Interestingly, there was a trend towards higher ARRs in the previously-treated participants for all three treatment allocations relative to the corresponding treatment-naïve cohorts. This suggests that as a whole, those previously on DMT had intrinsically more active disease relative to the treatment-naïve subgroup.

A highly significant reduction in the main MRI endpoint of the number of new/enlarging T2-lesions was also demonstrated with both fingolimod doses.[24] However, the rate of 3-month sustained disability progression was not lowered with fingolimod treatment, with the majority of patients in all three groups (~93%) not experiencing a worsening EDSS. This, in contrast with the 2-year long FREEDOMS trial, may be a reflection of the shorter study period used in TRANSFORMS. As with FREEDOMS, no dose-dependent therapeutic advantage of 1.25 mg over 0.5 mg was demonstrated in TRANSFORMS. Of note, TRANSFORMS is to date the only phase III study in multiple sclerosis which has demonstrated a treatment benefit over an established DMT.

Two other ongoing RCTs are evaluating fingolimod in RRMS[26,27] and a third in PPMS.[28] Given that in both TRANSFORMS and FREEDOMS, the 1.25 mg dose was associated with more side effects (described below) than the 0.5 mg dose without a corresponding increase in clinical effectiveness, the future company-sponsored drug development program will focus on the 0.5 mg dose which has already been approved for use in the United States.[29]

Safety

Fingolimod has generally been well-tolerated in the trials published to date, however it has been associated with frequent (although usually asymptomatic and/or self-resolving) cardiopulmonary side effects in addition to rare serious adverse events including life-threatening infections.[19,20,23,24]

The initial administration of fingolimod typically causes a transient asymptomatic decline in heart rate.[19,23,24] Some cases of symptomatic bradycardia and atrioventricular block have occurred in the phase II and III trials. It is felt that this side effect is due to S1P-receptor mediated potassium influx into atrial myocytes. A pooled analysis of the two phase III studies demonstrated dose-dependent bradycardia, with mean heart rate decreases of 8 and 11 beats per minute seen with the 0.5 mg and 1.25 mg doses, respectively. This analysis also confirmed that the bradycardia typically resolves over 6 hours after each dose.[30] The absolute magnitude of the bradycardia also declines over time with continued fingolimod exposure, dissipating after 1 month of treatment; although it can reoccur if the drug is re-started after a discontinuation period lasting longer than 2 weeks.[11] Mild asymptomatic decreases in blood pressure are also seen as a first-dose effect and resolve over a similar time-span as the bradycardia.[30] After this initial decrease, however, fingolimod treatment causes a mild but persistent increase in blood pressure.[23,24] Mild, dose-dependent, non-progressive decreases in forced expiratory volume have also been observed in the phase II and III trials. The rates of dyspnea with the marketed 0.5 mg dose were markedly different in the phase III trials; 0% in TRANSFORMS and 7.1% in FREEDOMS.

Macular edema, typically seen in the first 3–4 months of therapy, occurred in a dose-dependent manner in the phase III studies. The most recent long-term safety report pooling results from both FREEDOMS and TRANSFORMS noted 4 cases (0.3% of subjects) and 14 cases (1.1% of subjects) in those treated with 0.5 mg and 1.25 mg, respectively.[31] It is unclear how many patients were symptomatic. The product monograph states that patients should have full ophthalmological assessments at baseline and after 3–4 months of treatment to screen for asymptomatic cases.[11]

As expected given the mechanism of action of fingolimod, lymphocyte counts decreased by 73%–77% within 1 month of treatment initiation in both phase III trials. At 12 months (TRANSFORMS) and 24 months (FREEDOMS) the absolute lymphocyte counts were approximately the same with both the 0.5 mg and 1.25 mg doses; ~0.5 × 10^9/L in comparison

to ~1.8×10^9/L at baseline.[23,24] In the pooled phase III trial analysis, alanine aminotransferase (ALT) levels greater than 3 times the upper limit of normal occurred in 0.8% (0.5 mg) and 12% (1.25 mg) of patients, with 0.2%–0.3% of subjects experiencing a more significant greater than 10 fold ALT rise.

Nasopharyngitis, respiratory tract and urinary tract infections were all more commonly reported in fingolimod-treated patients, although these were rarely serious adverse events.[19,23,24] While the rates of mild herpes virus infections were similar in the fingolimod and placebo/IFNβ1a-treated subjects in the phase III studies, single fatal cases of disseminated varicella and herpes simplex encephalitis occurred in the 1.25 mg arm of TRANSFORMS.[23,24] Two other subjects in the high-dose arm of TRANSFORMS died after completion of the study. The first had an unexplained neurological deterioration and the second had metastatic breast carcinoma.

Due to the development of cutaneous malignancies in subjects treated with 5.0 mg in the phase II study, dermatological assessments were built into the two phase III trial protocols. In both FREEDOMS and TRANSFORMS, the overall rates of malignancy, including cutaneous malignancies, were not elevated relative to the control arms during both the published trials and their reported extension periods.[23,24,31]

Other serious adverse events observed with fingolimod use have included a single case of the posterior-reversible encephalopathy syndrome (PRES) in the 5.0 mg arm of the initial phase II trial[19] and one patient treated with 1.25 mg in the ongoing FREEDOMS II trial who developed a focal hemorrhagic and necrotic encephalitic lesion in the left temperoparietal region.[32] This presentation was complicated by complex partial seizures and the subject was left with a residual aphasia. Extensive investigations failed to demonstrate an etiology and the reporting authors hypothesized that an undetected viral infection or a fingolimod-associated autoimmune process was to blame. One case of left brachial artery vasospasm occurring 7 days after the initiation of fingolimod 1.25 mg in a TRANSFORMS study participant has also been reported.[33] According to the most recent reported phase III safety data and the product monograph, ischemic and hemorrhagic strokes and peripheral vascular disease have occurred in patients treated with 1.25 mg or 5.0 mg, however no vascular events have been observed at the marketed 0.5 mg dose.[11,31]

Patient Preference and Place in Therapy

The potential benefits to patients of a fixed-dose, once daily, orally administered DMT are obvious. No published or presented data exists to quantify the differences in health-related quality of life (HQOL) in fingolimod-treated patients relative to those on other DMTs.

While approved (at least in the United States) for all patients with RRMS, irrespective of previous DMT exposure, clinicians and patients will need to carefully decide how and when to utilize fingolimod in treatment-naïve individuals. It would not be unsurprising if initially fingolimod was used relatively sparingly in such patients until its long-term safety profile is better established. Treatment-naïve individuals with more severe disease may be more appropriate candidates for first-line fingolimod use given the comparative results of the TRANSFORMS study. The need for routine screening bloodwork, heart rate and pulmonary function monitoring and both ophthalmological and dermatological examinations may all be barriers to therapy depending on local resource availability and the extra time commitment required of patients. Cost may also be a factor limiting use. MS patients with active disease who are needle-phobic or decide against using any of the current first-line injectable agents may also be reasonable candidates. The phrase "active disease" is of course open to interpretation and it is to be expected that different clinicians and patients will have different thresholds for considering fingolimod therapy.

Conclusions

Fingolimod has been demonstrated to be effective in reducing relapse rates, disability progression and MRI disease activity over the short-term in both treatment-naïve and previously treated RRMS patients in two phase III RCTs. Despite the inherent

appeal of an oral agent, this therapy does seem to have a more concerning side-effect profile relative to IFNβ1a/b and GA. The decision to use fingolimod as a first-line therapy should be made on the basis of the evidence discussed above while acknowledging the areas of ongoing uncertainty. As with the first appearance of the currently established DMTs, uptake of this novel treatment option by MS patients and their treating neurologists will likely evolve over time as real-world experience is gained and as more data becomes available from ongoing clinical trials, extension studies and postmarketing registries.

Disclosures

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This paper is unique and not under consideration by any other publication and has not been published elsewhere. The author reports no conflicts of interest. The author confirms that he has permission to reproduce any copyrighted material.

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