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Long-Term Cardiac Safety and Tolerability of Fingolimod in Multiple Sclerosis: A Postmarketing Study

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Abstract

Fingolimod is the first oral disease-modifying therapy approved for multiple sclerosis (MS). The risks associated with the use of fingolimod include cardiovascular adverse events (AEs). First-dose observation (FDO) is required for all patients for at least 6 hours. We describe FDO data and long-term cardiac tolerability in a cohort of fingolimod-treated relapsing MS patients. Two hundred and twelve patients started fingolimod 0.5 mg once daily. Before the first administration, all subjects had an electrocardiogram (ECG) with cardiologist interpretation. Following administration they were monitored for 6 hours and underwent a cardiac monitoring every 3 months. In this cohort, there was a heart rate reduction at the VI hour of 9.6 ± 8 beats per minute ($P < .001$). Fifty-four individuals (25.5%) presented an abnormal ECG during the 6 hours. We experienced 1 case (0.22%) of symptomatic second-degree atrioventricular block. The mean follow-up period was 1.5 ± 0.7 years. During this period, 1 patient showed atrial fibrillation that needed to be treated. We also observed 5 cases of persistent increase in blood pressure. This postmarketing study shows that fingolimod is well tolerated and tha tcardiologic AEs are generally self-limited in the long term.

Keywords

cardiac, fingolimod, first-dose observation, multiple sclerosis, long-term safety

The scenario of specific therapies for multiple sclerosis (MS) is constantly evolving. After the era of beta interferons and glatiramer acetate, new agents are now available for MS patients. Despite the evidence of their higher efficacy, the safety profile has to be better defined.

Fingolimod (Gilenya; Novartis Pharma AG, Basel, Switzerland), was the first oral disease-modifying therapy (DMT) approved for the treatment of MS.[1–3] Its efficacy in reducing relapse rates, compared with both placebo and intramuscular interferon β-1a, and slowing disability progression, compared with placebo, was established in 3 phase 3 clinical trials: FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis),[4] FREEDOMS II,[5] and TRANSFORMS (Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis).[6] The trials examined the 0.5- and 1.25-mg doses of fingolimod, with the lower dose proving as efficacious as the higher dose; the 0.5-mg dose was then authorized because of its better safety profile.

Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator. S1P receptors have 5 identified subtypes, and their functions include lymphocyte recirculation, neurogenesis, neural cell migration, natural killer cell migration, endothelial cell function, vasoregulation, and cardiovascular development.[7] The effectiveness of fingolimod is due to the sequestration of primarily naive and memory T lymphocytes within lymph nodes, thus reducing lymphocyte presence in the blood.[1,2,7]

However, the presence of sphingosine in the cardiovascular system is also related to the occurrence of some cardiovascular side effects attributable to fingolimod: the initiation of the treatment, for example, determines a transient reduction of the heart rate (HR) and can also be associated with the slowing of atrioventricular (AV) conduction; the intensity of the negative chronotropic effect of the drug generally passes within 24 hours.[8,9] This reduction of the HR is probably linked to the activation, mediated by the S1P1 receptor, of the potassium channel coupled to G-protein in atrial myocytes; such activation could lead to hyperpolarization of the cells, reducing their

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excitability. S1P1 receptor internalization could also be related to the transient nature of this effect.[10]

In phase 2 and 3 clinical trials, the maximal reduction in the HR was observed 4–5 hours after the beginning of the treatment, with an average of 8 beats per minute (bpm), in patients treated with fingolimod 0.5 mg. Moreover, the HR rarely dropped below 40 bpm and returned to baseline within 1 month of continuous treatment. Bradycardia was usually asymptomatic, although some patients (0.5%) experienced slight to moderate symptoms (dizziness, fatigue, and/or palpitations), which were resolved within the first 24 hours. After the first dose administration, a first-degree arteriovenous block (AVB) was observed in 4.7% of treated patients and a second-degree AVB in less than 0.5%.[8]

With regard to the effects of fingolimod on QT interval at stable state (when the negative chronotropic effects of the drug were still present), the treatment led to a prolongation of the corrected QT (QTc), with no observed dose-response or exposure-response relationship.[9]

An important update on the cardiovascular effects of fingolimod is given by the presentation of the data of the FIRST study (Fingolimod Initiation and Cardiac Safety Trial),[11–13] in which patients with cardiovascular risk factors (concomitant use of beta-blockers, low HR, second-degree or higher conduction block, recurrent symptomatic bradycardia, positivity to the Tilt table test, diabetes, or chronic asthma), not included in previous clinical trials, were enrolled. This study showed no new areas of cardiovascular attention and has extended our knowledge of the previously reported short-term safety and tolerability profile of fingolimod, in relation to both first-dose effects and the first 4 months of treatment. Bradycardia adverse events (AEs) occurred in 0.6% of patients and were more frequent in individuals receiving beta-blockers and/or calcium channel blockers (3.3%) than in other subgroups (0.5%–1.4%); most events were asymptomatic, and all patients recovered without pharmacological intervention.

Another source of data was the analysis on the first-dose observation (FDO) results of the pivotal phase 3 trials (FREEDOMS TRANSFORMS, and FREEDOMS II), in which, the favorable tolerability profile of fingolimod, after the first dose was emphasized.[14]

A US study on a fingolimod-treated cohort also highlighted the good cardiologic safety profile of the drug in clinical practice.[15] A recent Italian trial, which resembled clinical practice in terms of comorbidity and concomitant medications,[16] provided results on the FDO consistent with previous clinical trials.

The cardiac safety and tolerability of fingolimod in an MS patient population are of interest, especially because of the lack of answers to long-term safety issues. The aim of this study is to present our postmarketing experience regarding the FDO data and long-term cardiac tolerability in an Italian cohort of relapsing MS fingolimod-treated patients.

Methods

We collected data from 212 patients with relapsing MS according to the McDonald-Polman criteria,[17–19] treated with fingolimod 0.5 mg, 1 capsule per os daily. All patients were followed at the Center of Diagnosis and Treatment of Demyelinating Diseases of the Department of Basic Medical Sciences, Neuroscience and Sense Organs of the University Hospital of Bari. Clinical and therapeutic information on our population was collected using the electronic iMed database. The first dose administration took place between December 2011 and June 2014.

The protocol of this study was approved by the local Institutional Review Board of the Univeristy of Bari, Italy. All subjects signed informed consent to treatment. All patients had a screening 12-lead electrocardiogram (ECG) with cardiologist interpretation and underwent a complete cardiac monitoring (ECG with cardiologist interpretation, echocardiogram, and blood pressure [BP] evaluation) every 3 months from the beginning of therapy.

The neurological conditions of patients were assessed using the Expanded Disability Status Scale (EDSS) score. The EDSS is a tool widely used to clinically measure and evaluate MS patients' level of functioning, providing a total score on a scale ranging from 0 to 10, with an EDSS of 0–3.5 related to fully ambulatory patients, 4.0–6.5 to ambulatory patients with possible need of constant bilateral assistance, 7.0–9.5 to patients restricted to the wheelchair, confined to bed with need of total and complete assistance, and 10 to death due to MS.[20]

For continuous data (current age, baseline EDSS score, age at disease onset, disease and treatment duration pre-fingolimod, QTc, BP, and HR values), the mean $\pm$ standard deviation [SD]) values were calculated. For categorical variables (sex, previous therapies, occurrence of AEs), absolute and relative incidence was calculated. Changes in the continuous data were analyzed post hoc with the Wilcoxon rank sum test. A chi-square analysis was performed to assess the association between categorical variables (sex and previous use of second-line agents) and the occurrence of ECG trace alterations during the 6 hours of monitoring. Mann-Whitney *U* tests were performed to study the association between the variations in cardiologic parameters and previous use of second-line therapies and sex. Mann-Whitney *U* tests were also performed to verify the association between continuous data (age, EDSS score, treatment or disease duration pre-fingolimod) and the occurrence of EGC alterations. Significance for all tests was defined as $P < .05$.

The most frequent cardiologic AEs were noted in terms of relative and absolute incidence.

All analyses were performed with SPSS software version 17.0.

Results

Demographics and disease history of the cohort are summarized in Table 1.

The mean follow-up period was 1.5 ± 0.7 years. One hundred and forty-seven patients (69.3%) were female, and 65 (30.7%) were male. The mean age at the first administration was 37.7 ± 9.5 years. The mean disease duration was 12.8 ± 7.7 years, and the mean EDSS score was 3.6 ± 1.5, which means that the patients were fully ambulatory but with moderate disability in at least 1 functional system.

The baseline cardiologic profile of our population is reported in Table 2. The mean QTc value was 424 ± 19.2 (427.3 ± 20.4 for women; 416.9 ± 13.9 for men; $P < .0001$).

Of the 212 patients, 31 (14.6%) presented preexisting comorbidity that could have influenced their cardiac safety: 9 patients had hypertension (treated with angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptors blockers, beta-blockers, and diuretics in 2, 3, 1, and 3 patients, respectively), 2 had diabetes (1 treated with long-acting insulin and the other with sulfonylurea drugs), and 20 had thyroid disorders (14 of which were treated with levotiroxine). All patients were in good control with treatment.

In our cohort, at the end of 6 hours of monitoring, the HR average was 66.8 ± 9.3 bpm, with a mean reduction of 9.6 ± 8 bpm ($P < .001$). The maximal reduction in HR was in the fourth hour, with an average reduction of 11.5 ± 7.9 bpm. During the monitoring, HR did not drop below 47 bpm. At the end of the monitoring, 13 patients (6%) showed an HR < 55 bpm, and the lowest value was 52 bpm; none of the patients experienced symptomatic bradycardia after FDO. Fifty-four (25.5%) presented a transient abnormal ECG during the 6-hour monitoring (Table 3). Seven of these 54 patients had preexisting comorbidities, and 5 of them received concomitant medication (in 2 cases subjects had a thyroiditis for which the endocrinologists did not recommend any treatment). No association was found between these changes in ECG tracings with the other baseline characteristics, even in those patients who underwent concomitant treatment with a potential effect on cardiac function (the higher risk in this sense was for the patient who was treated with beta-blockers; this patient, however, did not show ECG abnormalities).

We needed to prolong the cardiac monitoring for 2 patients: in 1 of them it was necessary to extend the observation for 3 hours because of the presence of a prolonged QTc (maximum value, 499 milliseconds); in the other case it was necessary to extend the monitoring for 2 hours for the presence of a significant change in HR (difference pre-/posttreatment, 22 bpm). Both patients were discharged without any further problems. Considering the effect of the drug on QT interval, at the end of FDO, we recorded a statistically significant reduction ($P < .0001$) on average of QTc of 4.4 ± 15.8 milliseconds (mean postdose QTc, 418.5 ± 19.6 milliseconds; 422.9 ± 19.3 for female subjects, 409.6 ± 17.1 for male subjects; $P < .0001$). Moreover, for another patient it was necessary to definitively suspend the treatment after the first dose because of the occurrence of a symptomatic second-degree AV block.

Table 1. Clinical and Demographic Characteristics of the Patients

	Total (n = 212)
Sex: M	30.7% (65)
F	69.3% (147)
Age at first dose of fingolimod, mean ± SD	37.7 ± 9.5
Age at disease onset, mean ± SD	25.2 ± 8.4
Disease duration pre-fingolimod, mean ± SD	12.8 ± 7.7
Treatment duration pre-fingolimod, mean ± SD	7.5 ± 4.5
EDSS score at first dose, mean ± SD	3.6 ± 1.5
Previous therapies	
Only first-line agents (β-IFNs and/or GA)	131 (61.8%)
First- and second-line agents (mostly NTZ)	81 (38.2%)

SD, standard deviation; EDSS, Expanded Disability Status Scale; β-IFNs, beta interferons; GA, glatiramer acetate; NTZ, natalizumab.

Table 2. Cardiovascular Baseline of the Cohort

	Total (n = 212)
QTc value, mean ± SD	424 ± 19.2
HR, mean ± SD	76.4 ± 10.6
Systolic BP, mean ± SD	116.3 ± 13.4
Diastolic BP, mean ± SD	69.8 ± 10.3

QTc, corrected QT; SD, standard deviation; HR, heart rate; BP, blood pressure.

Table 3. Electrocardiogram Abnormalities During the FDO

Abnormalities	Number of Patients
Prolonged QT	23
Ventricular extrasystoles	7
Incomplete right bundle branch block	6
Right focal block	5
Isolated first-degree AVB	5
Runover with ventricular stretch of marked sinus bradycardia	4
Prolonged QT with right focal block	2
Nonspecific repolarization in the front seat	1
Run of nonsustained ventricular tachycardia	1
	Total = 54

All the cardiovascular effects of the treatment are reported in Table 4. No statistical association was found between the variations in cardiologic parameters and the baseline characteristics of the cohort, even in those patients with preexisting comorbidities and concomitant medications.

At the end of FDO, monitoring of the BP showed an average reduction of 4.8 ± 12.4 mm Hg in systolic, and 3.8 ± 10.4 mm Hg in diastolic BP values ($P < .001$).

Starting at the sixth month follow-up, 5 patients showed a persistent increase in BP, which in 4 cases needed to be treated. From the third month of follow-up, another of our patients, a 54-year-old woman, showed atrial fibrillation (AF) that needed to be treated with beta-blockers.

Apart from these 6 cases, after 1 year of follow-up, vital signs remained within normal standards: the average BP was 121.1 ± 4.2 mm Hg for systolic and 77.3 ± 8.4 mm Hg for diastolic, and both these values were significantly lower than the ones observed at the end of the first dose monitoring ($P = .002$ and $P < .001$, respectively, for systolic and diastolic BP). The HR showed an average of 73 ± 9 bpm.

Also, the other cardiac parameters showed no abnormalities at the long-term follow-up: the mean QTc value was 415.7 ± 35 milliseconds (412.8 ± 26 milliseconds for female subjects, 420.7 ± 50 milliseconds for male subjects), and the Holter ECG showed no significant rhythm disorders or significant changes in ventricular repolarization, with the only exception being the patient with AF mentioned above. The mean ejection fraction was $66.7\% \pm 5\%$, and no pathological abnormalities were shown in echocardiocardiography.

Discussion

In this postmarketing experience, fingolimod appears well tolerated in regard to the cardiovascular profile. In our cohort 131 patients (61.8%) had been previously treated only with first-line agents (beta interferons and/or glatiramer acetate), whereas 81 (38.2%) had already experienced other second-line treatments (mostly the monoclonal antibody natalizumab), but previous DMTs did not seem to affect in any way the cardiovascular tolerability of the drug.

Table 4. Cardiovascular Effects of Fingolimod Treatment

Maximal HR variation (bpm)	-16 bpm
Lowest HR (bpm)	47
Incidence of atrioventricular block	1 (0.22%)
Postdose QTc (mean ± SD)	418.5 ± 19.55 milliseconds

HR, heart rate; bpm, beats per minute; SD, standard deviation; QTc, corrected QT.

In our cohort, the maximal reduction in HR occurred in the fourth hour. Instead, in the FREEDOMS pivotal trial, the maximal reduction in the mean resting pulse rate, compared with the baseline values, was 8 bpm in the fifth hour after fingolimod 0.5 mg intake. The onset of the slowing of the pulse rate was similar to the one observed in the patients with preexisting cardiac conditions in the FIRST study; the other study group, composed of patients without cardiovascular comorbidity, reached a mean nadir pulse rate in the fifth postdose hour.[11–13] We have to consider that in another US observational study,[15] the maximal drop in the HR was reported in the sixth hour.

As regards the entity of the HR changes, our experience showed a decrease of 9.6 ± 8 bpm. This value is lower than that observed in the US cohort (12 bpm) and more similar to the one found in the FREEDOMS study. However, in our cohort, this decrease in the pulse rate led to an HR that never dropped under 47 bpm, different from what happened in the FIRST study, in which 16 patients (1.3%) reached frequencies below 45 bpm during the monitoring period. This might be due to the presence in the FIRST study of a higher frequency of patients (5.0%) treated with beta-blockers or calcium channel blockers, which had a lower baseline mean pulse rate (as expected with these medications) that may have potentially predisposed these patients to more severe bradycardia.

One of our patients experienced a second-degree AVB, different from what happened in the pivotal trial, in which this event did not occur at the 0.5-mg dose. Also, in the Italian trial,[16] 2 cases of second-degree AVB and 1 case of first-degree AVB were detected.

Although mild prolongation of the QTc could be expected considering the drug mechanism of action, in our population there was a statistically significant reduction in the QTc interval. However, it should be noted that no significant dose- or concentration-dependent effects of fingolimod were observed on the QT interval in a placebo-controlled study of healthy volunteers.[21] We observed the presence of a longer QTc interval in women than in men, both in pre- and postdose observation, confirming this gendered predisposition reported in many studies.[22,23]

The vast majority of patients in our population were discharged after 6 hours, and a prolongation of the monitoring was required in only 2 cases (0.9%); this meant a lower frequency than the one observed in the Italian trial, in which extended monitoring was required in 34 subjects (3.8%). Neither ECG pre- and postdose, nor continuous ECG monitoring was mandated by the study protocol of the Italian trial; ECG was only performed at discharge or at any time during the 6 hours if clinically indicated and evaluated by a cardiologist. However, continuous monitoring may lead to more accurate surveillance during the first dose administration that could influence the decision about whether to discharge

patients taking into consideration their global cardiovascular profile, not only their HR, which was the most frequent reason for prolonged monitoring in the Italian trial (3.0% of cases). Another possible reason for the lower percentage in our study of patients who needed prolonged monitoring could be their more strict selection at the beginning of the therapy, working together with other specialists (more frequently endocrinologists and cardiologists) to avoid, where possible, the use of many medications that can cause bradycardia or influence cardiac conduction. Moreover, we have to consider that different from our study, the Italian trial reported the first dose events registered during the Expanded Access Program, a premarketing study that enrolled several patients with no other treatment options and probably with longer disease and therapeutic histories, too.

The FREEDOMS study showed a 6.1% incidence of increased BP during 2 years of follow-up, starting during month 2. In our 1.5-year follow-up, the incidence of this finding was 2.3% (5 cases), and all these cases showed up by the sixth month. An increase in BP may be due to the interactions with sphingosine-1-phosphate receptors in the smooth muscle. Four of the 5 patients who showed a higher BP underwent an antihypertensive treatment: 2 men, aged 48 and 45, both treated with ACE inhibitors for grade 1 hypertension, and 2 women, aged 40 and 49, who also had grade 1 hypertension. The younger woman was treated with ACE inhibitors and the second one with angiotensin receptor blockers because of the lack of tolerance to a first treatment with ACE inhibitors. All these patients reached target BP after an average of 2 months and showed no other cardiovascular complications during our follow-up period of 1.5 ± 0.7 years. The fifth patient mentioned above, a 34-year-old woman, instead showed isolated systolic hypertension, which her cardiologist managed with appropriate changes in her lifestyle, achieving the goal BP after 2 months.

Conclusion

Globally, therefore, the tolerability and cardiovascular profile of fingolimod in our real-life setting was confirmed safe after about 1.5 years of follow-up, even in those cases (14.6%) with cardiovascular comorbidity. One of the study limitations is the lack of a baseline assessment of the autonomic control of cardiovascular functions. Such a control could be useful to provide individualized monitoring after the first drug intake, as shown in a recent Italian study.[24] The new emerging therapies for MS can be very attractive both for patients and clinicians as a precious opportunity of treatment, and our population can be a good representation of what happens in everyday clinical practice. However, it is very important to properly evaluate and characterize the aspects of long-term safety on larger populations to assess the manageability of these drugs.

Declaration of Conflicting Interests

Dr. Paolicelli received honoraria for consultancy and/or speaking from Biogen Idec, Merck-Serono, Bayer-Schering, Sanofi-Aventis, TEVA, Novartis, and Genzyme.

Dr. Tortorella received honoraria for consultancy and/or speaking from Biogen Idec, Merck-Serono, Bayer-Schering, Sanofi-Aventis, TEVA, Novartis, and Genzyme.

Dr. Trojano received honoraria for consultancy or speaking from Biogen, Sanofi-Aventis, Merck Serono, Novartis, Genzyme, TEVA, and Bayer-Schering and research grants from Merck Serono, Biogen, and Novartis.

Dr. Direnzo received personal compensation for activities by TEVA.

Dr. D'Onghia received personal compensation for activities by TEVA.

Dr. Zoccolella and Dr. Manni have declared no competing interests.

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