The outbreak fingolimod cardiovascular side effects in relapsing-remitting multiple sclerosis patient: A longitudinal study in an Iranian population

Morteza Abdar[(1)], Payam Ebrahimifar[(2)], Masoud Etemadifar[(3)]

Original Article

Abstract

BACKGROUND: Fingolimod (FTY-720) has shown efficacy in relapsing multiple sclerosis (MS), while some side effects of this drug have been recognized that the most important is cardiovascular side effects. The aim of this study was to evaluate the cardiovascular side effects of FTY-720. However, the effect of fingolimod on cardiac has not been well recognized. This study was designed to evaluate the cardiovascular side effects of fingolimod in relapsing-remitting multiple sclerosis (RRMS) patient in an Iranian population.

METHODS: This prospective clinical trial study was performed on 200 RRMS patients. The patients received a single daily oral dose of fingolimod 0.5 mg. During the first 6 hours after the first fingolimod dose, the patients' vital signs and electrocardiographic traces were continuously monitored. Moreover, the patients followed up over 6 months after receiving fingolimod.

RESULTS: The results showed that pulse rate ($P < 0.001$), systolic blood pressure (BP) ($P < 0.001$), and diastolic BP ($P < 0.001$) were decreased significantly during 6 hours after receiving the first dose of fingolimod. The most reduction in vital sign was observed in 3 hours. Arrhythmia, bradycardia, and dizziness were the other complications of fingolimod, which were detected in our study.

CONCLUSION: All the side effects such as hypotension and bradycardia were happened in first 3 hours after receiving the fingolimod. Indeed, we advise clinicians to monitor the patients for first 6 hours after initiation of fingolimod to decrease worse side effects.

Keywords: Fingolimod, Cardiovascular, Side Effect, Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is considered as a chronic autoimmune disease with increasing prevalence and incidence,[1,2] which led to a significant expansion in the range of therapeutic options.[3] Therapeutic strategies direct immune modulation and control of inflammatory processes. First-line drugs for MS are interferon beta-1 and glatiramer acetate which have moderate efficacy and frequent side-effects. These features of first line drugs limited long-term adherence consequently restrict their efficacy compared with second-line therapies as fingolimod and natalizumab.[4,5]

Fingolimod (also known as FTY-720) has shown efficacy in relapsing MS,[6,7] which is an oral sphingosine-1-phosphate (S1P) receptor modulator that blocks lymph node egress of lymphocytes expressing the homing receptor CC-chemokine receptor 7 that may include autoreactive T and B-cell subsets, and patients become gradually lymphopenic after a few days of treatment.[8]

However, fingolimod has some side effects such as affecting on cardiac which is associated with a decrease in heart rate (HR) and slowing of atrioventricular (AV) conduction. This is a recognized pharmacological effect of fingolimod, mediated by modulation of S1PR subtype 1 (S1P1) on atrial myocytes, which is similar to vagal stimulation. The effect is typically transient, owing to the internalization/desensitization of S1P1,[9] leading to functional antagonism rather than agonism. However, the effect of fingolimod on cardiac has not been well recognized. Therefore, this study was designed to evaluate cardiovascular side effects of fingolimod in relapsing-remitting multiple sclerosis (RRMS) patient.

1- Professor, Department of Cardiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2- Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Professor, Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Payam Ebrahimifar, Email: payame1383@yahoo.com

Materials and Methods

This prospective clinical trial study was conducted in Neurology Department of Isfahan Alzahra Hospital, Center of Iran from August 2014 to December 2015. Inclusion criteria consisted of patient referred to neurology department of Alzahra Hospital with a diagnosis of RRMS with age > 18-year-old, expanded disability status scale (EDSS) between 0.5 and 6.5 and having indication to receive fingolimod. Exclusion criteria consisted of patients with other immune system diseases in addition to MS, concurrent malignancy, active infection, use of any drug potentially affecting cardiac rhythm or function within the 4 weeks preceding study entry, uncontrolled diabetes, macular edema and advanced diabetic retinopathy, previous cardiac disease or abnormal electrocardiographic (ECG) findings, having contraindications for receiving fingolimod [(1) History of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack in the last 6 months, (2) heart failure functional Class 3 or 4, (3) Mobitz Type II-3rd degree atrioventricular block (AVB)–sick sinus syndrome, (4) baseline QTc interval ≥ 500 ms, and (5) taking Class Ia or Class III antiarrhythmic drugs].

A total of 215 patients with an RRMS, who had been diagnosed by neurologist and based on inclusion and exclusion criteria were included in the study. We consecutively enrolled patients with RRMS whose neurologists had advised them to start treatment with a single daily oral dose of fingolimod 0.5 mg. 15 patients excluded due to having contraindications for receiving fingolimod (two patients), uncontrolled diabetes (four patients), loss to follow-up (four patients), other immune system diseases (one patient), abnormal ECG (one patient), and previous cardiac disease (three patients).

Finally, 200 patients completed the study. The study received ethics approval from the Ethics Committee of Isfahan University of Medical Sciences (394, 246), and all participants gave written informed consent.

During the first 6 hours after the first fingolimod dose, the patients' vital signs and ECG traces were continuously monitored to detect any decrease in HR or the prolongation of any ECG interval; the monitoring period was extended in the case of patients who developed significant bradycardia or PQ prolongation. Patients' vital signs and ECG traces were measured each hour for 6 hours after receiving first fingolimod dose.

Since the incidence of bradycardia could make heart palpitations for patients, about feeling heart palpitations in patients were asked and recorded. According to some reports mentioned that fingolimod consumption has been associated with the development chest pain; therefore, existence of angina within 6 hours was asked from patients.

In the absence of significant changes in blood pressure (BP), pulse rate (PR) and symptoms, the subsequent doses will continue outside clinics daily. The patient was admitted to visit and receive medication monthly, and BP and HR were recorded. Due to constant changes, particularly an increase in BP may occur several months after starting medication, the patients will be re-examined at 3 and 6 months. The study flowchart is presented in figure 1.

Data were analyzed and reported only for patients who completed the trial. Statistical analysis of data was performed using SPSS software (version 22, IBM Corporation, Armonk, NY, USA) software. The analysis was performed using descriptive statistics such as mean and standard deviation and analytical statistics such as t-test and chi-square tests. Repeated measurement ANOVA was used to explore the interaction effects of time on PR, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Statistical significance was set at 0.05.

Results

About 15 patients were dropped out, and finally, 200 patients completed the study. The mean age of patients were 32.19 ± 6.44 years and 147 (73.5%) patients were female. Moreover, the mean score of EDSS of patients were 2.58 ± 1.19. As seen the mean of PR before starting fingolimod for patients was 81.60 ± 7.92 per minutes. While the fingolimod was started for patients, the mean of PR decreased, which were 80.40 ± 7.56, 77.60 ± 6.34, 69.30 ± 8.62, 63.60 ± 7.27, 63.00 ± 7.35, 65.87 ± 6.21, and 69.19 ± 5.27/minutes in half, 1-6 hours after receiving fingolimod for each hour, respectively. The peak of reduction in PR was at 4 hours after receiving fingolimod. Moreover by following the patients after 3 and 6 months after receiving the first dose of fingolimod, the mean of PR was 81.34 ± 9.40 and 80.94 ± 9.37 per minutes. 1-6 hours after receiving fingolimod, patients mean of PR was altered significantly from baseline ($P < 0.001$). After 3 and 6 months follow-up, patients PR measuring revealed statistically significant difference from baseline ($P < 0.001$) (Table 1 and Figure 2).

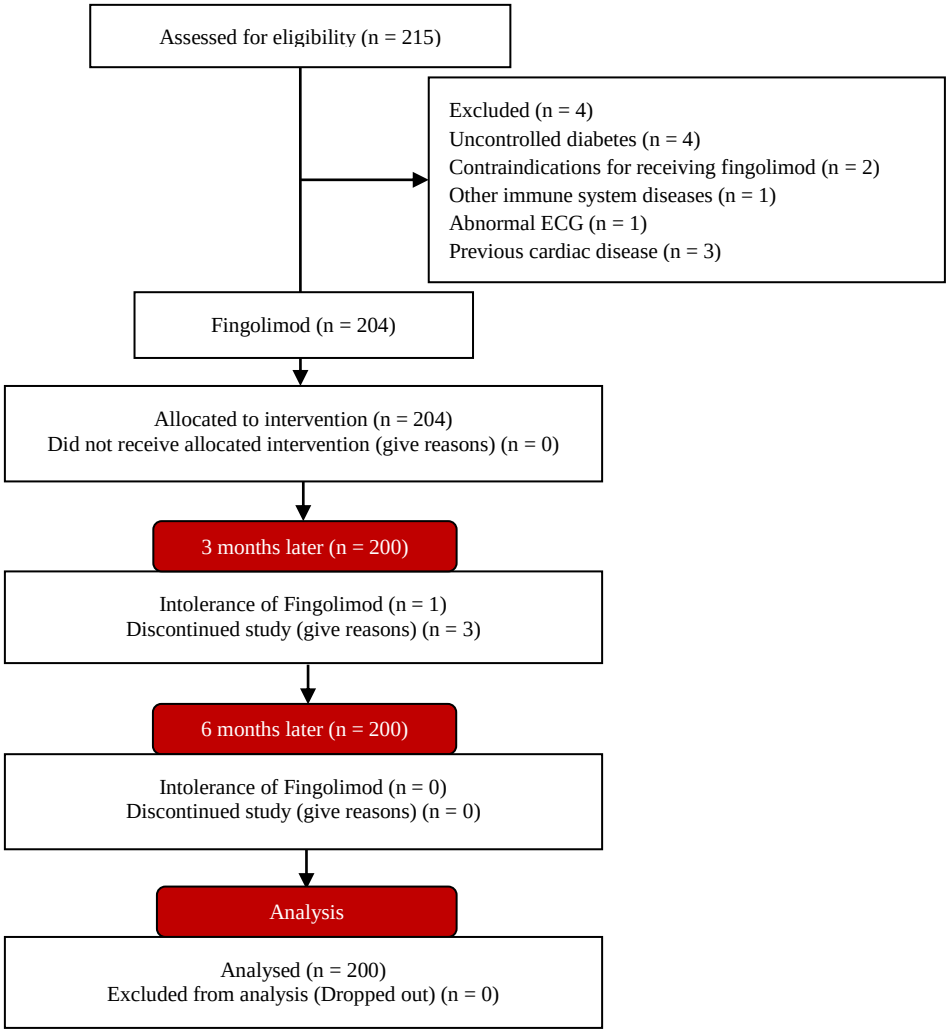

Figure 1. Study flowchart

Table 1. Pulse rate (PR) changes in patients receiving fingolimod during 6 months of follow-up confidence interval (CI 95%)

PR	Mean ± SD	P
Base	81.60 ± 7.92	< 0.001
After half hour	80.40 ± 7.56	
After 1 hour	77.63 ± 6.34	
After 2 hours	69.30 ± 8.62	
After 3 hours	63.61 ± 7.27	
After 4 hours	63.00 ± 7.35	
After 5 hours	65.87 ± 6.21	
After 6 hours	69.19 ± 5.27	
After 3 months	81.34 ± 9.40	
After 6 months	80.94 ± 9.38	

PR: Pulse rate; SD: Standard deviation

Furthermore, the mean of SBP before starting fingolimod for patients, was 120.27 ± 9.85 mmHg. While the fingolimod was started for patients, the mean of SBP decreased, which were 119.65 ± 9.59, 117.77 ± 10.58, 112.10 ± 11.44, 108.45 ± 10.89, 109.70 ± 10.24, 112.32 ± 9.63 and 114.22 ± 8.91 mmHg in half, 1-6 hours after receiving fingolimod for each hour, respectively.

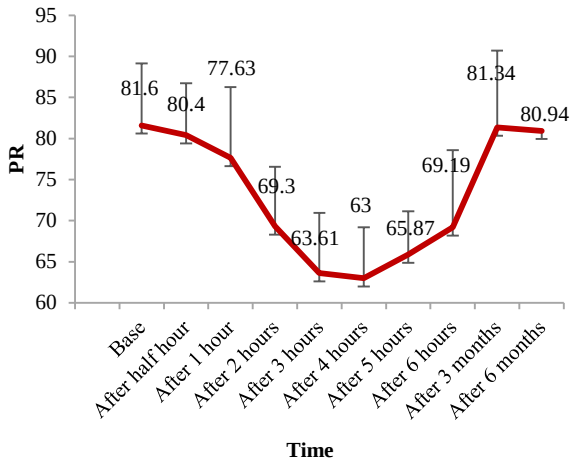

Figure 2. Pulse rate changes in patients receiving fingolimod during 6 months of follow-up
PR: Pulse rate

The peak of reduction in SBP was at 3 hours after receiving fingolimod. Moreover by following the patients after 3 and 6 months after receiving the first dose of fingolimod, the mean of SBP was 122.35 ± 9.58 and 122.72 ± 9.15 mmHg. 1-6 hours after receiving fingolimod, patients mean of SBP was altered significantly from baseline (P < 0.001). After 3 and 6 months follow-up, patients SBP measuring revealed statistically significant difference from baseline (P < 0.001) (Table 2 and Figure 3).

Table 2. Systolic blood pressure (SBP) changes in patients receiving fingolimod during 6 months of follow-up confidence interval (CI 95%)

SBP	Mean ± SD	P
Base	120.27 ± 9.85	< 0.001
After half hour	119.65 ± 9.59	
After 1 hour	117.77 ± 10.58	
After 2 hours	112.10 ± 11.44	
After 3 hours	108.45 ± 10.89	
After 4 hours	109.70 ± 10.24	
After 5 hours	112.32 ± 9.63	
After 6 hours	114.22 ± 8.91	
After 3 months	122.35 ± 9.58	
After 6 months	122.72 ± 9.15	

SBP: Systolic blood pressure; SD: Standard deviation

As obtained, the mean of DBP before starting fingolimod for patients, was 70.45 ± 6.69 mmHg. While the fingolimod was started for patients, the mean of DBP decreased, which were 69.48 ± 7.12, 68.59 ± 6.34, 65.83 ± 5.80, 64.04 ± 5.34, 64.37 ± 5.11, 65.02 ± 5.57 and 66.92 ± 4.33 mmHg in half, 1-6 hours after receiving fingolimod for each hour, respectively.

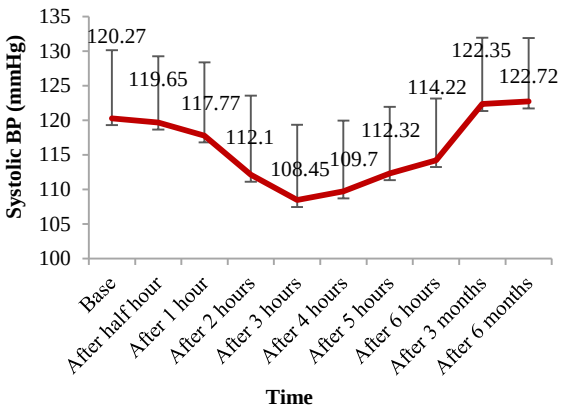

Figure 3. Systolic blood pressure changes in patients receiving fingolimod during 6 months of follow-up
BP: Blood pressure

The peak of reduction in DBP was at 3 hours after receiving fingolimod. Moreover by following the patients after 3 and 6 months after receiving the first dose of fingolimod, the mean of DBP was 70.92 ± 7.52 and 71.62 ± 7.71 mmHg (P < 0.001). 1-6 hours after receiving fingolimod, patients mean of DBP was altered significantly from baseline (P < 0.001). After 3 and 6 months follow-up, patients DBP measuring revealed statistically significant difference from baseline (P < 0.001) (Table 3 and Figure 4).

Table 3. Diastolic blood pressure (DBP) changes in patients receiving fingolimod during 6 months of follow-up confidence interval (CI 95%)

DBP	Mean ± SD	P
Base	70.45 ± 6.69	< 0.001
After half hour	69.48 ± 7.12	
After 1 hour	68.59 ± 6.34	
After 2 hours	65.83 ± 5.80	
After 3 hours	64.04 ± 5.34	
After 4 hours	64.37 ± 5.11	
After 5 hours	65.02 ± 5.57	
After 6 hours	66.92 ± 4.33	
After 3 months	70.92 ± 7.52	
After 6 months	71.62 ± 7.71	

DBP: Diastolic blood pressure; SD: Standard deviation

The most complications rate of fingolimod was bradycardia, which was seen more at 4 hours after receiving the first dose (72 patients (36%) (P < 0.001), moreover, dizziness was the second complications which were seen more at 2 and 3 hours after drug was administrated (35 patients 17.5%) (P < 0.001) (Table 4).

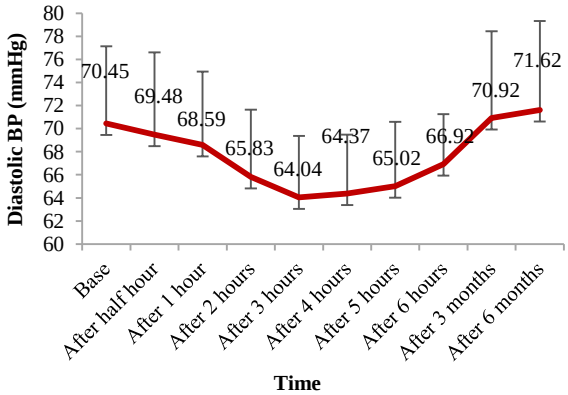

Figure 4. Diastolic blood pressure changes in patients receiving fingolimod during 6 months of follow-up
BP: Blood pressure

Discussion

Our results showed that the first dose of fingolimod was associated with a transient, mostly asymptomatic, decrease in HR, which was in

consistent with previous studies.[6,7,10,11] A larger maximal change in HR was observed at 4 hours after receiving fingolimod. On the other hand, the maximal change in SBP and DBP was measured as a change from baseline 3 hours post-dose of fingolimod. Although the occurrence of bradycardia was rare in the overall study population, more cases of bradycardia were observed during the first 4 hours of treatment.

Table 4. Complications in patients receiving fingolimod during 6 hours of follow-up

Complications	Time (hours)	n (%)	P
Headache	After 1	0	0.998
	After 2	1 (0.5)	
	After 3	2 (1.0)	
	After 4	0	
	After 5	0	
	After 6	0	
Dizziness	After 1	8 (4.0)	< 0.001
	After 2	18 (9.0)	
	After 3	35 (17.5)	
	After 4	35 (17.5)	
	After 5	24 (12.0)	
	After 6	19 (9.5)	
Chest pain	After 1	0	0.998
	After 2	1 (0.5)	
	After 3	2 (1.0)	
	After 4	0	
	After 5	0	
	After 6	0	
Bradycardia	After 1	26 (13.0)	< 0.001
	After 2	45 (22.5)	
	After 3	59 (29.5)	
	After 4	72 (36.0)	
	After 5	64 (32.0)	
	After 6	42 (21.0)	

The overall incidence of AVBs following treatment initiation was low. Mobitz Type I second-degree AVBs and 2:1 AVBs occurred in 6% of patients in the first 6 hours post-dose, which were new-onset AVBs post-dose. Consistent with previous findings, conduction abnormalities were asymptomatic and no patients developed a Mobitz Type II second-degree AVB or complete AVB.

The study findings confirm that cardiac effects following the first dose of fingolimod are transient, which observed in the first 6 hours post-dose; this is consistent with previous studies.[6,7,11] Fingolimod is an oral S1P receptor modulator that blocks lymph node egress of lymphocytes expressing the homing receptor C-C chemokine receptor type 7 that patients become gradually lymphopenic after a few days of treatment.[8] However, S1P receptors are expressed by other cells like cardiac myocytes[12] and glial cells (astrocytes and oligodendrocytes)[13,14] and may promote physiological changes and activation of downstream signaling yet to be fully clarified.

All super-agonist of the pleiotropic S1P receptor (S1P1-3) in heart are stimulated using S1P which leads to activation of (Gi, Gq, and G12/13) but only S1P1 and S1P3 receptors are activated using fingolimod, which leads to activation of Gi.[12,15] Thus, the underlying mechanism of bradycardia is due to the activation of inwardly rectifying Gà1-protein-regualted potassium channel (IKACh) channels in atrial myocytes and endothelial cells). The function of acetylcholine-regulated KACh is stimulated by S1P. S1PR regulates HR through binding to its receptors on the surface of atrial myocytes.[16] This inhibited cardiac pacemaker activity is similar to the vagally-mediated cardiac effects through the same G protein-gated potassium channel with different pathway fingolimod induces dephosphorylation of cTnI in ventricular myocytes.

Fragoso et al.[17] evaluated cardiovascular complications in RRMS patients during the first dose of fingolimod due to transitory effects in S1P receptors expressed in the cardiac myocytes. They showed that the severe bradycardia happened in 6.7% (12/180) and AVB in 1.7% (3/180) which is within the frequency found in other studies.[6,7]

Symptomatic bradycardia, which occurs in about 0.5% of cases is most often self-limiting.[18] Rarely, the occurrence of fatal bradyarrhythmia using fingolimod has also been reported.[12] These effects have also been observed in healthy volunteers.[15] The decrease in mean nadir HR is up to 10 bpm after first does without incremental decrease in HR after day 2 of the drug.[5]

Fingolimod has been shown to have nonsignificant effects on circadian rhythm, oxygen exchange, airflow, and hemodynamic variables as cardiac output and systemic vascular resistance during 14 days treatments in healthy volunteers.[19,20] Benign AVB (Type I or Wenckebach) has reported using fingolimod.[21] An approximate,[22-24] MS increase in PR-interval has been reported using fingolimod, without any change on QRS or QT intervals despite slowing AV conduction, the incidence of Mobitz Type II AVB and 2:1 AVB is respectively. Conduction abnormalities showed to regress during the time and in therapeutic doses, higher degrees of the block were not seen.[24]

Limitation: Our study had no control group, and the duration of the study was relatively short

compared with other studies. However, the aim of this study was to investigate early dosing with fingolimod, with a specific focus on HR and rhythm disturbances and BP during treatment initiation. Owing to small and uneven group sizes, inferential statistical testing was not performed.

Conclusion

Beneficial effects of fingolimod could be higher than its cardiovascular complications through administration of this agent under close observation regarding its side-effects on the cardiovascular system. Moreover, all the side effects such as hypotension and bradycardia were happened in first 3 hours after receiving the fingolimod. Indeed, we advise clinicians to monitor the patients for first 6 hours after initiation of fingolimod to decrease worse side effects.

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Conflict of Interests

Authors have no conflict of interests.

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