REVIEW ARTICLE

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Oral fingolimod for the treatment of patients with relapsing forms of multiple sclerosis

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SUMMARY

Fingolimod, a sphingosine 1-phosphate receptor modulator, is the first oral treatment approved by the US Food and Drug Administration for the treatment of relapsing forms of multiple sclerosis (MS). The aim of this review was to provide a concise, comprehensive overview of the clinically relevant mechanism of action, efficacy and safety information available for fingolimod. Key data were derived from two international, Phase III, double-blind, randomised trials (TRANSFORMS and FREEDOMS) performed over 12 and 24 months, respectively, which evaluated fingolimod 0.5 and 1.25 mg daily in 1703 patients with relapsing forms of MS. In TRANSFORMS, there was a 52% reduction in the annualised relapse rate (ARR) with fingolimod 0.5 mg vs. 30 μg intramuscular interferon beta-1a (0.16 vs. 0.33; $p < 0.001$) at 1 year. In FREEDOMS, there was a 55% decrease in ARR at 2 years with fingolimod 0.5 mg vs. placebo (0.18 vs. 0.40; $p < 0.001$). Risk of disability progression, confirmed at 3 months, was also reduced by 30% over the 2-year study period with fingolimod vs. placebo ($p = 0.02$). Significantly fewer new or enlarged lesions on T_2-weighted images were seen in both studies (TRANSFORMS, $p = 0.002$ vs. interferon beta-1a at 1 year; FREEDOMS, $p < 0.001$ vs. placebo at 2 years). Overall, fingolimod 0.5 mg was well tolerated by patients. Transient, generally asymptomatic bradycardia and infrequent atrioventricular block were seen with the administration of the first dose. Macular oedema and serious infections occurred infrequently. Reversible, asymptomatic elevations of liver enzymes could also occur. As the first approved oral disease-modifying treatment, fingolimod offers patients a convenient alternative to regular self-injection for the treatment of relapsing forms of MS. In addition to high efficacy with a relatively acceptable safety profile, fingolimod provides a therapy with a new mechanism of action.

Review Criteria

Information included in this review was gathered from published randomised clinical trials and from US prescribing information to present data relating to the efficacy and safety of fingolimod in patients with relapsing forms of MS.

Message for the Clinic

Fingolimod is a sphingosine 1-phosphate receptor modulator with a novel mechanism of action that is approved for the treatment of relapsing forms of MS. Fingolimod reduces relapses more effectively than typically prescribed intramuscular interferon beta-1a and delays disability progression. Associated safety risks are bradyarrhythmia and atrioventricular block following initial dose, infrequently occurring macular oedema, risk of infection and asymptomatic elevations of liver enzymes. Fingolimod is an effective therapy for relapsing forms of MS in a convenient oral dose.

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Disclosures

BS has received speaking and consulting honoraria from Bayer, Biogen Idec, EMD Serono, Novartis, Pfizer and TEVA Pharmaceuticals. APR has received consultancy honoraria from Novartis, EMD Serono, Pfizer, TEVA Pharmaceuticals, Bayer Healthcare, Genzyme, and Acorda. KT is an employee of the sponsor (Novartis Pharmaceuticals Corporation) and has equity or ownership interest.

Introduction

Multiple sclerosis (MS) is the most common inflammatory, demyelinating disorder of the central nervous system (CNS) (1). An estimated 2.5 million people worldwide have MS, with almost 0.5 million of those in the USA (2). Over time, as MS progresses, the transmission of electrical nerve impulses is disrupted due to an abnormal immune attack on myelin and potential damage to neurons. The trigger for these unpredictable autoimmune 'attacks' remains unknown, but may be attributed to a combination of genetic and/or environmental factors (1,3).

The most frequently prescribed therapies for relapsing forms of MS, interferon beta and glatiramer acetate, reduce annualised relapse rates by an average of 29–34% in 2-year studies and require intramuscular or subcutaneous injections ranging from daily to weekly (4–7). Natalizumab (an α4 integrin antagonist) given by monthly intravenous infusion has been shown to reduce annualised relapse rates by 68% in patients with relapsing forms of MS compared with patients receiving placebo (8). Natalizumab is licensed in Europe for highly active disease, irrespective of treatment status. However, because of an associated increased risk of progressive multifocal leukoencephalopathy (PML), natalizumab is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies (9–11).

Fingolimod (FTY720) has a novel mechanism of action compared with other available disease-modifying therapies for MS. Fingolimod 0.5 mg was approved in the USA in September 2010 for the treatment of relapsing forms of MS by reducing the

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frequency of relapses and delaying the progression of disability. Fingolimod 0.5 mg is a capsule given orally once daily. Here, we review and summarise for healthcare professionals, the clinical efficacy, mechanism of action and safety information on fingolimod. This includes key data from two international, Phase III, double-blind, randomised trials that studied 1703 patients with relapsing forms of MS treated with fingolimod (0.5 and 1.25 mg) (12,13). Please note that the recommendations given within this review are based on US prescribing information and may differ by country.

What is fingolimod?

Mechanism of action

Fingolimod is the first-in-class of sphingosine 1-phosphate (S1P) receptor modulators and has a novel mechanism of action (14). Fingolimod is rapidly phosphorylated *in vivo* to its biologically active form, fingolimod-phosphate, by sphingosine kinases (15). In its phosphorylated state, fingolimod is known to bind all but one of the five S1P receptor subtypes with high affinity (16).

It has been shown that fingolimod exerts its therapeutic effects in the immune system *via* lymphocyte S1P receptors (14). Fingolimod reversibly sequesters lymphocytes in the lymph nodes, preventing the egress of autoreactive lymphocytes into the peripheral circulation and across the blood–brain barrier into the CNS (17–21). In animal studies of experimental autoimmune encephalitis, a model of MS, fingolimod has been shown to reduce lymphocyte trafficking (14,22,23).

As a consequence of reversible sequestration of circulating lymphocytes within lymphoid tissues, fingolimod treatment is associated with a reversible reduction in lymphocyte count (24). Lymphocyte count decreases to approximately 60% of baseline within 4–6 h of the first fingolimod dose and to approximately 30% of baseline (or 500 cells/μl) after 2 weeks of treatment. Low lymphocyte counts are maintained with chronic treatment, while neutrophil counts are mildly reduced to 80% of baseline (25). Increases in peripheral lymphocyte count are evident in the days after stopping fingolimod treatment, and typically return to normal (approximately 1000–4800 cells/μl) within 1–2 months (26).

Pharmacokinetics

Absorption of oral fingolimod is relatively slow with a T_{max} of 12–16 h, while oral bioavailability is high (93%) (26). Steady-state blood concentrations are achieved within 2 months of daily administration (26,27). Importantly, from a practical perspective, fingolimod may be taken without regard to the timing of meals or their fat content (27). Metabolism of fingolimod is *via* the hepatic cytochrome P450 system (28). Drug–drug interactions are unlikely because other drugs are not metabolised by the cytochrome P450 isoenzyme that metabolises fingolimod, CYP4F2 (29). Close monitoring for side effects is necessary when fingolimod is used concomitantly with systemic ketoconazole (an antifungal medication) because of an increase in fingolimod exposure by up to 70% (30). Based on population pharmacokinetics analysis to date, there were no apparent clinically relevant effects when the following medications were co-administered with fingolimod: fluoxetine; paroxetine, carbamazepine, baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin and corticosteroids (26). Fingolimod has not been administered concomitantly with antineoplastic, immunosuppressive or immune-modulating therapies, but combined treatment with these agents would be expected to increase the risk of immunosuppression. Nonetheless, a standard course of intravenous corticosteroids was allowed to treat relapses as clinically warranted during fingolimod trials (12,13). The terminal half-life of fingolimod is 6–9 days with approximately 81% of orally administered doses excreted slowly in the urine as inactive metabolites (26). Severe hepatic impairment doubles exposure to fingolimod (31). However, no adjustments in fingolimod dosage are necessary with mild or moderate hepatic impairment (26). The appropriate dose for patients with renal failure is 0.5 mg. Patients with severe renal failure do not demonstrate an increase in elimination half-life (26).

Efficacy of fingolimod

Fingolimod's efficacy and safety were evaluated in two large, recently published, Phase III, randomised, and controlled trials in patients with relapsing forms of MS. TRANSFORMS (Trial Assessing Injectable Interferon vs. FTY720 Oral in Relapsing forms of MS) was a 12-month study comparing fingolimod to intramuscular interferon beta-1a, and FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in MS) was a 24-month study comparing fingolimod to placebo (12,13). Baseline characteristics of the patient populations in these two studies are shown in Table 1. Both studies evaluated fingolimod 0.5 and 1.25 mg daily doses. However, because fingolimod 1.25 mg is a non-approved daily dose in the USA, data relating to this dose will not be considered in this review. In both studies, the primary end-point was the annualised relapse rate. Key secondary end-points in the active-controlled

Table 1 Baseline characteristics of patients in TRANSFORMS and FREEDOMS (12,13)

	TRANSFORMS		FREEDOMS	
Characteristics	**Fingolimod 0.5 mg *N* = 431**	**Interferon beta-1a *N* = 435**	**Fingolimod 0.5 mg *N* = 425**	**Placebo *N* = 418**
Demographic				
Median age, years (range)	37.0 (18–55)	36.0 (18–55)	36.0 (18–55)	37.0 (18–55)
Median EDSS score (range)*	2.0 (0–5.5)	2.0 (0–5.5)	2.0 (0–5.5)	2.0 (0–5.5)
Disease history				
Median time from first MS symptoms to randomisation, years (range)	6.0 (0–34)	6.0 (0–40)	6.6 (0–35)	7.0 (0–32)

*The Expanded Disability Status Scale (EDSS) ranges from 0 to 10, with higher scores indicating greater disability. There were no significant between-group differences at baseline for any characteristic in either study. MS, multiple sclerosis.

study were (i) the number of new or newly enlarged hyperintense lesions on T_2-weighted magnetic resonance imaging (MRI) scans and (ii) the time to 3-month confirmed disability progression, as measured on the Expanded Disability Status Scale (EDSS; which ranges from 0 to 10, with higher scores indicating greater disability) by at least a 1-point increase from baseline, or a 0.5-point increase for patients with a baseline score of 5.5 (32). In the placebo-controlled study (FREEDOMS), 3-month confirmed disability progression was the only key secondary end-point. The number of new or newly enlarging T_2 lesions was also assessed by MRI in this study.

TRANSFORMS

TRANSFORMS was a 12-month, double-blind, double-dummy trial of 1292 patients with relapsing forms of MS randomly assigned to receive either an oral daily dose of fingolimod (0.5 or 1.25 mg) or an intramuscular weekly dose of interferon beta-1a (30 μg) (13). Patients included in this study were 18–55 years of age, with a diagnosis of MS according to the revised McDonald criteria, (33) a relapsing–remitting disease course and at least one documented relapse during the previous year or at least two relapses during the previous 2 years. They had a score of 0–5.5 on the EDSS (32). Exclusion criteria included a documented relapse or corticosteroid treatment within 30 days prior to randomisation, natalizumab treatment within 6 months prior to randomisation, active infection, macular oedema, presence of drug- or disease-induced immunosuppression, or clinically significant co-existing systemic disease. In total, 1292 patients were randomised to receive fingolimod 0.5 mg daily ($N = 431$), fingolimod 1.25 mg daily ($N = 426$) or intramuscular interferon beta-1a 30 μg weekly ($N = 435$) (13).

In the TRANSFORMS study, a statistically significant 52% reduction in the annualised relapse rate was observed with fingolimod 0.5 mg compared with 30 μg interferon beta-1a (0.16 vs. 0.33; $p < 0.001$; Figure 1A). The percentages of relapse-free patients at 12 months were 83% and 69% for the fingolimod

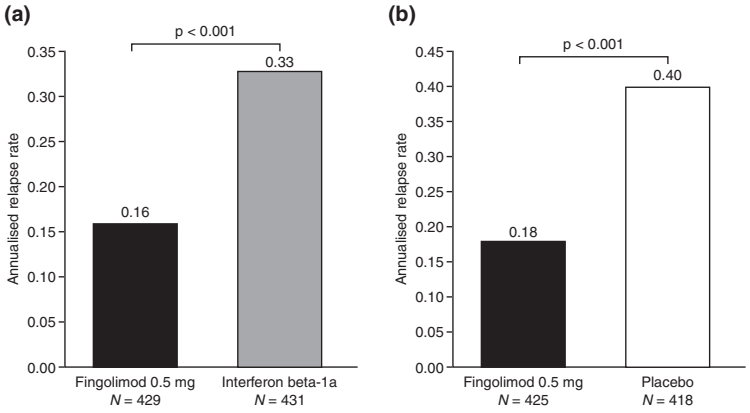

Figure 1 Annualised relapse rates, defined as the number of confirmed relapses per year, in (A) TRANSFORMS (13) and (B) FREEDOMS (12)

Table 2 Key secondary efficacy outcomes in TRANSFORMS and FREEDOMS (12,13)

	TRANSFORMS		FREEDOMS		p-value*	
	Fingolimod 0.5 mg *N* = 429	Interferon beta-1a *N* = 431	Fingolimod 0.5 mg *N* = 425	Placebo *N* = 418	TRANSFORMS	FREEDOMS
New or newly enlarged lesions on T_2-weighted images [Mean (median)]	1.6 (0.0)	2.6 (1.0)	2.5 (0.0)‡	9.8 (5.0)§	0.0024	<0.001
Hazard ratio† of disability progression (95% CI)	0.71 (0.42, 1.21)	–	0.70 (0.52, 0.96)	–	0.21	0.02

*p-value represents fingolimod 0.5 mg vs. interferon beta-1a for TRANSFORMS and fingolimod 0.5 mg vs. placebo for FREEDOMS.
†Estimate of the relative risk of the event of disability progression on fingolimod compared with control. ‡*n* = 370. §*n* = 339.

0.5 mg vs. interferon beta-1a groups, respectively ($p < 0.001$). The number of new or newly enlarged T_2 lesions over 12 months in TRANSFORMS was significantly reduced in the fingolimod-treated group vs. the interferon beta-1a-treated group [mean (median) 1.6 (0.0) vs. 2.6 (1.0) respectively, p = 0.0024; Table 2] (13). However, as might be expected in a short 12-month study, confirmed disability progression was relatively infrequent (> 90% of patients exhibited no confirmed disability progression in either group). Hence, no significant difference was detected in terms of the time to the confirmed progression of disability [hazard ratio (95% CI) 0.71 (0.42, 1.21), p = 0.21; Table 2] (13).

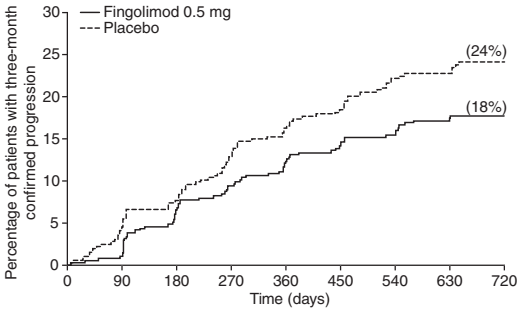

Figure 2 Kaplan–Meier estimates for time to disability progression, confirmed after 3 months, as measured with the EDSS scale in the FREEDOMS trial (12). EDSS, The Expanded Disability Status Scale

FREEDOMS

FREEDOMS was a 24-month, double-blind, double-dummy trial of 1272 patients with relapsing forms of MS randomly assigned to receive either an oral daily dose of fingolimod (0.5 or 1.25 mg) or placebo (12). Patient eligibility was as described previously for TRANSFORMS, with the additional exclusion criterion that interferon beta [beta-1a (intramuscular or subcutaneous) or beta-1b (subcutaneous)] or glatiramer acetate therapy had to be stopped at least 3 months prior to randomisation. In total, 1272 patients were randomised to receive fingolimod 0.5 mg daily (*n* = 425), fingolimod 1.25 mg daily (*n* = 429) or placebo (*n* = 418) (12).

Statistically significant differences were observed at 24 months between the fingolimod and placebo group on the primary end-point of annualised relapse rate (55% reduction; 0.18 vs. 0.40, $p < 0.001$; Figure 1B). The percentages of patients relapse-free at 24 months were 70% and 46% for the fingolimod 0.5 mg and placebo group, respectively ($p < 0.001$). The risk of disability progression, defined as an increase of one point in the EDSS score (or half a point, if the baseline EDSS score was equal to 5.5), confirmed on neurological evaluations 3 months apart, was reduced by 30% with fingolimod 0.5 mg compared with placebo [hazard ratio (95% CI) 0.70 (0.52, 0.96), p = 0.02; Table 2 and Figure 2]. Risk of disability progression confirmed after 6 months (an additional secondary study outcome) was reduced by 37% with fingolimod 0.5 mg vs. placebo (p = 0.01). There was a significant reduction in the number of new or newly enlarged hyperintense lesions on T_2-weighted MRI scans in the fingolimod-treated vs. placebo groups [mean (median) 2.5 (0.0) vs. 9.8 (5.0), respectively, $p < 0.001$; Table 2] (12).

Safety of fingolimod

In the FREEDOMS study, the overall incidences of adverse events and serious adverse events were similar between the fingolimod 0.5 mg and placebo groups (Table 3). The most common serious adverse events were bradycardia (four fingolimod-treated and one placebo-treated patient), MS relapse (four fingolimod-treated and one placebo-treated patient),

Table 3 Summary of all adverse events and most commonly reported adverse events in the placebo-controlled FREEDOMS study (safety population) (12,26)

	Fingolimod 0.5 mg *N* = 425 %	Placebo *N* = 418 %
All adverse events		
Any event	94.4	92.6
Any serious event	10.1	13.4
Any event leading to discontinuation of study drug	7.5	7.7
Death	0.0	0.5
Adverse events that occurred in ≥ 1% of patients in either group and reported for fingolimod 0.5 mg at ≥ 1% higher rate than placebo		
Infections		
Influenza viral infections	13	10
Herpes viral infections	9	8
Bronchitis	8	4
Sinusitis	7	5
Gastroenteritis	5	3
Tinea infections	4	1
Cardiac disorders		
Bradycardia	4	1
Nervous system disorders		
Headache	25	23
Dizziness	7	6
Paresthesia	5	4
Migraine	5	1
Gastrointestinal disorders		
Diarrhoea	12	7
General disorders and administrative site conditions		
Asthenia	3	1
Musculoskeletal and connective tissue disorders		
Back pain	12	7
Skin and subcutaneous tissue disorders		
Alopecia	4	2
Eczema	3	2
Pruritus	3	1
Investigations		
ALT/AST increased	14	5
GGT increased	5	1
Weight decreased	5	3
Blood triglycerides increased	3	1
Respiratory, thoracic and mediastinal disorders		
Cough	10	8
Dyspnoea	8	5
Psychiatric disorders		
Depression	8	7
Eye disorders		
Vision blurred	4	1
Eye pain	3	1
Vascular disorders		
Hypertension	6	4
Blood and lymphatic system disorders		
Lymphopenia	4	1
Leukopenia	3	< 1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltranspeptidase.

chest pain (four fingolimod-treated and two placebo-treated patients) and basal cell carcinoma (four fingolimod-treated and three placebo-treated patients). All serious adverse events occurred in < 1% of patients. The most commonly reported adverse events (incidence greater than 10% and greater than placebo) that occurred in fingolimod 0.5 mg-treated patients were headache, influenza, diarrhoea, back pain, liver enzyme elevations and cough (12). Adverse events reported in the fingolimod 0.5 mg group in TRANSFORMS were generally similar to those reported in FREEDOMS (13).

Fingolimod causes a transient dose-related decrease in heart rate (bradycardia) and atrioventricular conduction following the first dose. This is likely caused by stimulation of the $S1P_3$ receptor subtype, which regulates sinus rhythm on cardiomyocytes (while lymphocyte recirculation appears to be mediated by the $S1P_1$ receptor subtype) (34). The decrease in heart rate is seen within an hour of the first dose, is maximal 6 h after the first dose, and returns to baseline within 1 month of continued treatment (35). Such patients were generally asymptomatic, but they infrequently experienced mild to moderate dizziness, fatigue, palpitations or chest pain that resolved within 24 h of treatment (12). First- and second-degree atrioventricular block following the initial 0.5 mg dose were each observed in 0.1% of patients (26). Conduction abnormalities tended to be transient and asymptomatic, and resolved within 24 h of treatment without needing to intervene with atropine or isoproterenol. Two patients in the FREEDOMS trial received treatment for symptoms of bradycardia (one treated with atropine and one with isoproterenol); both were in the higher non-approved fingolimod 1.25 mg group. The US Food and Drug Administration (FDA)-approved label recommends that all patients are observed for symptoms associated with bradycardia during the first 6 h following their first dose. Fingolimod treatment does not affect autonomic responses of the heart, or the impact of exercise on heart rate (26). If fingolimod therapy is discontinued for over 2 weeks, the same precautions for first-dose observation should apply on reintroduction of treatment (26). The basis for the first-dose effect on heart rate and desensitisation with prolonged exposure is unclear, but may involve fingolimod-induced internalisation, and subsequent degradation, of the S1P receptor on atrial myocytes, which occurs without stimulation of the receptor (36).

Caution should be exercised in patients who may be at particular risk of developing bradycardia or heart blocks (e.g. patients receiving Class Ia or Class III antiarrhythmic drugs, beta-blockers, calcium channel blockers, those with a low heart rate, history

of syncope, sick sinus syndrome, prolonged QT interval, second degree or higher conduction block, ischaemic heart disease or congestive heart failure). A recent electrocardiogram (ECG) is recommended in these patients (26).

In the controlled studies, the overall rate of infections (72%) and serious infections (2%) was similar with fingolimod 0.5 mg and placebo, with the exception of bronchitis, and to a lesser extent pneumonia, being more common in fingolimod-treated patients (26). Two patients receiving fingolimod 1.25 mg (higher than the recommended dose), in the TRANSFORMS study died of herpetic infections. The first occurred in a patient without a history of primary *Varicella zoster* virus (VZV) infection or VZV vaccination, who was exposed to chicken pox in a childcare/nursery setting during a course of high-dose corticosteroid therapy for suspected MS relapse. The other death was caused by herpes simplex encephalitis, treated initially with intravenous steroids for suspected MS relapse, and 1 week later with antiviral therapy. In both cases, fingolimod had been discontinued. No deaths resulting from viral infections occurred in patients treated with fingolimod 0.5 mg (13). Patients should be directed to report symptoms of infection during treatment and for 2 months after stopping treatment. Fingolimod should not be initiated in patients with active acute or chronic infections. The FDA-approved label recommends that a recent complete blood check (CBC) should be obtained prior to treatment (26).

Patients taking fingolimod should avoid the use of live or live attenuated vaccines during, and for 2 months after stopping, fingolimod therapy (26). As for any immune-modulating drug, before initiating fingolimod therapy, patients without a history of chicken pox or without vaccination against VZV should be tested for antibodies. VZV vaccination of antibody-negative patients is recommended 1 month prior to starting treatment.

The risk of developing macular oedema is known to be dose-related, with greatest risk at higher doses, occurring predominantly in the first 4 months of treatment (37). In the controlled studies, macular oedema occurred in 0.4% of patients on fingolimod 0.5 mg (26). The macular oedema generally cleared or improved after stopping therapy. An ophthalmological examination is recommended at baseline and 3–4 months following initiation of therapy. In patients with diabetes or uveitis, regular ophthalmological examinations are recommended, because these patients are at higher risk of macular oedema on fingolimod (26).

Increases in liver enzymes may occur in fingolimod-treated patients. In clinical trials, 8% of patients receiving the 0.5 mg dose of fingolimod had liver transaminase levels that were at least three times the upper limit of normal (ULN) compared with 2% of patients on placebo. Elevations of five-fold the ULN occurred in 2% of patients on fingolimod 0.5 mg and 1% of patients on placebo (12). Elevations of liver enzymes typically occur within the first 3–4 months of treatment, and levels return to normal within 2 months of stopping treatment. Recent transaminase and bilirubin levels (within 6 months) should be available prior to treatment initiation. Liver enzymes should be re-assessed if symptoms suggestive of hepatic injury occur, according to the FDA label (26). However, any additional monitoring of treatment is always dependent on the discretion of the treating clinician.

In MS clinical trials, a mean increase in blood pressure of 2 mmHg in systolic pressure and 1 mmHg in diastolic pressure was detected within 2 months of starting fingolimod 0.5 mg treatment (26). Hypertension was reported as an adverse reaction in 5% of patients receiving fingolimod 0.5 mg and 3% of patients on placebo (26). Therefore, it is recommended that blood pressure be monitored (26).

Fingolimod has not been studied in pregnant women. However, in animal studies, teratogenicity was seen in fingolimod-treated rats. Women of childbearing potential should use contraception to avoid pregnancy for 2 months after stopping fingolimod treatment (26).

A summary of recommendations when prescribing fingolimod is shown in Table 4. At-risk patients should be fully informed and involved in the risk–benefit assessment prior to initiating treatment.

Discussion

Fingolimod, a first-in-class S1P receptor modulator, has recently been approved by the FDA in the USA for the treatment of relapsing forms of MS. It has a novel mechanism of action, reversibly sequestering lymphocytes in lymph nodes, and preventing their egress into the circulation and subsequent entry into the CNS, where they can cause inflammatory damage (14).

Fingolimod has demonstrated superiority compared with a commonly prescribed injectable therapy (intramuscular interferon beta-1a) for patients with relapsing forms of MS, on relapse- and MRI-related outcome measures. In TRANSFORMS, a randomised, double-blind, 12-month trial, fingolimod 0.5 mg was associated with a 52% decrease in annualised relapse rate vs. intramuscular interferon beta-1a (13). In the fingolimod-treated group, the percentage of patients

Table 4 Recommendations and practical guidance for fingolimod therapy, based on US prescribing information (26)

CBC	Results should be available within 6 months prior to treatment
Liver transaminases and bilirubin levels	Results should be available within 6 months prior to treatment
	Monitor if patient develops symptoms of hepatic dysfunction (e.g. nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice and dark urine)
	Discontinue therapy if severe hepatic injury is confirmed
ECG	Obtain within 6 months prior to treatment in:
	Patients using antiarrhythmics (e.g. Class Ia, Class III, beta-blockers and calcium channel blockers)
	Patients with second degree or higher AV block, sick sinus syndrome, prolonged QT interval, ischaemic heart disease, congestive heart failure, slow heart rate (< 55 bpm) or irregular heart beat
Ophthalmological examination	Baseline examination
	After 3–4 months of treatment
	Regularly thereafter in patients with diabetes mellitus or uveitis
	If patient reports a visual disturbance [e.g. blurriness or shadows in the centre of vision, blind spot in centre of vision, sensitivity to light, unusually coloured (tinted) vision]
Antibodies for VZV	Patients with no history of chicken pox or vaccination against VZV should be tested for VZV antibodies prior to treatment
	If antibody negative, VZV vaccination should be considered
	Fingolimod treatment should be postponed for 1 month after VZV vaccination
Pulse and blood pressure	Measure just before and for 6 h following the first dose
	Monitor regularly during treatment
Infection	Patients with active acute or chronic infections should not start treatment until the infections are resolved
	Instruct patients to report symptoms of infection (e.g. fever, chills, tiredness, body aches, nausea and vomiting) during treatment and for 2 months after discontinuation
	Consider suspending treatment if a patient develops a serious infection
Pregnancy	Fingolimod should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus
	Counsel women of childbearing potential on the need to use effective contraception during therapy and for 2 months after discontinuation
Treatment initiation	Observe all patients for 6 h after first dose
	If patient shows symptoms of bradycardia, repeat pulse and blood pressure measurements, assess need for additional monitoring procedures and intervention, and continue observation until symptoms have resolved
	If fingolimod is discontinued for over 14 days, patients should be observed for 6 h after first dose when treatment is restarted
Respiratory function	If clinically indicated, spirometric evaluation of respiratory function and diffusion lung capacity for carbon monoxide
Vaccinations	Avoid live attenuated vaccines during treatment and for 2 months after discontinuation
Ketoconazole	Monitor patients on concomitant ketoconazole closely

CBC, complete blood check; ECG, electrocardiogram; AV, atrioventricular; bpm, beats per minute; VZV, *Varicella zoster* virus.

relapse-free at 12 months was 14% greater, and numbers of new or newly enlarged lesions assessed by T_2-weighted MRI scans were reduced, compared with the intramuscular interferon beta-1a-treated group (13). In FREEDOMS, fingolimod demonstrated superiority vs. placebo across relapse-, disability- and MRI-related outcomes. Fingolimod 0.5 mg reduced annualised relapse rates by 55% vs. placebo and the percentage of relapse-free patients at 24 months was 25% greater in patients taking fingolimod. The risk of disability progression, confirmed at 3 months, was reduced by 30% over the 2-year study period with fingolimod vs. placebo. Patients in the fingolimod-treated group also had fewer new or newly enlarged lesions on T_2-weighted MRI scans at study end-point (12).

Fingolimod was studied in 1703 patients with relapsing forms of MS in a Phase III program and was found to have an acceptable safety profile. The overall incidence of infections was similar to placebo, with the exception of a slight increase in lower respiratory tract infections with fingolimod (12). The first dose of fingolimod is associated with a generally transient, asymptomatic decrease in heart rate and/or atrioventricular conduction, which warrants monitoring for symptoms of bradycardia (incidence 0.5%) during the 6 h following the first administration. Macular oedema, although infrequently seen with fingolimod treatment (incidence 0.4%), should be monitored by ophthalmological examinations at least at baseline and at 3–4 months after treatment initiation. Reversible, asymptomatic elevations in liver enzyme levels such as alanine aminotransferase are relatively common with fingolimod therapy. The long-term safety profile of fingolimod has yet to be established.

Important aspects of choosing a medication include mode of administration, tolerability, and ease of use. Conventionally, disease-modifying MS drugs used as first-line agents have been administered by intramuscular or subcutaneous injection on a daily to weekly basis. However, some patients suffer from anxiety related to needle phobia (38,39) and may experience injection-site reactions, such as swelling, redness, pain, lipoatrophy and necrosis (40,41). Hence, an oral treatment option for patients with MS directly addresses both the burden of disease and burden of treatment in relapsing forms of MS, and appears to provide a more convenient and effective treatment alternative.

Author contributions

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