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# Fingolimod versus High Dose Interferon Beta-1a in Multiple Sclerosis: A Randomized Clinical Trial

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**ABSTRACT**

**Background:** High dose Interferon Beta and Fingolimod are efficient in Multiple Sclerosis.
**Objectives:** Comparison the efficacy of these two drugs in patients with treatment failure on low dose interferon beta.
**Materials and Methods:** The MS patients (McDonald criteria 2010) with the history of unbeneficial treatment on low dose interferon beta participated in this randomized clinical trial in MS clinic in a university hospital in Isfahan from 2014 to 2016. They were randomly assigned to two groups receiving high dose interferon beta-1a (Recigen) or Fingolimod. The number of relapses, EDSS, and Magnetic Resonance Imaging (MRI) findings were evaluated at the beginning, 3, 9, 12, and 18 months after intervention. The t-test and Mann Whitney U test and ANCOVA in SPSS version 20 were used.
**Results:** A total of 120 MS patients with the mean age of 38.07±9.0 years included in this study and 35.8% of whom were males.
The mean EDSS was lower in Fingolimod group from the 9th month to the end of intervention (1.80±1.05 vs. 2.17±0.95 in the 9th month and 1.95±0.92 vs. 2.30±0.96 in 18th month). The mean number of relapses was lower in Finglimod group significantly in the 12th and 18th months (0.91±0.76 vs. 1.27±0.77 in the 12th and 0.6±0.55 vs 1.0±0.71 in the 18th month). The mean values of new T2 lesions (1.00 vs. 1.47) and gadolinium enhancing lesions (0.467 vs. 0.817) were lower in Fingolimod group at the end of the study.
**Conclusion:** Both treatments were beneficial with a significant superiority of Fingolimod.

**Keywords:** Fingolimod; Interferon Beta; Multiple Sclerosis



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## Introduction

Multiple Sclerosis (MS) is a chronic autoimmune inflammatory condition in central nervous system (CNS) leading to myelin and axonal injury [1]. The prevalence of MS is more in females and affects young adults in 70-80% of cases [2]. The incidence and prevalence of MS in Iranian population were reported 9.1 and 71.6 in every 100,000 individuals, respectively [3].

The etiology of MS is unknown, but several lines of evidence suggest that autoimmune process develops in genetically susceptible host following exposure to environmental risk factors. Widespread inflammatory demyelination and axonal injury with scattered distribution in the CNS make a lot of symptoms including blurred vision, deterioration of the motor and sensory functions, changes in bowel and bladder function, and pain and fatigue [4]. Although there is no definitive or etiological cure for MS, the primary aims of disease-modifying therapies (DMTs) have been to prevent new relapses, attenuate disease progression, ameliorate symptoms of disease, reduce the accumulation of disability, and improve patient outcomes by modulating or suppressing the immune system. Despite the promise of the available traditional DMTs for treating patients with relapsing remitting MS (RRMS) including interferon beta (IFNβ)-1a (Avonex®, Rebif®), IFNβ-1b (Betaseron®), and glatiramer acetate (GA; Copaxone®), a substantial number of treated patients do not benefit from these drugs and continue to experience disease activity [5].

Fingolimod (FTY720) is a sphingosine like synthetic analogue that modulates sphingosine-1-phosphate receptors. After rapid phosphorylation, Fingolimod-P acts as a super agonist of sphingosine-1-phosphate-1 receptor on thymocytes and lymphocytes and induces internalization of these receptors and protects these immune cells from signals which are necessary for releasing from secondary lymphoid tissues. This redistribution to lymph nodes reduces recirculation of lymphocytes to CNS [6-8]. According to interaction between Fingolimod and receptors on neural cells, this medication may have neuro-protective and reparative effects [9].

Prior to the approval of Fingolimod for MS treatment, injectable DMTs such as IFNβ-1a and IFNβ-1b were commonly administered for MS patients. Although IFNβ products may differ in dosage, dosing frequency, duration, and routes of administration, they were shown to decrease relapse rates by approximately 30% and slow down the accumulation of the neurological disability. IFNβ action leads to less T-cell activation and lower level of proinflammatory cytokines and a shift toward immunoregulatory cytokines. Besides, transferring of inflammation through blood-brain barrier will be limited. However, high rates of early treatment discontinuation with IFNβ due to intolerable side effects or injection related reasons and also development of neutralizing antibodies may influence the efficacy of IFNβ for reducing the frequency of relapses and slowing progression of the disease [10]. IFNβ consists of low dose IFN-β-1a prescribed IM weekly and high dose IFN-β-1a injected 3 times a week, and beta IFN-β-1b used every other day also.

There are several studies which have evaluated the effects of Fingolimod and interferon beta in comparison to placebo and shown the efficacy of these medications in reducing relapses and improving disease symptoms [11,12]. In RRMS patients, escalation treatment from interferon to Fingolimod reduced disease relapses and the number of $T_2$ and gadolinium enhancing lesions on Magnetic Resolution Imaging (MRI) [13]. Notwithstanding such findings, still there is lack of data on efficacy of Fingolimod versus high-dose interferon. In this study, the effects of Fingolimod were

evaluated versus high dose interferon beta-1a on clinical and MRI outcomes in MS patients treated with low dose interferon previously but had failure.

## Materials and Methods

### *Study design and participants*

A randomized clinical trial was conducted from January 2014 to October 2016 in MS clinic in an academic hospital in Isfahan, Iran affiliated to Isfahan University of Medical Sciences (IUMS). From 150 eligible assessed patients, 10 have not met inclusion criteria, 8 declined to participate, 5 refused to continue treatment and 7 would not be followed. The key eligibility criteria were as follows: willingness to participate in the study, age of more than 18 years, a relapsing-remitting course of MS based on revised McDonald criteria (2010), score of less than 5.5 on the Expanded Disability Status Score (EDSS), having at least one attack on treating with low dose interferon beta for the past year, experience of treatment failure on interferon beta. Treatment failure or non-responder define as 1. Relapse rate (e.g. ≥1 per year), or 2. Increased neurological impairment (e.g. EDSS increased by 1 point in 1 year), or 3.both of them [14]. The key exclusion criteria were previous MS disease therapy (except low dose IFNβ-1a), concomitant use of other MS immunomodulatory drugs, allergic reaction to any of the drugs used in the study, pregnancy or breastfeeding, clinically significant systemic disease, progressive forms of MS, plasma exchange within the past 3 months, immune-suppression (drug or disease induced), active infection, macular edema, coexisting systemic disease, malignancies, bone marrow dysfunction, previous suicide attempts or current suicidal ideation, unable to access the MRI center, and lack of appropriate adherence to study protocol.

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki (64$^{th}$ WMA General assembly, Fortaleza, Brazil, OCT 2013). The protocol was approved by institutional review board at IUMS; patients gave written informed consent before any study-related procedures were performed.

The study was registered at the Iranian Registry of Clinical Trials (identifier: IRCT2015112025146).

### *Randomization and blinding*

Using simple random allocation software, eligible patients were assigned into two groups of 18-month treatment regimen: (1) oral Fingolimod (Osve company) capsules in dose of 0.5 mg once daily; (2) high dose interferon beta-1a (Recigen from Cinagen company) 44 mcg every 48 hours subcutaneously. To ensure that all assessments remained unbiased regarding study group assignment, the assessors were not aware of the treatment allocations. Although, initially, a treated physician was in charge of assessing cases to determine their eligibility for entrance into the study, subsequent clinical assessments were performed by an independent qualified neurologist not involved in the treatment and blinded to the study groups with no access to medical records.

### *Study procedures and endpoints*

The patients were visited at baseline and four separated time points (3, 9, 12, and 18 months after treatment). The primary clinical endpoint was the number of relapses defined as new, worsening, or recurrent neurologic symptoms occurred at least 30 days after the

onset of preceding relapses and lasted 24 hours without fever or any infection accompanied by increasing at least half a point on the EDSS [8]. The secondary clinical endpoint was changes in the EDSS score. Disease activity was evaluated by the number of gadolinium (Gd) enhanced lesions and new lesions on $T_2$ weighted images based on MRI scans at baseline and after treatment completion. Patients were examined at scheduled intervals and at unscheduled visits in the case of suspected relapse. If patients experienced any side effects of medications, they were treated and excluded from the study. Besides clinical and imaging findings, all complications and adverse events were recorded in especially designed check-list.

### *Statistical analysis*

The statistical analyses were performed using SPSS version 20 (SPSS crop. Chicago, IL, USA). For quantitative and qualitative variables, mean±standard deviation (SD) and percentages were expressed, respectively. The Kolmogorov–Smirnov test was used to test normal distribution of quantitative data. For evaluating differences between the groups, independent samples t-test and Mann-Whitney U test were used. Differences among the groups were assessed via analysis of covariance (ANCOVA), using the baseline score as a covariate. All statistical tests were two-tailed, and a *P*-value of less than 0.05 was considered the significance threshold.

## Results

### *Study sample*

Participant's flow is shown in CONSORT diagram (Figure 1).

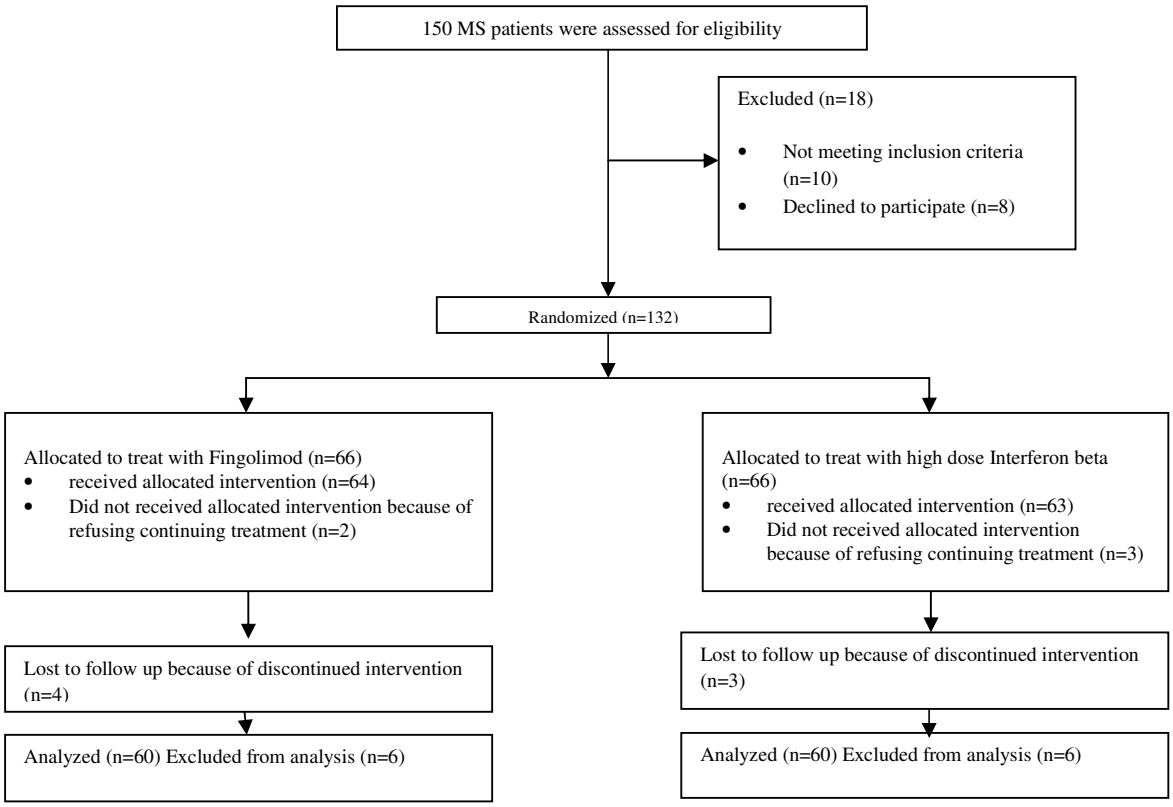


**Fig 1.** Profile of a randomized control trial of MS patients treated with Fingolimod or high dose Interferon beta.

The baseline demographics and disease variables are summarized in Table 1. At inclusion, 43 patients were males (35.8%), and the mean±SD age of patients was 38.07±9.0. The mean ± SD duration of MS was 5.61±4.72 years. The mean±SD of EDSS score was 2.43±1.44 in the Fingolimod group and 2.50±1.49 in the interferon group. The mean±SD number of relapse was 2.27±0.91 and 2.25±0.72 in Fingolimod and Interferon groups, respectively. Independent sample t-test showed no statistical differences between two groups regarding age, gender, duration of MS, EDSS, and the number of relapses.

**Table 1.** Baseline demographic and clinical characteristics of multiple sclerosis patients.

| Characteristics | Fingolimod group (n=60) | Interferon group (n=60) | *p -value** |
|---|---|---|---|
| Age, (Mean±SD) year | 38.22 ±9.09 | 37.93 ±8.91 | 0.863 |
| Mean duration of MS | 5.80 ±5 | 5.43 ±4.44 | 0.672 |
| EDSS score (Mean±SD) | 2.43 ±1.44 | 2.50 ±1.49 | 0.80 |
| Relapse rate | 2.27 ±0.918 | 0.728 ±2.04 | 0.912 |
| MS: Multiple Sclerosis; EDSS: Expanded Disability Status Score,**t-test* | | | |

### *Clinical endpoints*

Table 2 indicates the details of EDSS score in both groups at different time points. There was not any significant differences in mean EDSS score between both groups during the first three months of intervention. However, ANOVA test showed that these mean EDSS score differences between two groups, significantly increased in the Fingolimod one after month 9.

**Table 2.** Mean EDSS in both Fingolimod and Interferon groups in different time points

| Time of Evaluation | Groups | EDSS (mean±SD) | 95% Confidence Interval | *p-value* |
|---|---|---|---|---|
| At the beginning | Fingolimod | 2.43±1.44 | 2.06-2.81 | 0.804 |
| | Interferon β | 2.50±1.49 | 2.12-2.88 | |
| 3rd month | Fingolimod | 2.04±1.28 | 1.73-2.35 | 0.546 |
| | Interferon β | 2.17±1.13 | 1.87-2.48 | |
| 9th month | Fingolimod | 1.80±1.05 | 1.54-2.05 | 0.042* |
| | Interferon β | 2.17±0.95 | 1.91-2.42 | |
| 12th month | Fingolimod | 2.0±1. 02 | 1.75-2.25 | 0.044* |
| | Interferon β | 2.36±0.90 | 2.11-2.60 | |
| 18th month | Fingolimod | 1.95±0.92 | 1.71-2.19 | 0.045* |
| | Interferon β | 2.30±0.96 | 2.06-2.54 | |
| *Repeated measure of ANOVA tests | | | | |

Table 3 indicates the mean number of relapses in patients in both intervention groups. Based on ANOVA analysis, from beginning to the end of month 9, there were no significant differences in the mean number of relapses between the Fingolimod and Interferon groups. However, at month 12 and 18 after intervention, the mean number of relapses decreased significantly in the Fingolimod group compared to the high-dose interferon group.

**Table 3.** The mean number of relapses in both Fingolimod and Interferon groups in different time of evaluation

| Time of Evaluation | Groups | Number of Relapses (mean±SD) | 95% Confidence interval | *p-value** |
|---|---|---|---|---|
| At the beginning | Fingolimod | 2.27±0.91 | 2.05-2.48 | 0.912 |
| | Interferon β | 2.25±0.72 | 2.04-2.46 | |
| 3rd month | Fingolimod | 1.83±0.96 | 1.61-2.06 | 0.357 |
| | Interferon β | 1.98±0.81 | 1.76-2.21 | |
| 9th month | Fingolimod | 1.43±0.90 | 1.23-1.64 | 0.649 |
| | Interferon β | 1.50±0.67 | 1.30-1.70 | |
| 12th month | Fingolimod | 0.91±0.76 | 0.71-1.11 | 0.014* |
| | Interferon β | 1.27±0.77 | 1.07-1.46 | |
| 18th month | Fingolimod | 0.6±0.55 | 0.43-0.76 | 0.002* |
| | Interferon β | 1.0±0.71 | 0.83-1.16 | |
| *Repeated measure of ANOVA tests | | | | |

### *MRI endpoints*

Tables 4 show at baseline no significant difference in the mean number of lesions in $T_2$ weighted and Gd-enhanced lesions in both groups. At the end of intervention, the mean values of new lesions in $T_2$ weighted imaging and gadolinium enhanced lesions in patients receiving Fingolimod were significantly lower than patients who received interferon.

**Table 4.** The number of new T2 lesions and Gad enhanced lesions in both fingolimod and interferon groups at the beginning and end of study.

| Visit time | Groups | The number of new T2 lesions | | | The number of Gad enhanced lesions | | |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | *p-value* | Mean | SD | *p-value* |
| At the beginning | Fingolimod | 2.67 | 4.25 | 0.632 | 1.47 | 1.89 | 0.865 |
| | Interferon β | 2.68 | 4.30 | | 1.58 | 2.27 | |
| 18th month | Fingolimod | 1.00 | 1.61 | 0.024 | 0.467 | 0.791 | 0.016 |
| | Interferon β | 1.47 | 1.85 | | 0.817 | 1.27 | |

## Discussion

This study showed that both Fingolimod and high dose interferon beta-1a can decrease relapse rate, EDSS, new MRI lesions. However, the data showed that Fingolimod is more effective than high dose interferon beta-1a in improving clinical and MRI outcomes.

The bulk of available literature indicates that Fingolimod is more effective in patients with RRMS with respect to relapse rate, EDSS, and disability progression as compared to interferon beta and placebo [1,2]. The findings are in line with a study by Cohen *et al.* [8] who evaluated the efficacy of Fingolimod in comparison with high-dose interferon in 1153 RRMS patients. Although EDSS was not significantly changed, they found that Fingolimod is a more effective drug to decrease relapse rate and improve MRI outcome.

In the present study, the number of new $T_2$ weighted lesions and Gd-enhanced lesions significantly decreased after 18 months treatment with Fingolimod. In another similar study on MS patients treated with 0.5 mg Fingolimod or interferon beta, the number of new $T_2$ weighted lesions and Gd-enhanced lesions dropped significantly in favor of the Fingolimod group [15]. Interestingly, Kappos et al. treated 281 MS patients with Fingolimod and demonstrated that after two years treatment, 91% of patients were free from gadolinium lesions [11].

In the current study, patients treated by low dose interferon for one year prior to the study experienced treatment failure. The findings strongly suggest that changing treatment strategy from low dose interferon to Fingolimod is more effective than changing to high dose interferon. Khatri *et al.* [13] showed that escalation strategy from weekly injected interferon to Fingolimod was accompanied by improving their function, clinical manifestations, and MRI outcomes in 1027 MS patients. Moreover, most studies indicate that high dose interferon is more effective in reducing the number of lesions on MRI than low-dose interferon. There is only one study which indicates no difference between low dose and high dose interferon regarding MRI outcomes [16,17].

Pharmacokinetic and pharmacodynamics of Finglolimod makes it as one of the potent DMTs. Orally administered DMT is a favorable remedy among MS patients compared to injected interferon; hence, patients are more adherent to their medication which could lead to better outcome. Moreover, there is only one study which estimated the cost effectiveness of Fingolimod versus interferon. They showed that higher efficacy of Fingolimod was associated with higher cost, compared to interferon [18]. This assumption needs to be confirmed by further studies. The interpretation of the results is limited by sample size and short follow up.

## Conclusion

The present randomized clinical trial indicated that 18 months treatment with Fingolimod had superior efficacy over high-dose interferon in patients who experienced treatment failure on low-dose interferon. Therefore, Fingolimod which is now in the second line of MS treatment in most countries including Iran should be suggested the first. Further studies with larger sample size and longer follow up are warranted to confirm the efficacy of Fingolimod in patients with treatment failure on low-dose interferon.

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## Conflict of Interest

The authors have no conflict of interest.

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