**DOI:** *http://dx.doi.org/10.18502/cjn.v22i2.13339*

*Current Journal of Neurology*

**Review Paper**

Curr J Neurol 2023; 22(2): 110-4

# Alternate dosing of fingolimod in relapsing-remitting multiple sclerosis: A systematic review

Received: 08 Dec. 2022
Accepted: 01 Feb. 2023

Fereshteh Ghadiri[1], Omid Mirmosayyeb[2], Mohammad Ali Sahraian[1], Abdorreza Naser Moghadasi[1], Mahsa Ghajarzadeh[3]

[1] Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[2] Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Universal Council of Epidemiology, Universal Scientific Education and Research Network, Tehran University of Medical Sciences, Tehran, Iran

**Keywords**
Fingolimod Hydrochloride; Alternate Dose; Daily Dose; Multiple Sclerosis

**Abstract**

**Background:** Fingolimod is approved in relapsing-remitting multiple sclerosis (RRMS) with the recommended dose of 0.5 mg daily. To tackle possible adverse events, some clinicians may reduce the dose of fingolimod, mainly in the alternate-day form. We systematically reviewed the literature for efficacy measures of this method.

**Methods:** PubMed (Medline®), Web of Science, Embase, Scopus, and the Cochrane Library databases were searched until April 9, 2021. Clinical studies (other than case reports and case series), in English, were included. Then, publications concerning alternate dose fingolimod (including every other day, every two or three days) were selected. Those studies concerning reduced daily dose (any daily dose less than 0.5 mg/day) were excluded to focus on alternate dosing.

**Results:** Four observational studies were included. Data on Ohtani et al. study were limited. Three other studies were of good quality based on the Newcastle-Ottawa Scale. A total of 296 patients on the standard dose were compared to 276 patients on the alternate dosage. The most common reason for switching to the alternate dose was lymphopenia, followed by elevated liver enzymes. Two studies concluded that the alternate dosing could be a safe, yet effective strategy in patients with intolerable adverse effects of daily dose. However, Zecca et al. warned about the high possibility of disease reactivation. Due to the differences in outcome measures of the studies, meta-analysis was not applicable.

**Conclusion:** This systematic review highlights the ambiguity of evidence on safety and efficacy of alternate dosing of fingolimod, encouraging further research on the subject.

**How to cite this article:** Ghadiri F, Mirmosayyeb O, Sahraian MA, Naser Moghadasi A, Ghajarzadeh M. Alternate dosing of fingolimod in relapsing-remitting multiple sclerosis: A systematic review. Curr J Neurol 2023; 22(2): 110-4.



Corresponding Author: Mohammad Ali Sahraian
Email: sahraian1350@gmail.com

## Introduction

Multiple sclerosis (MS) is the most prevalent cause of nontraumatic neurologic disability in young ages.[1] Its prevalence has risen over the past three decades and is believed to increase over the next ten years.[2] Taken together with no cure in hand, a notable socioeconomic burden is imposed by the disease. However, treatment options are expanding in recent years. One of the giant leaps on the road was the introduction of oral disease-modifying therapies (DMTs), among which fingolimod was the first.

Fingolimod (FTY720) is a derivate of myriocin, a natural complex amino acid, isolated from the fungus, Isaria sinclairii about 20 years ago.[3] It is a non-selective sphingosine-1-phosphate receptor (S1PR) modulator, resulting in sequestration of central memory (T and B) cell lymphocytes in the peripheral lymphoid organs through a complex mechanism.[4] Along with other therapeutic effects, it could control inflammatory responses responsible for MS.[5] It was approved in relapsing-remitting MS (RRMS) in 2010, with the recommended dose of 0.5 mg daily.[6] Despite obvious benefits in decreasing relapse rates, brain magnetic resonance imaging (MRI) lesion burden, and grey matter atrophy,[5] it comes with rare but noticeable adverse effects. Cardiac problems especially with the first dose, macular edema, and serious infections are the most critical side effects.[7,8] Currently, guidelines recommend periodic monitoring of liver enzymes and complete blood cell count. The drug should be withdrawn if the lymphocyte count drops below $200 \times 10^6$ /L and liver function tests (LFTs) increased by $\geq 5 \times$ upper normal limit. To overcome the disadvantages and have the benefits at the same time, some clinicians may reduce the dose of fingolimod, mainly in the alternate-day form. Nonetheless, no clear picture of restarting protocol exists.

Here, we systematically reviewed the studies on the efficacy of alternate dose fingolimod in MS to see if there is enough supporting evidence. The results would be of help to plan the best strategy when facing the dug adverse events.

## Materials and Methods

Study design and search strategy: This systematic review was conducted according to a predesigned protocol, approved by all the authors. PubMed (Medline®), Web of Science, Embase, Scopus, and the Cochrane Library databases were searched until April 9, 2021. A broad search strategy was performed with the keywords ("Multiple Sclerosis" OR "MS" OR "demyelinating diseases" OR "demyelinating disorders") AND ("fingolimod" OR "gilenya" OR "FTY720").

Study selection and data extraction: Abstracts and titles of studies were screened by two independent reviewers. Clinical studies (other than case reports and case series), in the English language, were included. Excluded were preclinical studies, case reports, case series, and those in non-English languages. In the next step, publications concerning alternate dose fingolimod (including every other day, every two or three days) were selected. Those studies concerning reduced daily dose (e.g., 0.25 mg/day) were not included. Full texts of the selected articles were reviewed as the screening process. The steps are summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 1).

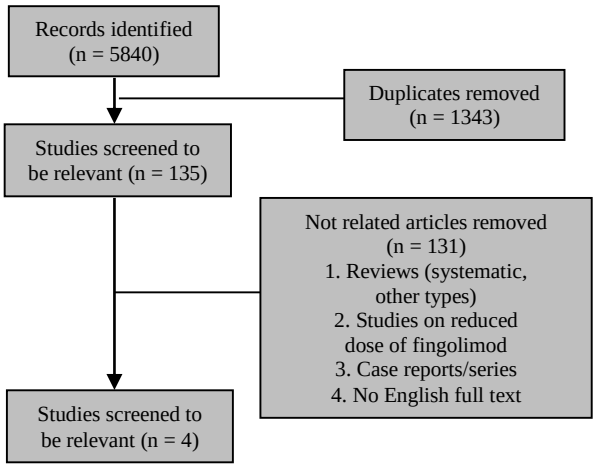


**Figure 1.** Flow diagram of including studies

Extracted data were: study details (title, first author, publication year, type of study, follow-up duration, country), demographic characteristics (number, age at onset and age at intervention, gender ratio), disease characteristics [baseline and final Expanded Disability Status Scale (EDSS), baseline and final annualized relapse rate (ARR), number of gadolinium-enhancing lesions, side effects, reasons and time of switch from daily to alternate dose].

A third reviewer resolved any disagreements.

## Results

Only four studies were finally included:

- Ohtani et al., 2017: Drug holiday therapy of

fingolimod in Japanese relapsing-remitting multiple sclerosis[9]
- Zecca et al., 2017: Half-dose fingolimod for treating relapsing-remitting multiple sclerosis: Observational study[10]
- Longbrake et al., 2018: Effectiveness of alternative dose fingolimod for multiple sclerosis[11]
- Ramos-Lopes et al., 2020: Clinical effectiveness of reduced fingolimod dose in relapsing-remitting multiple sclerosis-a Portuguese cohort[12]

The four studies are summarized in table 1. All were retrospective observational studies.

Data on Ohtani et al.[9] study was limited. Three other studies were of good quality based on Newcastle-Ottawa Scale adapted for cohort studies. A total of 296 patients on standard dose of fingolimod were compared to 276 patients on alternate dosage. Female to male ratio of available data was 204:62 (3.29).

The most common reason for switching to alternate dose was lymphopenia, followed by elevated liver enzymes.

Ramos-Lopes et al.[12] and Longbrake et al.[11] concluded that the alternate dosing could be a safe, yet effective strategy in patients with intolerable adverse effects of daily dose. However, Zecca et al. warned about the high possibility of disease reactivation in patients treated with alternate administration.[10]

Due to the differences in outcome measures of the studies, meta-analysis was not applicable.

## Discussion

This systematic review highlights the ambiguity of evidence on safety and efficacy of alternate dosing of fingolimod. Fingolimod is considered a high efficacy drug (just following monoclonal antibodies) with a lower discontinuation rate than many other DMTs. In fact, it is shown to be the most efficacious oral DMT with the lowest dropout rate.[13]

There are plenty of randomized controlled trials (RCTs) comparing different higher doses of the drug (5 and 1.25 vs. the final standard dose of 0.5 mg).[14] Only Cree et al. showed that 0.25 mg/day could still significantly reduce new or newly enlarging T2 and gadolinium-enhancing T1 lesions compared with glatiramer acetate. Although the final results were in favor of the superior 0.5 mg dose considering efficacy and safety, pharmacodynamic effects of fingolimod (bradycardia, cardiac conduction defects, and decreased lymphocyte count) were reported at a lower incidence in the 0.25 mg group compared with the 0.5 mg group.[15] Still increased infection rates (e.g., lower respiratory tract and herpes virus infections) appear to be dose independent.[16] Of note is the significant heterogeneity among 10 controlled trials investigating the same dose (0.5 mg/day) regarding adverse events ($I^2$: 85%).[14]

The rationale behind the alternate dosing is the prolonged half-life (6 to 9 days) and stable plasma concentration,[17] besides a number of adverse events resulting in discontinuation of the drug. As evidence is emerging on effects of fingolimod in apoptosis inhibition, suppressing amyloid β-protein (Aβ) deposition, increasing brain derived neurotrophic factor,[18] angiogenesis enhancement, microglial activation,[19] and triggering remyelination,[20] it is attracting scientists as a neuroprotective agent. Having this benefit and anti-inflammatory effects, along with its long half-life and stable plasma concentration, may explain its remaining efficacy even after alternate dosing.

Since 2013, case series of nondaily dosage were reported by Tanaka et al.,[21] Yamout et al.,[22] and Merlini et al.[23] These small studies mainly focused on the effect of alternate dosing on adverse events of daily fingolimod, especially lymphopenia. These primary results indicated the positive effects of reduced dosage on lymphocyte count and liver enzymes. Nevertheless, data on disease activity after dose switch were scarce.

To more precisely investigate the efficacy and safety of nondaily dose, Zecca et al. designed a multicentric retrospective observational study, which showed that besides correction of lymphopenia and liver enzymes, a significant proportion of the patients experienced breakthrough disease after the dose switch, especially younger cases and those with history of recent natalizumab use (i.e., those with more inflammatory disease state). On the other hand, no association of gender, baseline EDSS, relapses in the year before the start of the drug, duration of daily fingolimod treatment before alternate dosage, T2 lesion load, with the risk of ongoing disease activity under alternate dose was found.[10]

Longbrake et al. proposed that the increased disease activity was mostly seen in those with active disease on MRI while on daily fingolimod.[11] Otherwise, well-controlled patients on daily fingolimod did not show disease reactivation after switch to nondaily dosing. They did not find any association of previous natalizumab administration with disease reactivation after the dose switch.[11]

**Table 1.** Studies concerning alternate dose fingolimod, their characteristics and outcomes

| Study | Ohtani et al. | Zecca et al. | Longbrake et al. | Ramos-Lopes et al. |
|---|---|---|---|---|
| Type of study | Unicentric retrospective observational study | Multicenter retrospective observational study | Multicenter retrospective observational study (before-after) | Unicentric retrospective observational study |
| Country | Japan | Switzerland, Italy | 12 centers in the US, 1 in Lebanon, 1 in Spain | Portugal |
| Number of patients (0.5/day) | 27 | 63 | 170 | 36 |
| Number of patients (alternate) | 10 | 60 | 170 | 36 |
| Follow-up (month) (0.5/day) | Median: 12 | Mean ± SD: 22.90 ± 12.20 | Median: 12 (ranged from 1 to 102) | NA (at least 6) |
| Follow-up (month) (alternate) | Median: 12 | Mean ± SD: 12.40 ± 7.60 | Median: 14 (ranged from 1 to 70) | NA (at least 6) |
| Disease duration (mean ± SD) (mean: year) (SD: month) (0.5/day) | NA | 13.10 ± 7.90 | 9.60 ± 6.90 | 14.80 ± 9.60 |
| Disease duration (mean ± SD) (mean: year) (SD: month) (alternate) | NA | 11.80 ± 7.90 | 9.60 ± 6.90 | 14.40 ± 8.60 |
| Age at intervention onset (mean ± SD) (0.5/day) | NA | 43.60 ± 11.20 | 41.20 ± 10.40 | 45.80 ± 10.20 |
| Age at intervention onset (mean ± SD) (alternate) | NA | 41.00 ± 10.00 | 41.20 ± 10.40 | 46.40 ± 9.50 |
| Female/male (0.5/day) | NA | 35/28 | 125/45 | 27/9 |
| Female/male (alternate) | NA | 51/9 | 125/45 | 28/8 |
| Baseline EDSS [median (IQR)] (0.5/day) | NA | 2 (1.5-3.5) | Reported by PDSS score: 0 (0-6) | 3 (2.75) |
| Baseline EDSS [median (IQR)] (alternate) | NA | 2 (1.5-3.5) | Reported by PDSS score: 0 (0-6) | 2.5 (1.88) |
| Final EDSS (median) (0.5/day) | NA | NA | NA | 2 |
| Final EDSS (median) (alternate) | NA | NA | NA | 2 |
| Baseline ARR (0.5/day) | Median (IQR): 1 (1.5) | Mean ± SD: 0.51 ± 0.69 | NA | Mean ± SD: 0.41 ± 0.41 |
| Baseline ARR (alternate) | Median (IQR): 1 (1.5) | Mean ± SD: 0.75 ± 0.89 | Mean ± SD: 0.10 ± 0.54 | Mean ± SD: 0.27 ± 0.59 |
| Final ARR (0.5/day) | Median (IQR): 0.11 (0.29) | Mean ± SD: 0.04 ± 0.14 | NA | Mean: 0.40 |
| Final ARR (alternate) | Median (IQR): 0.00 (0.32) | Mean ± SD: 0.49 ± 1.19 | Mean ± SD: 0.20 ± 0.63 | Mean: 0.30 |
| Side effects (n) (0.5/day) | NA | NA | NA | NA |
| Side effects (n) (alternate) | 0 | 4 (persistent leuco-lymphopenia), 1 (infection) | 14 (29%) | 0 |
| Reason for switch to alternate [n (%)]: | NA | | NA | |
| Lymphopenia | | 45 (75.0) | | 32 (88.9) |
| Elevated liver enzymes | | 13 (21.7) | | 4 (11.1) |
| Others | | 2 (3.3) | | 0 (0) |
| Time before switch to alternate dose (month) (mean ± SD) | NA | 10.30 ± 9.20 | 18 | 18.50 ± 16.00 |
| Prior natalizumab | NA | 22 (26.4) | 9% | 19 (26.4) |
| Patients with enhancing lesions (0.5/day) | NA | 7 (13.5) | 14% | NA |
| Patients with enhancing lesions (alternate) | NA | 10 (22.2) | 18 | NA |
| Key findings | | Disease reactivation in a significant proportion of patients on every-other-day dosage of fingolimod | The efficacy and safety of alternate dosing in those with good disease control but profound lymphopenia or other adverse events while on daily dose | The effectiveness of fingolimod despite the reduction of the dose |
| Quality assessment | | Good | Good | Good |

SD: Standard deviation; NA: Not available; EDSS: Expanded Disability Status Scale; IQR: Interquartile range; ARR: Annualized relapse rate; PDDS: Patient-Determined Disease Steps

They argue that similar to the study by Zecca et al., enrolling middle-aged cases with long disease duration, relatively low disability, and similar rates of prior exposure to DMT, predicts less inflammatory MS activity.[24] However, the latter was methodologically different considering the baseline ARR in daily and alternate groups, explaining the discrepancy. What Ramos-Lopes et al.[12] found is in line with the Longbrake et al. results.

## Conclusion

It appears that studies on the subject suffer from small sample sizes, lack of randomized designs, and heterogeneity in study populations and outcome measures. Therefore, no exact evidence-based guideline could be introduced to tackle the drug adverse events. However, as there are some preliminary data approving the alternate strategy, further research on the subject is encouraged.

## Conflict of Interests

The authors declare no conflict of interest in this study.

## Acknowledgments

None.

## References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2002; 359(9313): 1221-31.
2. Amini P, Almasi-Hashiani A, Sahraian MA, Najafi M, Eskandarieh S. Multiple sclerosis projection in Tehran, Iran using Bayesian structural time series. BMC Neurol 2021; 21(1): 235.
3. Chiba K. Discovery of fingolimod based on the chemical modification of a natural product from the fungus, Isaria sinclairii. J Antibiot (Tokyo) 2020; 73(10): 666-78.
4. Mullershausen F, Zecri F, Cetin C, Billich A, Guerini D, Seuwen K. Persistent signaling induced by FTY720-phosphate is mediated by internalized S1P1 receptors. Nat Chem Biol 2009; 5(6): 428-34.
5. Cohan S, Lucassen E, Smoot K, Brink J, Chen C. Sphingosine-1-Phosphate: Its pharmacological regulation and the treatment of multiple sclerosis: A review article. Biomedicines 2020; 8(7): 227.
6. Food and Drug Administration. GILENYA (fingolimod) capsules. [Online]. [cited 2014]; Available from: URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022527s009lbl.pdf
7. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010; 362(5): 402-15.
8. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362(5): 387-401.
9. Ohtani R, Masahiro M, Akiyuki U, Tomohiko U, Hiroki M, Satoshi K. Drug holiday therapy of fingolimod in Japanese relapsing-remitting multiple sclerosis. J Neurol Sci 2017; 381: 792-3.
10. Zecca C, Merlini A, Disanto G, Rodegher M, Panicari L, Romeo MAL, et al. Half-dose fingolimod for treating relapsing-remitting multiple sclerosis: Observational study. Mult Scler 2018; 24(2): 167-74.
11. Longbrake EE, Kantor D, Pawate S, Bradshaw MJ, von GG, Chahin S, et al. Effectiveness of alternative dose fingolimod for multiple sclerosis. Neurol Clin Pract 2018; 8(2): 102-7.
12. Ramos-Lopes J, Batista S, Barradas P, Campelo I, Correia I, Nunes C, et al. Clinical effectiveness of reduced fingolimod dose in relapsing remitting multiple sclerosis-a Portuguese cohort. Neurol Sci 2021; 42(3): 1039-43.
13. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: A systematic review and network meta-analysis. J Neurol 2020; 267(12): 3489-98.
14. Wu X, Xue T, Wang Z, Chen Z, Zhang X, Zhang W, et al. Different doses of fingolimod in relapsing-remitting multiple sclerosis: A systematic review and meta-analysis of randomized controlled trials. Front Pharmacol 2021; 12: 621856.
15. Cree BAC, Goldman MD, Corboy JR, Singer BA, Fox EJ, Arnold DL, et al. Efficacy and safety of 2 fingolimod doses vs glatiramer acetate for the treatment of patients with relapsing-remitting multiple sclerosis: A randomized clinical trial. JAMA Neurol 2020; 78(1): 1-13.
16. Zhao Z, Ma CL, Gu ZC, Dong Y, Lv Y, Zhong MK. Incidence and risk of infection associated with fingolimod in patients with multiple sclerosis: A systematic review and meta-analysis of 8,448 patients from 12 randomized controlled trials. Front Immunol 2021; 12: 611711.
17. David OJ, Kovarik JM, Schmouder RL. Clinical pharmacokinetics of fingolimod. Clin Pharmacokinet 2012; 51(1): 15-28.
18. Angelopoulou E, Piperi C. Beneficial effects of fingolimod in Alzheimer's disease: molecular mechanisms and therapeutic potential. Neuromolecular Med 2019; 21(3): 227-38.
19. Shang K, He J, Zou J, Qin C, Lin L, Zhou LQ, et al. Fingolimod promotes angiogenesis and attenuates ischemic brain damage via modulating microglial polarization. Brain Res 2020; 1726: 146509.
20. Miron VE, Jung CG, Kim HJ, Kennedy TE, Soliven B, Antel JP. FTY720 modulates human oligodendrocyte progenitor process extension and survival. Ann Neurol 2008; 63(1): 61-71.
21. Tanaka M, Park K, Tanaka K. Reduced fingolimod dosage treatment for patients with multiple sclerosis and lymphopenia or neutropenia. Mult Scler 2013; 19(9): 1244-5.
22. Yamout BI, Zeineddine MM, Sawaya RA, Khoury SJ. Safety and efficacy of reduced fingolimod dosage treatment. J Neuroimmunol 2015; 285: 13-5.
23. Merlini A, Rodegher M, Perrone P, Patti F, Messina MJ, Romeo M, et al. P1083: Fingolimod every-other-day as a possible strategy to overcome fingolimod-induced severe lymphopenia in MS patients Poster]. Mult Scler 2015; 21(S11): 557-8.
24. Derfuss T, Ontaneda D, Nicholas J, Meng X, Hawker K. Relapse rates in patients with multiple sclerosis treated with fingolimod: Subgroup analyses of pooled data from three phase 3 trials. Mult Scler Relat Disord 2016; 8: 124-30.