Fingolimod in multiple sclerosis: profile of use in habitual practice

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ABSTRACT

Objectives Fingolimod is the first oral drug indicated in monotherapy as a modifier of the course of very active relapsing-remitting multiple sclerosis (RRMS). The safety profile of fingolimod is well established in clinical trials and post-marketing studies. Our objective was to study the profile of fingolimod use in our health area.

Methods A retrospective, observational, descriptive study was performed on the use of fingolimod in adult patients diagnosed with RRMS between January 2015 and February 2017 or until suspension of treatment in a reference hospital in north-western Spain.

Results A total of 55 patients were included with a mean±SD time of treatment with fingolimod of 26±14.6 months (range 2–53). Thirteen patients permanently discontinued the treatment (10 due to outbreaks/disease progression and 3 due to adverse effects). No statistically significant differences were found between the percentage of patients who discontinued fingolimod and who had received only one previous treatment and those who had received two or more treatments. No cases of symptomatic bradycardia were reported.

Conclusions Fingolimod is a safe treatment for patients with multiple sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is a chronic disease of the CNS of unknown aetiology, characterised by inflammation, demyelination, glial scarring and neuroaxonal damage, producing varying degrees of persistent neurological damage.¹ In the case of relapsing-remitting MS (RRMS), outbreaks occur frequently—that is, episodes of neurological dysfunction that last for days or weeks and usually remit partially or totally, especially in the initial stages of the disease. However, approximately 10% of patients experience progressive neurological deterioration without outbreaks, suffering so-called primary progressive MS.²

The WHO estimates that more than 1.3 million people suffer from MS worldwide, with Europe being the continent with the largest number of patients diagnosed, having 48% of the cases globally.³ The prevalence of this disease in Spain is 42–125 cases per 100 000 inhabitants, and the annual incidence rate is 2.1–5.3 cases per 100 000 inhabitants.⁴

Current treatment guidelines recommend starting a disease-modifying therapy in patients with a definitive diagnosis of RRMS to decrease the frequency of outbreaks and the degree of accumulated disability.^{5 6}

In the past two decades the European Medicines Agency has approved numerous medications indicated for the treatment of RRMS, all of which are characterised by their ability to decrease the frequency of outbreaks and accumulated disability, improve clinical variables and exert favourable effects on MRI. Drugs administered parenterally (interferon β and glatiramer acetate) are advantageous as their safety profiles are supported by greater experience in clinical practice; however, they have the disadvantage of their route of administration.

Fingolimod is the first oral drug indicated in monotherapy as a treatment modifier of the course of RRMS which is very active despite a course of complete and appropriate treatment with at least one disease-modifying therapy or as a first alternative in cases of very rapid evolution. Fingolimod was approved by the Food and Drug Administration in 2010 and by the European Medicines Agency in 2011.

Fingolimod phosphate is an analogue of the sphingosine-1-phosphate receptor (S1P) that inhibits the exit of potentially autoreactive lymphocytes from the lymph nodes to the CNS,^{7 8} and is thus considered a selective immunosuppressant. Given its lipophilic nature, fingolimod can cross the blood–brain barrier, acting directly on S1P receptors located on the cells of the CNS and thus potentially exerting a direct effect on these cells.^{9 10}

The efficacy and safety data that led to the approval of fingolimod were obtained in several phase III clinical trials. In the FREEDOMS I trial and its extension, FREEDOMS II,^{11 12} fingolimod was compared with placebo, whereas the TRANSFORMS trial¹³ examined fingolimod versus intramuscular interferon-1a. In these studies, fingolimod achieved a reduction in the risk of progression of disability and the number of inflammatory lesions, as well as an improvement in several measures of cranial magnetic resonance and cerebral atrophy. The recommended dosage of fingolimod is 0.5 mg once a day. The most frequently reported adverse events (AEs) in clinical trials were elevated transaminases, headache, bradycardia, herpes infection and macular oedema.

The objective of this study was to describe the use and safety profile of fingolimod in a tertiary level hospital, which is the only hospital of this level in our geographical area (2754 km²).

METHODS

We performed a retrospective, observational, descriptive study of the use of fingolimod in adult patients diagnosed with RRMS. This study included

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all patients older than 18 years of age treated with fingolimod between January 2015 and February 2017 or up to treatment suspension in a reference hospital in north-western Spain. Patients who commenced treatment in another autonomous community were excluded as we did not have access to their electronic medical records.

The medical records were reviewed through the IANUS application (electronic health record programme of the Galician Health Service) and the following variables were evaluated: demographic data, date of initiation and suspension of treatment, previous therapies for the treatment of MS and clinical parameters (heart rate before the administration of the first dose and after 6 hours, and change in lymphocyte count). AEs and causes of treatment suspension (temporary or permanent) were also analysed. In the case of permanent suspensions, the new drug chosen was identified.

Data were analysed using SPSS V.19 software. Descriptive analyses were carried out by calculating the number and percentage for categorical variables, whereas continuous variables were presented as mean $\pm$ SD. Group differences were compared using Fisher's exact test.

RESULTS

A total of 59 patients were included in the analysis, of which four were excluded due to a lack of data regarding the start of treatment. The included population (55 patients) comprised mainly women (66.6%), with a mean $\pm$ SD age of 42 $\pm$ 9.2 years (range 24–60). The mean age at the time of diagnosis of RRMS was 29 $\pm$ 8.6 years and the mean time from diagnosis to the start of treatment with fingolimod was 10.5 years (range 1–26 years). At the time of data collection, the average time to treatment with fingolimod was 26 $\pm$ 14.6 months (range 2–53).

Among the included patients, two (3.6%) were treatment-naïve, 41 (74.6%) had only received previous therapy and 12 (21.8%) received fingolimod as the third or fourth line of treatment.

In our institute, the initiation or change in treatment for patients with MS requires the approval of the Central Autonomous Commission of Multiple Sclerosis.

Regarding previous therapies, most patients had been treated with some type of immunomodulatory drug (29 interferon- β 1b, 19 interferon- β 1a, or 14 glatiramer acetate) and eight natalizumab (figure 1). The change from natalizumab to fingolimod was motivated by the presence of antibodies against the John Cunningham virus and the consequent risk of developing progressive multifocal leukoencephalopathy in six patients, and due to lack of efficacy in a further two patients.

No patient reported significant bradycardia. The mean heart rate prior to the administration of the first dose of fingolimod was 73 $\pm$ 10.6 beats/min and decreased to 64 $\pm$ 8.9 beats/min after 6 hours. Furthermore, no significant ECG alterations were detected.

Figure 1 Previous treatment.

Table 1 Cause of discontinuation and new treatment chosen

Permanent suspension (n)	New treatment chosen (n)
Progression/outbreaks (10)	Alemtuzumab (9) Without treatment (1)
Adverse effects (3)	Dimethyl fumarate (3)
► Urinary tract infection (2)	
► Lymphopenia (1)	

In relation to the lymphocyte count, and taking into account the mechanism of action of fingolimod, the mean value decreased from 2.02 $\pm$ 0.78 $\times$ 10⁹/L prior to the start of treatment to 0.65 $\pm$ 0.23 $\times$ 10⁹/L after 1 month of treatment, and reached 0.59 $\pm$ 0.22 $\times$ 10⁹/L at 6 months after starting treatment.

During the study period a total of 20 patients (36.4%) stopped treatment with fingolimod temporarily or permanently. Temporary suspension occurred in nine patients (16.4%), caused by the appearance of AEs in seven cases: persistent lymphopenia (4), urinary tract infection (1), continued elevation of transamines (1) and detection of macular oedema (1). Pregnancy planning caused the interruption of treatment in two patients.

Thirteen patients (23.6%) permanently discontinued treatment, of whom two had temporarily suspended treatment due to the appearance of lymphopenia and urinary tract infection. In 10 cases (77%) the suspension was motivated by disease progression and the presence of outbreaks, and by AEs (persistent lymphopenia and recurrent urinary tract infections) in the remaining 23%. The mean time from treatment initiation to permanent discontinuation was 25.1 $\pm$ 14.5 months (range 9–53). Alemtuzumab was the drug used by nine of the 10 patients who discontinued treatment with fingolimod due to disease progression; one patient at the time of data collection was not receiving treatment for his disease. In the three patients who stopped treatment due to AEs, the new treatment selected was dimethyl fumarate (table 1).

Five patients discontinued fingolimod in the first 12 months of treatment: two due to lymphopenia (months 2 and 11), one due to macular oedema (month 3), one due to urinary tract infection (month 8) and one due to disease progression (month 9).

No statistically significant differences were found between the percentage of patients who discontinued fingolimod and who had received only one previous treatment and those who had received two or more treatments ($p=0.334$). The number of previous treatments was not associated with an increased risk of discontinuations in the first 12 months ($p=0.317$).

The previous treatments used by patients and the discontinuation time of treatment with fingolimod are shown in table 2.

Other AEs detected that did not cause treatment suspension due to their mild and transient nature were headache, fatigue, constipation and visual alterations.

DISCUSSION

Based on our findings, fingolimod was used mainly as a second-line drug in patients diagnosed with RRMS, and only two of the 55 patients in our dataset started treatment with fingolimod immediately after diagnosis. These data are in alignment with the recommendations of the RRMS clinical treatment guidelines, in which fingolimod is recommended as second-line therapy, thus restricting its use as a first-line option in patients presenting with aggressive forms of RRMS.^{2,14} In a previous study by Ontaneda *et al*,¹⁵ only 3.5% of patients were treatment-naïve and 41.6% of patients started fingolimod as second-line treatment,

Table 2 Previous treatments and discontinuation time

	No discontinuation	Suspension in the first 12 months		Suspension after 12 months
		Temporary	Permanent	
Naïve	1	0	0	1
Interferon	19	2	2	11
Glatiramer acetate	4	0	1	0
Natalizumab	1	0	0	0
Interferon+glatiramer acetate	6	0	0	0
Interferon+natalizumab	2	0	0	2
Glatiramer acetate+natalizumab	1	0	0	0
Interferon+glatiramer acetate+natalizumab	1	0	0	1

compared with 74.6% in our study. However, our data support those published by Yamout *et al*,¹⁶ where 88.5% of patients started fingolimod as second-line treatment.

Al-Hashel *et al*¹⁷ conducted a retrospective study between 2011 and 2013 that included 175 patients with an average time to treatment with fingolimod of 21.7 ± 9 months. The percentage of discontinuations/suspensions was 11.4%, mainly due to disease progression and the presence of outbreaks (45%). In another multicentre study that included 906 patients with an average time to treatment with fingolimod of 158 ± 94 days, 35% of patients developed mild to moderate AEs and 2.4% experienced severe AEs. Treatment with fingolimod was suspended in 9.0% of patients, and in 4.4% of patients the suspension was due to AEs, including increased transaminases, autoimmune thrombocytopenia, troponin elevation and herpetic dermatitis. The suspension rate reported in these previous studies is lower than the 23.6% (13 patients) obtained in our study. If we analyse the reasons for suspension, our data support those of Al-Hashel *et al* which showed that disease progression and the presence of outbreaks were the main reasons for discontinuation (70%). However, Laroni *et al* found that AEs were the main cause of suspension.¹⁸ Hersh *et al*¹⁵ conducted a study with 317 patients and a mean follow-up time of 322 ± 129 days and found that fingolimod was discontinued after 248 ± 151 days from the start of treatment in 24.8% of patients. AEs reported in this study were the reason for 13.1% of suspensions, while disease progression of the disease and outbreaks accounted for 7.2%. The suspension rate reflected in this study is similar to that obtained in our study (23.6%), and this alignment may be attributable to a longer follow-up period.

By analysing the suspensions that occurred in the first 12 months after treatment initiation, we observed that five patients (10.9%) discontinued treatment, of which four were due to the appearance of AEs (lymphopenia, urinary tract infection and macular oedema) and one was due to disease progression. These findings are in accordance with the discontinuation frequency reported in a study carried out in a Galician population in 2016, in which only 5.6% of patients discontinued treatment during the first year (1.9% due to AEs and 3.7% because of disease progression).¹⁹

The small sample sizes did not allow for the detection of potential trends between naïve patients, patients who had only received previous therapy and especially those who had received two or more lines of treatment. We did not analyse the influence of previous drugs (immunomodulatory versus natalizumab) on the percentage of fingolimod suspensions.

In our study, and attributable to the pharmacodynamics of fingolimod, the lymphocyte count decreased sharply after the first month of treatment, showing a reduction from

$2.02 \pm 0.78 \times 10^9/L$ to $0.65 \pm 0.23 \times 10^9/L$ and remaining stable during long-term treatment. Francis *et al*²⁰ analysed the lymphocyte values obtained in phase II and phase III studies and their repercussion on the rate of infection. In patients treated with fingolimod 0.5 mg in the FREEDOMS study, the lymphocyte count decreased from a value of $1.86 \times 10^9/L$ prior to the start of treatment to $0.55 \times 10^9/L$ 2 weeks after treatment initiation, and remained at a stable level after 24 months of treatment ($0.49 \times 10^9/L$). This reduction in lymphocyte count did not translate into a higher rate of infections compared with placebo, however. Patients whose peak lymphocyte level was $<0.2 \times 10^9/L$ had a higher infection rate (74%) than those whose peak level was $>0.4 \times 10^9/L$ (51%). These data indicate that fingolimod does not destroy lymphocytes, but instead causes a selective and reversible retention of naïve T lymphocytes, memory T lymphocytes and B cells present in lymph nodes, causing multiple immune functions to be preserved during treatment.²¹

From a cardiological perspective, the initiation of treatment with fingolimod can produce a transient decrease in heart rate and an associated delay in atrioventricular conduction, including total and transitory atrioventricular block. In our study, no patient suffered significant alterations in heart rhythm or ECG abnormalities; these data agree with previous studies.²² Laroni *et al* studied the tolerability of the first dose of fingolimod 0.5 mg in a cohort of 906 patients, of which 2% suffered some AEs at the cardiovascular level including bradycardia (1.3%) and second-degree atrioventricular block type Mobitz I (0.2%). Treatment with fingolimod was suspended in only two patients (0.2%), of whom one discontinued due to persistent bradycardia (heart rate 59 beats/min) and another due to a second-degree atrioventricular block type Mobitz I that resolved spontaneously.²³

In this study no neoplasms were detected, although the follow-up period may have been insufficient to detect this AE. No deaths were reported.

The main limitations of the study were its observational, retrospective and unicentric design, short follow-up period and the small sample sizes.

Fingolimod is proposed as a safe therapy for the treatment of RRMS. Its oral administration improves the quality of life and

What this paper adds

What is already known on this subject

- The efficacy and safety profiles of fingolimod have been well established in clinical trials.

What this study adds

- This study shows the real-world use and safety of fingolimod.

the level of patient satisfaction. However, future studies in real-world clinical practice are necessary to detect less frequent AEs, or those occurring with long-term fingolimod treatment.

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