

# Clinical effectiveness and safety of fingolimod in relapsing remitting multiple sclerosis in Western Iran

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## ABSTRACT

**الأهداف:** للتحقيق في الفعالية السريرية وسلامة fingolimod في سكان المنطقة الغربية الإيرانية.

**الطريقة:** تم إجراء هذه الدراسة كدراسة رصدية محتملة بين مارس 2014م وأكتوبر 2015م. ستون مريضاً يعانون من الانتكاس التحويلي المتعدد التصلب المتعدد (RRMS) الذين أحيلوا إلى عيادة MS لمستشفى الإمام الرضا التابع لجامعة كيرمانشاه للعلوم الطبية، عولجت إيران بـ 0.5 ملغ من كبسولات إيمسوليمود عن طريق الفم مرة واحدة يومياً لمدة 12 شهراً. كانت النتائج السريرية وشملت معدل الانتكاس السنوي، وتغير مقياس حالة العجز (EDSS)، ونسبة المريض بدون أعراض، والآثار الجانبية.

**النتائج:** تم ملاحظة انخفاض بنسبة 85% في معدل الانتكاس السنوي مقارنة مع خط الأساس (من  $1.8 \pm 1.35$  إلى  $0.27 \pm 0.58$ ,  $p=0.001$ )، وكان 76.66% من المرضى خاليين من الانتكاس بعد التدخل لمدة 12 شهراً. بالإضافة إلى ذلك، تم قياس انخفاض كبير في EDSS من 3.32 في الأساس إلى 2.97 ( $p=0.001$ ). كانت الأحداث السلبية العامة في دراستنا مشابهة لتلك الموجودة في الدراسات السابقة.

**الخلاصة:** تؤكد الدراسة الحالية على فعالية fingolimod كعلاج الخط الثاني في المرضى RRMS الغربية الإيرانية. وكانت الآثار الجانبية Fingolimod خفيفة عموماً ومقبولة.

**Objectives:** To investigate the clinical effectiveness and safety of fingolimod in the western Iranian population.

**Methods:** This study was performed as a prospective observational study between March 2014 and October 2015. Sixty patients with relapsing remitting multiple sclerosis (RRMS) who were referred to the MS clinic of Imam Reza Hospital, which is affiliated with Kermanshah University of Medical Sciences, Iran, were treated with 0.5 mg oral fingolimod capsules once daily for 12 months. The outcomes were clinical and included the annualized relapse rate, expanded

disability status scale (EDSS) change, proportion of relapse-free patient, and side effects.

**Results:** An 85% reduction in the annualized relapse rate compared with the baseline (from  $1.8 \pm 1.35$  to  $0.27 \pm 0.58$ ,  $p=0.001$ ) was observed, and 76.66% of patients were free from relapse after the 12-month intervention. In addition, a significant reduction of EDSS was measured from 3.32 at baseline to 2.97 ( $p=0.001$ ). The overall adverse events in our study were similar to those in previous studies.

**Conclusion:** The present study confirms the effectiveness of fingolimod as a second-line therapy in western Iranian RRMS patients. Fingolimod side effects were generally mild and tolerable.

*Neurosciences 2018; Vol. 23 (2): 129-134  
doi: 10.17712/nsj.2018.2.20170434*

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*Received 9th March 2017. Accepted 14th February 2018.*

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Fingolimod is unique among the disease-modifying drugs (DMD) introduced for the treatment of multiple sclerosis (MS). It is the first oral DMD after years of using injectable drugs, and it has a novel mechanism of action.<sup>1</sup> Fingolimod is a lipophilic sphingosine-like molecule that rapidly transforms to fingolimod phosphate in the body and acts by binding to the sphingosine 1 phosphate (S1P) receptor family. In particular, its functional antagonist action on S1P receptor 1 (S1PR1) on the surface of lymphocytes

in peripheral lymph nodes leads to the inhibition of lymphocyte egress from secondary lymphoid tissue and prevents auto-reactive lymphocytes from reaching the central nervous system (CNS). Fingolimod action on S1P receptors in the CNS has been shown in vitro and animal model studies to promote neuroprotective and regenerative events.<sup>2</sup> In clinical trials and among DMDs, fingolimod has been associated with the most consistent reduction of brain atrophy.<sup>3</sup> However, fingolimod's action on S1P receptors outside the lymph nodes and the CNS leads to drug side effects, including bradycardia and heart block, macular edema, and hypertension. A heightened risk of infections secondary to reduced circulating lymphocytes by fingolimod also occurs.<sup>1</sup> According to previous pivotal clinical trials comparing fingolimod with a placebo<sup>4</sup> or intramuscular interferon,<sup>5</sup> fingolimod had superior efficacy in the annual relapse rate and produced brain magnetic resonance imaging outcomes with generally mild and tolerable side effects. The drug was approved by Food and Drug Administration (FDA) as a first-line DMD and by European Medicines Agency (EMA) as a second-line DMD.<sup>6</sup> However, in direct comparison trials with intramuscular interferon, fingolimod was not superior in reducing disability progression.<sup>5,7</sup> To the authors' knowledge, no available direct randomized clinical trials have been conducted on comparing fingolimod with other oral therapies, glatiramer acetate, and natalizumab.<sup>8</sup> New complications in the post-marketing phase have been observed: progressive multifocal leukoencephalopathy (PML),<sup>9</sup> cases of severe herpes simplex virus encephalitis<sup>10</sup> and varicella zoster encephalitis in an immunized patient,<sup>11</sup> cases of tumefactive MS under fingolimod treatment,<sup>12</sup> and other rare complications.<sup>3</sup> Although the clinical efficacy and safety of fingolimod have been established in pivotal clinical trials, concerns remain about its emerging complications in subsequent trials and the differences in its effectiveness and safety in different ethnic populations. A different ethnic feature can directly affect both the genetic sensitivity to MS and the pharmacogenomics data associated with MS drug therapies. Confirmation of the effectiveness and safety profile of fingolimod in different ethnic populations is critical to better optimize the MS treatment algorithm.<sup>13</sup>

**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.

The present study investigated the clinical effectiveness and safety of oral fingolimod in the western Iranian MS population with a relapsing remitting course.

**Methods. Search method.** We searched MEDLINE, Ovid, CINAHL, EBSCO, and Pub Med from 2009 to 2017 for full-text articles written in English with proper subject terms: 1) multiple sclerosis, 2) Fingolimod, 3) efficacy, and 4) side effects.

**Study design.** To investigate the effectiveness and safety of oral fingolimod in RRMS, a prospective observational study (IRCT code: 201406018323N10) was conducted. Eligible patients were enrolled in the study from the RRMS patients referred to the MS clinic of Imam Reza Hospital, which is affiliated with Kermanshah University of Medical Sciences, Iran, for drug escalation to a second-line DMD between March 2014 and October 2015. Written informed consent was obtained, and the study inclusion and exclusion criteria were investigated. The study was conducted in accordance with the international conference on Harmonization Guidelines for Good Clinical Practice<sup>14</sup> and the Declaration of Helsinki.<sup>15</sup>

The study inclusion criteria were as follows: diagnosis of RRMS according to the revised McDonald criteria 2010,<sup>16</sup> aged 18–50, unfavorable response to first-line DMDs (at least one relapse in the previous year or 2 relapses in the previous 2 years while on treatment with adequate first-line DMDs), and vaccination against varicella zoster virus (VZV) or positive serum VZV antibody. The study exclusion criteria included primary or secondary progressive MS, presence of any chronic systemic disease other than MS, malignancy, infections, recent treatment with immunosuppressant drugs, pregnancy or lactation, inoculation with live attenuated vaccines in the previous 2 months, history of cardiovascular or cerebrovascular events in the previous 6 months, decompensated heart failure or class III/IV heart failure, atrioventricular block (AVB) or sick sinus syndrome, prolonged QT interval, use of class Ia or III antiarrhythmic drugs, macular edema or uveitis, abnormal liver function test (LFT), abnormal renal function test, WBC count less than 3500/mm<sup>3</sup>, and lymphocyte count less than 800/mm<sup>3</sup>. A history of well-controlled diabetes mellitus and the use of  $\beta$ -blockers or calcium-channel blockers were not contraindications.

Study intervention was initiated for eligible patients through the administration of 0.5 mg daily oral fingolimod capsules (Fingolid®, Osvah Pharmaceuticals, Tehran, Iran). All patients were hospitalized for at least 6 h after the administration of the first dose of

fingolimod to monitor the cardiac complications of the first dose. Patients were visited in week 2 and in months 1, 2, 3, 6, 9, and 12 after drug initiation. At each visit, heart rate and blood pressure, probable side effects, and MS relapses were recorded. The EDSS scores were recorded every three months. The LFT and CBC were conducted at baseline and every 3 months. Lipid profile was tested at baseline and after the 12-month study. All patients were visited by an ophthalmologist to check for macular edema after three months of drug initiation or if they had ophthalmic complaints at any time during the study.

The study investigated changes in clinical end points before and after switching from a first-line DMD (interferon or glatiramer acetate) to fingolimod. The study end points included annualized relapse rate (defined as the number of confirmed relapses per year), proportion of relapse-free patients, mean EDSS changes, side effects, and confirmed disability progression (defined as an increase of one point in the EDSS or half a point if the baseline EDSS score is equal to or more than 5.5 confirmed after three months, with an absence of relapse at the time of assessment and with persistent EDSS progression during the three-month follow up). In addition, time to first relapse and time to disability progression were measured.

Relapses were defined as new neurologic symptoms that lasted at least 24 h without fever or infection. An increase of at least half a point in the EDSS score, of one point in each of the two EDSS functional system scores, or of 2 points in one EDSS functional system score (excluding scores for the bowel-bladder or cerebral functional systems) must have occurred. Patients with

relapse were hospitalized and treated with 5 daily doses of 1000 mg intravenous methylprednisolone.

**Statistical analysis.** Statistical analysis was performed using Stata 14. Aside from the descriptive summarization of data by the mean and the standard deviation, data were analyzed by t-test, chi-square test, Fisher's exact test, and repeated measure analysis of variance (ANOVA) test.

**Results.** In total, 133 patients were referred to the study. From the primary pool, 65 patients were included in the study intervention, but only 60 (92.3%) completed the 12-month intervention. Two patients withdrew their consent, 2 discontinued fingolimod

**Table 1 -** Baseline characteristics of the study population.

Characteristics	n (%)	Mean±SD	Min-Max
<b>Age (years)</b>			
18-30	24 (40)	32.55 (6.78)	18-45
31-45	36 (60)		
<b>Sex</b>			
Female	49 (81.7)		
Male	11 (18.3)		
<b>Disease duration (years)</b>			
1-7	33 (55)	7 (3.45)	1-14
8-14	27 (45)		
<b>Annualized relapse rate</b>			
1-4	57 (95)	1.8 (1.35)	1-8
5-8	3 (5)		
<b>EDSS</b>			
0-3	30 (50)	3.3 (1.11)	1.5-6
3.5-6	30 (50)		
EDSS - expanded disability status scale			

**Table 2 -** Study variable changes before and after 12 month treatment by 0.5 mg fingolimod.

Study variables	Before intervention	After 12 months	P-value
	Mean±SD		
Annualized relapse rate (attack/year)	1.8±1.35	0.27±0.58	0.001
EDSS	3.32±1.1	2.97±1.17	0.001
Lymphocyte count (no/mm <sup>3</sup> )	2262.12±874.4	729.77±227.36	0.001
WBC count (no/mm <sup>3</sup> )	7223.83±2366.03	4831.08±3462.71	0.001
ALT (mg/dl)	22.13±12.77	27.52±15.75	0.001
AST (mg/dl)	20.34±7.54	22.9±6.47	0.061
Systolic blood pressure (mmHg)	111.83±7.97	112.42±6.73	0.065
Diastolic blood pressure (mmHg)	73.83±7.56	74.15±6.10	0.062
Total cholesterol (mg/dl)	189.38±36.69	190.05±41.89	0.065
LDL cholesterol (mg/dl)	111.10±31.70	115.33±33.81	0.075
Triglyceride (mg/dl)	130.23±53.95	129±53.10	0.065
ALT - Alanine aminotransferase, AST - Aspartate aminotransferase, LDL - Low-density lipoprotein WBC - White blood cells, EDSS - Expanded disability status scale			

**Table 3** - Adverse events during 12 month study.

Adverse events	n	(%)
Upper Respiratory tract Infection	20	(3.33)
Headache	10	(16.66)
Urinary Tract Infection	8	(13.33)
Menstrual irregularity	5	(8.33)
Pneumonia	3	(5.0)
Dyspnea	3	(5.0)
Anxiety	2	(3.33)
Influenza	1	(1.66)
Dyspepsia	1	(1.66)
Restless Leg Syndrome	1	(1.66)
Depression	1	(1.66)

to become pregnant, and one discontinued the intervention because of side effects of fingolimod. The patients who completed the 12-month study duration (n=60) were included in the statistical analysis. Before switching to fingolimod, 51 patients used interferon and 9 used glatiramer acetate. Table 1 shows the baseline characteristics of the study population.

In terms of the end points related to drug effectiveness, an 85% reduction in the annualized relapse rate compared with the baseline (from  $1.8 \pm 1.35$  to  $0.27 \pm 0.58$ ,  $p=0.001$ ) was observed. About 76.66% of the patients were relapse-free after the 12-month intervention, and only 14 (23.33%) had at least one relapse during the same time period. Among the patients who had relapse during the intervention, 12 had one relapse and only 2 patients had more than one relapse during the 12-month treatment. On average, time to first relapse was 5.21 months. Only 13% of the patients had relapses after three months of drug initiation. The EDSS changes from baseline showed a significant reduction after the 12-month intervention (from 3.32 to 2.97,  $p=0.001$ ). Confirmed three-month disability progression occurred in only one patient (1.66%).

Overall 40 patients (66.66%) reported adverse effects during the 12-month intervention; most of the side effects were mild and did not need any intervention. Only one adverse event led to hospitalization and drug discontinuation due to a panic attack in less than one month of drug initiation. Fingolimod was not tolerated by the patient, who was eventually excluded from the study.

Although some degree of bradycardia was observed in all patients during the first-dose monitoring, no cases of symptomatic bradycardia, severe bradycardia with heart rate less than 45 beat per minute, AVB, or

arrhythmia were observed. Twenty-one patients (35%) needed extended monitoring beyond first 6 h because their heart rate did not reach 80% of the baseline after 6 h. An increase of 0.52 mmHg in systolic blood pressure and 0.32 mmHg increase in diastolic blood pressure were observed after 12 months, but no cases of hypertension were found during the 12-month intervention.

As expected, because of the fingolimod mechanism of action, a significant reduction of lymphocyte count from the baseline was observed after the 12-month intervention (from 2262.12 to 729.77,  $p=0.001$ ). In the last month of the study (month 12), all patients had a lymphocyte count of  $200/\text{mm}^3$ – $1500/\text{mm}^3$ . An increase in ALT, reaching to its maximum 1.5-fold the normal in the third month, was observed, but no case of increased ALT to threefold the normal upper limit was seen. No significant changes were found in the lipid profile of total cholesterol, LDL cholesterol, and triglycerides from the baseline after the 12-month intervention. Changes in the study variables from the baseline are listed in Table 2.

The most common adverse effects were infections, but none of them were severe or required hospitalization or drug discontinuation. No case of PML was found, and no death occurred. The most common adverse effects in order of frequency were as follows: upper respiratory tract infection, headache, urinary tract infection, and menstrual cycle abnormalities. No case of macular edema was recorded. Table 3 shows the adverse events and the corresponding number of the incidents.

**Discussion.** The present study confirmed the effectiveness of fingolimod as second-line therapy in western Iranian RRMS patients after switching from first-line DMDs. Fingolimod use led to the 85% reduction in the annualized relapse rate and a relapse-free percentage of 76%.

Our findings were consistent with those of previous clinical trials.<sup>4,5,7,17-19</sup> Although the amount of EDSS reduction in our study was greater than those in previous trials, note that the baseline EDSS in our study population was greater than those in other studies and that 40% of our patients had their last MS relapse in less than three months from fingolimod initiation. Our study revealed the efficacy of fingolimod in patients with highly active RRMS despite previously receiving DMTs. This is consistent with findings from Derfuss et al. who analyzed the clinical and magnetic resonance imaging outcomes over 24 months in patients with highly active RRMS from FREEDOMS and FREEDOMS II. They observed significant reduction of EDSS, annualized

relapse rates, brain volume loss and Gd-enhancing T1 lesion counts compared with placebo.<sup>20</sup> We did not evaluate predictors of treatment outcomes in our patients. Lattanzi et al. showed that early disease activity on MRI could predict disease progression.<sup>21</sup>

The overall adverse events in our study were similar to those in previous studies,<sup>4,5,7,17-19</sup> but some differences were observed. A 45-year-old woman with no previous history of psychiatric problems experienced a panic attack. Restless leg syndrome was found in our patients. Menstrual cycle irregularities occurred in 8.33% of the cases, including one case of polymenorrhea and 4 cases of oligomenorrhea. Gynecology and endocrinology evaluations in all cases were negative. This complication was not reported in pivotal clinical trials, but Alroughani et al. reported three cases of secondary amenorrhea after fingolimod was administered to Middle Eastern patients but did not present any explanation.<sup>22</sup> Ethnic differences could account for the different safety profiles of fingolimod in our study.

Another difference in the side effects of Fingolimod in our study was the low incidence of elevated liver enzymes compared with other clinical trials. No case of alanin transferase elevation of more than threefold was found in our patients in contrast to 8.5% in the FREEDOMS trial, 8% in the TRANSFORMS trial,<sup>5</sup> and 7% in FREEDOMS II.<sup>19</sup> The need for extended cardiac monitoring during the first-dose initiation of fingolimod was much higher in our study (35%) than in other trials.<sup>23,24</sup> All of the patients were eligible to the discharge criteria after 8 h of the first-dose cardiac monitoring period. Ethnic differences in drug metabolism could have played a role in this observation.

The drug discontinuation rate in our study was 7.7%, similar to that in Lattanzi et al.'s study, which evaluated a one-year persistence to dimethyl fumarate, fingolimod, and teriflunomide. In their study, the drug discontinuation rates were 9.8% for fingolimod, 21.9% for dimethyl fumarate, and 23.6% for teriflunomide; this finding indicated that patients starting on fingolimod were more likely to persist on the drug than those starting on dimethyl fumarate and teriflunomide after one year.<sup>25</sup> The strict exclusion criteria and the complete evaluation for premorbid conditions that predispose to fingolimod complications could have accounted for the low incidence of side effects in the present study. This study is limited by a small sample size and the lack of a control group. Overall, regardless of ethnic differences, fingolimod is effective in controlling relapses and in improving of EDSS in RRMS patients. Fingolimod is well tolerated in western Iranian RRMS patients, and

the side effects can usually be managed in an outpatient setting. Close observation and follow up are required to determine the infrequent serious adverse effects.

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## References

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