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REVIEW

Patient experience and practice trends in multiple sclerosis – clinical utility of fingolimod

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Abstract: Targeting sphingosine-1-phosphate pathway with orally available immune-modulatory fingolimod (Gilenya™) therapy ameliorates relapsing–remitting multiple sclerosis (RRMS) by decreasing relapse rate as shown in FREEDOMS and TRANSFORMS. Fingolimod has also been shown to be superior to interferon-beta therapy as evidenced by TRANSFORMS. Albeit multiple benefits in treatment of multiple sclerosis including high efficacy and ease of administration, potential untoward effects such as cardiotoxicity, risk of infection, and cancer exist, thus mandating careful screening and frequent monitoring of patients undergoing treatment with fingolimod. This review outlines mechanism of action, observations, side effects, and practice guidelines on use of fingolimod in treatment of RRMS.

Keywords: sphingosine-1-phosphate, RRMS, FREEDOMS, TRANSFORMS, side effects, IFNβ

Introduction

Fingolimod (Gilenya™) is the first US Food and Drug Administration (FDA)-approved oral therapy for treatment of multiple sclerosis (MS) based on two Phase III pivotal trials, FREEDOMS and TRANSFORMS.[1–4] Fingolimod targets the sphingosine-1-phosphate (S1P) pathway by regulation of lymphocyte trafficking from secondary lymphoid organs into the systemic circulation (Table 1).[5–8] Interaction of the sphingolipid ligand, S1P, in the blood or lymph with the G protein-coupled receptor S1P receptor 1 (S1PR1) on lymphocytes is necessary for lymphocyte egress from lymph nodes into blood and lymph.[9–11] The critical role played by S1P–S1PR1 interaction in immune trafficking is perturbed by fingolimod, a functional antagonist of S1PR.[12,13] Fingolimod sequesters lymphocytes in the spleen and lymph nodes by inducing receptor internalization and degradation, causing lymphopenia and sparing the central nervous system from immune attack by myelin-reactive lymphocytes.[11] Fingolimod has been shown to effectively decrease relapse rate up to 50% and is superior to interferon-beta (IFNβ) therapy.[14–17] However, since fingolimod signals via most of the S1PRs (S1PR1 and 3–5), untoward effects in systems expressing these receptors, including cardiovascular and visual systems (such as cardiac rhythm abnormalities and macular edema), have been observed in patients treated with fingolimod.[18–21] Furthermore, due to fingolimod's action on lymphopenia, side effects related to serious infections and cancer risk, possibly by interfering immune surveillance function of lymphocytes, are also observed.[18] In the post-market experience, rebound disease activity (most likely due to reversing fingolimod's effect on lymphocyte egress) is observed upon discontinuation of the therapy.[22–25] Thus, careful patient selection with rigorous and frequent monitoring and pre-consideration of optimal treatment sequencing are required for patients undergoing fingolimod

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Table 1 S1PR in the immune system

Subtypes	Tissue expression	Function of S1PR
S1P1	CNS (neurons, astrocytes, oligodendrocytes, microglial cells)	CNS: migration of neuronal cells toward areas of damage; regulation of oligodendrocyte survival, function, and modulation of myelination following injury; regulation of microglial number and activation; and maintenance of blood–brain barrier
S1P3	Cardiovascular Immune	Cardiovascular: heart rate control
S1P4	Lymphoid tissue	
S1P5	Natural killer cells CNS (oligodendrocytes)	

Abbreviations: S1P, sphingosine-1-phosphate; S1PR, S1P receptor; CNS, central nervous system.

therapy.[26–29] This review article presents a comprehensive review of screening, monitoring, side effects, and efficacy in the clinical practice utilizing fingolimod for the treatment of relapsing–remitting MS (RRMS).

Screening before initiating therapy

Baseline screening and ongoing monitoring are required for fingolimod treatment to avoid potential serious side effects (Figure 1).[29,30] The recommended baseline screening includes electrocardiogram (ECG) for cardiac rhythm abnormalities, ophthalmologic examination to evaluate for macular edema, serological test for immunity to varicella zoster virus (VZV) infection, complete blood count, liver function tests, blood pressure, and urine pregnancy test for females during reproductive age.[30] Additional recommendations include pulmonary function test, dermatological examination, and serological test for viral hepatitis and tuberculosis, when clinically indicated. A detailed evaluation such as referral to cardiology (for abnormal ECG) and dermatology proceeds if baseline screening is abnormal. Active immunization against VZV is recommended for nonimmune cases.[30,31] Review of past medical history and medication list for potential drug interactions is also recommended as part of prescreening. Special attention is paid to patients with diabetes and uveitis due to the increased risk of developing macular edema with fingolimod therapy.[32,33] Cardiac rhythm abnormalities such as torsades de pointes, bradycardia, or conduction block could occur, especially in patients who are concurrently

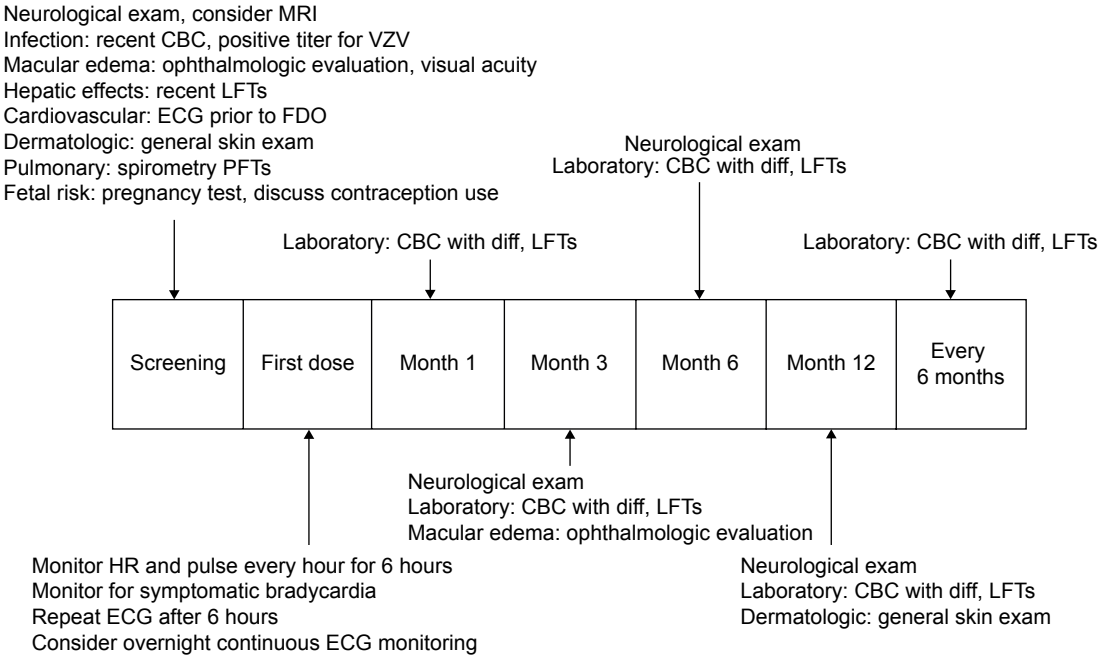

Figure 1 Proposed algorithm for patient management upon screening, FDO, and long-term follow-up for fingolimod therapy.
Abbreviations: MRI, magnetic resonance imaging; CBC, complete blood count; VZV, varicella zoster virus; LFT, liver function test; ECG, electrocardiogram; FDO, first-dose observation; PFT, pulmonary function test; diff, diffusion; HR, heart rate.

on medications that can cause prolonged QT interval (eg, citalopram, chlorpromazine, haloperidol, methadone, erythromycin), or interfere with cardiac conduction (eg, beta blockers, diltiazem, verapamil, digoxin).[34,35] Interval monitoring of follow-up ophthalmologic examination (at 3–4 months following treatment initiation), complete blood counts, and hepatic function tests are recommended.[1,2] Continuous monitoring of infection is recommended until 2 months after discontinuation of fingolimod. Women of childbearing potential should use effective contraception during and for 2 months after stopping therapy, since fingolimod therapy may cause fetal abnormalities.[1,2] Regular monitoring for hypertension is also recommended throughout the duration of therapy.[1,2,30]

Patients undergoing fingolimod therapy receive more rigorous screening compared to those undergoing other disease-modifying therapies (DMTs). This may delay the initiation of therapy; however, patients in our practice have expressed satisfaction with thorough screening prior to starting therapy.

First-dose observation

The first-dose observation (FDO) is a 6-hour monitoring session assessing for cardiac rhythm abnormalities, especially bradycardia, after initiation of fingolimod therapy. FDO includes monitoring for heart rate, cardiac rhythm, and blood pressure every hour, and ECG at 0 hour and 6 hours after taking first dose of fingolimod.[36] The cardiovascular side effects during FDO from FREEDOMS and TRANSFORMS studies are bradycardia as being the most common cardiovascular event followed by first-degree atrioventricular (AV) block, second-degree AV block Mobitz type 1, sinus arrhythmia, and ventricular premature beats.[36] The new FDA-revised FDO monitoring includes a repeat ECG prior to discharge based on potential cardiac rhythm abnormalities following first dose of fingolimod.[37,38] FDO is carried out as an outpatient procedure in most facilities where patients are observed on a cardiac monitor for 6 hours with access to a rapid response team. Extended monitoring is recommended for those patients who demonstrate the following: 1) heart rate <45 beats per minute, 2) a continued downward trend, 3) new-onset second-degree or more severe conduction block, 4) symptomatic bradycardia, and 5) prolonged QTc interval (QTc >470 ms in females and >450 ms in males) following 6-hour FDO monitoring.[37] Overnight continuous cardiac monitoring in a medical facility for FDO is recommended for patients with a preexisting cardiac condition or on concurrent medication that can interfere with cardiac conduction; patients with a prior cardiac history have not shown increased incidence of adverse events with FDO.[39–41] Common complaints during FDO in our practice include headache, mild nausea, and symptomatic bradycardia in order of frequency. The guidelines for patients requiring repeat FDO are discontinuation within first 2 weeks of therapy, interruption of 1 or more days during weeks 3–4 of therapy, interruption of 7 or more days after 4 weeks of therapy, and interruption of 14 or more days anytime during treatment.[1,37]

Untoward effects associated with fingolimod use

Side effects associated with fingolimod reported in FREEDOMS and TRANSFORMS are abnormal laboratory finding, infections, cardiovascular side effects, macular edema, malignancies, pulmonary side effects, and rare cases of posterior reversible encephalopathy syndrome. Less serious side effects include headache and hypertension.[1,2]

Laboratory test abnormalities

Lymphopenia was the most common abnormal laboratory test leading to drug discontinuation in the FREEDOMS studies.[42,43] Peripheral blood lymphocyte counts decreased up to 20%–30% from baseline within the first month of initiation of fingolimod therapy.[20] Lymphopenia is often reversible and normalized approximately 45–135 days following discontinuation of fingolimod.[44] Elevated alanine aminotransferase (ALT) (up to three or more times the upper limit of normal) was observed as the second most common abnormal laboratory finding.[1,2] ALT levels also normalized spontaneously after discontinuation of fingolimod without permanent hepatic dysfunction.[1,2]

Risk of infection

The overall incidence of infections in FREEDOMS and TRANSFORMS studies was similar in the treatment and placebo groups; however, a slightly higher incidence of bronchitis, influenza, and herpes viral infections (including herpes zoster infection) was observed in the fingolimod treatment groups.[30] Other common infections included upper respiratory tract infections, nasopharyngitis, urinary tract infections, and sinusitis.[30] Two fatal cases of reactivation of latent herpes virus (in the fingolimod 1.25 mg treatment group), a case of fatal disseminated VZV infection, and a case of fatal herpes simplex virus type 1 encephalitis in TRANSFORMS study were also observed.[1–3,30] Other infections such as reactivation of human papilloma virus, John Cunningham virus (in a post-natalizumab case), tuberculosis, and cytomegalovirus

were also reported; however, post-marketing data did not reveal an increased rate of occult infections.[45] About 20% of our patient cohort on fingolimod (n=50) have reported symptoms of vaginitis, recurrent upper respiratory, and sinus infections; however, the etiology is unclear.

Cardiovascular side effects

Fingolimod binds to S1PR1 in the heart, which can result in heart rhythm abnormalities such as bradycardia, therefore necessitating FDO.[36–41] Maximal decrease in heart rate occurs at 4–6 hours, which is the basis of rationale for the 6-hour monitoring period.[20] Symptomatic (eg, dizziness, chest discomfort, palpitations, and/or fatigue) bradycardia was observed in less than 1% of subjects.[43,46] In FREEDOMS and TRANSFORMS studies, symptomatic bradycardia during FDO resolved within 24 hours without pharmacological interventions.[1,2] Fingolimod is also known to induce cardiac conduction abnormalities, including first- and second-degree AV block, on the 6-hour post-dose ECG; patients who continued on treatment did not have persistent cardiac conduction abnormalities.[34,35] We have had infrequent cases of symptomatic bradycardia leading to discontinuation of fingolimod as seen with patients in our practice.

Macular edema

Another potential side effect associated with the upregulation of S1PR in the vascular endothelial cells of the macula is fingolimod-associated macular edema (FAME).[28–32] Most of the cases with FAME in FREEDOMS and TRANSFORMS studies were asymptomatic; the overall incidence of FAME was 0.5% in the 0.5 mg group, with complete resolution following discontinuation of therapy.[1,2] FAME generally occurred within 3–4 months of fingolimod initiation, although there has been a case report of early bilateral macular edema following fingolimod therapy within the first 3 months.[32,33] Therefore, a follow-up ophthalmologic examination at 3–4 months post-fingolimod initiation is recommended. Few cases of unresolved macular edema were identified in the higher dose (1.25 mg) fingolimod group.[20] In our patient cohort, we have seen two cases of symptomatic FAME which appeared 3–4 months after fingolimod initiation. Both cases had complete resolution of visual disturbance within 2–3 months after discontinuing fingolimod.

Risk of malignancy

An increased risk of malignancies was found in association with fingolimod therapy in the TRANSFORMS and FREEDOMS studies. Most common malignancies found in association with fingolimod use are dermatological malignancies (Bowen's disease, n=1; basal cell carcinoma, n=10; and malignant melanoma, n=4).[20,21] Other malignancies reported in the studies are breast cancer (n=5) with a fatal case of metastatic breast cancer in a patient who died 10 months after discontinuing fingolimod.[47] Although there were at least three case reports of lymphoma in the fingolimod treatment group during drug development, a general consensus has not been reached on the risk of lymphoma with fingolimod.[48]

Pulmonary side effects

Respiratory effects including mild reductions in 1-second forced expiratory volume and diffusion capacity for carbon monoxide were observed in FREEDOMS and TRANSFORMS.[1,2] Spirometry and diffusion lung capacity tests are recommended if clinically indicated.[1] We have a standard protocol assessing for pulmonary function status through spirometry testing prior to FDO.

Pregnancy

Although fingolimod is classified as pregnancy category C, there have been cases of teratogenicity in live births during fingolimod clinical development.[49] Exposure to fingolimod in the first trimester resulted in five cases of abnormal fetal development in 66 pregnancies.[49,50] The available pregnancy registry data continue to provide important information regarding use of fingolimod in women of childbearing potential with the known risk of possible fetal malformation and teratogenic effects.[51,52] The current recommendation for women of childbearing potential is to use effective contraception during fingolimod therapy and for at least 2 months after discontinuation of fingolimod.[1]

Tumefactive MS and rebound relapses

To date, 16 case reports in the literature describe worsening MS disease activity or even development of tumefactive demyelinating lesions (TDL) following fingolimod therapy.[53–55] TDL are extremely rare and were observed in patients with established diagnosis of MS leading to the suspicion of a causal relationship between the use of fingolimod and development of TDL.[55,56] The diagnosis of progressive multifocal leukoencephalopathy (PML) was entertained in this particular patient with TDL, since the patient was on natalizumab therapy before starting fingolimod; however, the patient was found to have "rebound" disease activity along with the development of TDL.[57–60] It would seem prudent

to monitor clinical progression and magnetic resonance imaging (MRI) activity for worsening disease activity in fingolimod-treated patients regardless of disease duration and prior DMT history.

Post-market experience

Sudden death in a hypertensive patient on calcium-channel blockers and beta blockers within 24 hours following first-dose fingolimod prompted the FDA and the European Medicines Agency (EMA) to recommend a modification in the FDO to include hourly heart rate and blood pressure monitor and an ECG (either continuous, according to the EMA, or pre-dose and 6 hours post-dose, according to the FDA) as well as excluding patients on medications that can cause cardiac rhythm abnormalities.[37,38] Despite the recommendations, two open-label studies on fingolimod treatment initiation resulted in overall satisfactory safety and tolerability in patients with concomitant diseases, and no cardiac adverse events were observed in association with fingolimod use.[34,39] On the contrary, a case report in 2013 identified that three (out of 59) patients without known cardiovascular disease were found to have cardiac rhythm abnormalities (eg, sinus bradycardia with idioventricular escape rhythm that lasted 45 seconds and second-degree AV block Mobitz type 1).[34] Additional post-marketing reports have raised concern over the risk for PML in patients who were originally treated with natalizumab.[60] A confirmed case of PML was reported in 2012 in a patient who was treated with natalizumab for 42 months prior to fingolimod therapy.[61] The second case of PML was observed in a patient treated with fingolimod, who did not have prior exposure to natalizumab.[62] The third reported case of PML was observed in a patient 3.5 months after fingolimod initiation and 4.5 months after natalizumab discontinuation.[61,62]

Efficacy

Fingolimod met the primary end point of annualized relapse rate reduction across both Phase III trials. With the exception of time to disability progression in TRANSFORMS, secondary end point measures including MRI data were statistically significant in FREEDOMS and TRANSFORMS.[63,64] More importantly, TRANSFORMS showed greater efficacy in relapse rate reduction over IFNβ in a 12-month study (Table 2).[1,2] Brain volume loss has been specifically studied in FREEDOMS, which found that fingolimod 0.5 mg dose significantly reduced brain volume loss up to 24 months vs placebo irrespective of the presence or absence of gadolinium-enhancing lesions, T2 lesion load, previous treatment status, or level of disability.[65] Long-term data to support ongoing reduction in disability progression and brain volume loss are not available at this time, but studies to assess fingolimod safety and tolerability continue (Table 3).[66,67]

Suggested treatment algorithm

Clinicians and patients across MS centers continue to struggle with selecting the most effective MS therapy for a particular patient with RRMS, and to assess whether drug benefits outweigh risks of treatment (Figure 2).[68–70] As the first of three first-line oral therapies for the treatment of RRMS, fingolimod presents a suitable option for patients with recent diagnosis of MS or those with suboptimal response and/or compliance to injectable first-line immune therapies.[71] Clinicians tend to switch patients to fingolimod (from natalizumab) based on the patients' risk for development of PML based on serological status for John Cunningham virus, and those with neutralizing antibodies against natalizumab.[72] A washout period of approximately 3 months has been recommended when switching from natalizumab to fingolimod,

Table 2 Summary of pivotal trials

Study	Study design	Treatment arms	Primary end point	Main result
TRANSFORMS[4]	n=1,292, 12-month, double-blind, parallel-group, active comparator, multicenter	Fingolimod 0.5 mg orally, daily	ARR reduction over 12 months	ARR: 0.16–0.20 (vs 0.33; $P<0.001$ for each dose vs IFNβ-1a)
		Fingolimod 1.25 mg orally, daily		Relapse free: 80%–83% of patients (vs 69%; $P<0.0001$ for each dose vs IFNβ-1a)
		IFNβ-1a 30 μg intramuscularly, weekly		
FREEDOMS[3]	n=1,272, 24-month, double-blind, parallel-group, placebo-controlled, multicenter	Fingolimod 0.5 mg orally, daily	ARR reduction over 24 months	ARR: 0.16–0.18 (vs 0.40; $P<0.001$ for each dose vs placebo)
		Placebo		Relapse free: 70%–75% of patients (vs 46%; $P<0.001$ for each dose vs placebo)

Abbreviations: ARR, annualized relapse rate for confirmed relapses; IFNβ-1a, interferon beta-1a.

Table 3 Summary of other clinical trials

Study	Study design	Treatment arms	Primary end point	Results
FREEDOMS II[43]	Phase II, 6-month, double-blind, parallel-group, placebo-controlled, multicenter	Fingolimod 0.5 mg orally, daily Fingolimod 1.25 mg orally, daily Placebo	Total number of Gd+ lesions on T1-w MRI at month 6	Free from Gd+ lesions: 82%
FIRST[34]	Phase IIIb, 4-month, open-label, single-arm, multicenter	Fingolimod 0.5 mg orally, daily ×16 weeks	Evaluate the short-term safety and tolerability profile of fingolimod 0.5 mg with focus on cardiac safety	Cardiac effects following FDO are transient, mostly asymptomatic, and observed in the first 6 hours post-dose Suggest no increased risk of symptomatic or serious cardiac events during treatment initiation in patients with preexisting cardiac conditions or in those receiving beta blockers or calcium-channel blockers
CFTY720[45] DIT03[40]	Non-comparative, open-label, multicenter (Italy)	Fingolimod 0.5 mg orally on FDO	Evaluate the safety and tolerability data associated with initial dose of Fingolimod	Safety and tolerability in "real-world" setting was similar to what was seen in pivotal trials
EPOC[46,71]	6-month, randomized, active comparator, open-label, multicenter	Fingolimod 0.5 mg orally, daily IFNβ-1a 44 μg subcutaneous, 3 times a week GA 20 mg, subcutaneous, daily	Evaluate the safety and tolerability and patient outcomes who are changing from previous disease-modifying therapy to fingolimod	Safety and tolerability similar to what was seen in pivotal trials

Abbreviations: Gd+, gadolinium-enhanced; T1-w, T1-weighted; MRI, magnetic resonance imaging; FDO, first-dose observation; IFNβ-1a, interferon beta-1a; GA, glatiramer acetate.

but duration of washout period depends on the disease activity and other comorbidities such as the immune status of the patient.[73]

Patient adherence

It is well recognized that medication adherence is not always 100% with either oral or injectable DMTs for multiple reasons.[74,75] Fingolimod provides an attractive alternative to injectable DMTs due to the ease of administration. However, a retrospective study on medication compliance showed that approximately 27% of fingolimod users discontinued within 1 year of treatment initiation.[75] Socioeconomic factors play a role in patient adherence to drug treatment with increasing out-of-pocket and copayments and lack of insurance

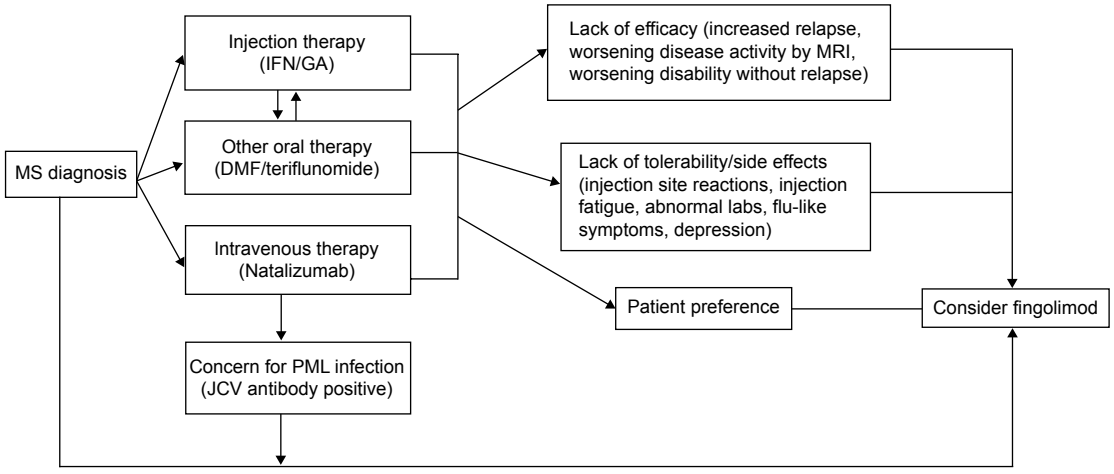

Figure 2 Proposed algorithm to start fingolimod for treatment-naïve patients and prior disease-modifying therapy use.
Abbreviations: MS, multiple sclerosis; IFN, interferon; GA, glatiramer acetate; DMF, dimethyl fumarate; PML, progressive multifocal leukoencephalopathy; JCV, John Cunningham virus; MRI, magnetic resonance imaging.

coverage.[76,77] The Consortium of MS Centers recently outlined that the main reasons for patients switching DMTs in MS included efficacy, safety, prescriber- or payer-related reasons, and patient-related reasons which included difficulty with adherence, desire to try different administration methods, and perceived lack of efficacy.[78] Most of the patients in our practice have discontinued fingolimod primarily due to side effects of the medication and perceived lack of efficacy. Typically, patients who have switched from injection therapy are pleased with the ease of oral administration of fingolimod, despite the lack of comprehensive long-term safety data.

Conclusion

Fingolimod is the first FDA-approved oral therapy for the treatment of RRMS as shown by two large Phase III studies, FREEDOMS and TRANSFORMS.[1] Clinical efficacy of fingolimod was observed to be superior to placebo and IFNβ-1a in reducing relapse rate and MRI activity. However, thorough screening, FDO, and long-term follow-up are recommended in order to avoid potential side effects associated with fingolimod therapy. Fingolimod presents as a treatment option as a first-line therapy for patients with new-onset RRMS or those switching therapies due to intolerability and/or lack of efficacy of prior DMTs. However, studies on long-term efficacy, safety, and mechanism of action of fingolimod remain to be further pursued for therapeutic optimization and to avoid undesirable side effects.

Disclosure

Jong-Mi Lee has received consulting agreements or service as speaker (Biogen Idec, Teva Pharmaceuticals, and Genzyme). The other author reports no conflicts of interest in this work.

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