Current Journal of Neurology

Review Paper

Curr J Neurol 2020; 19(3): 138-45

The efficacy and safety of oral disease-modifying therapies for relapsing-remitting multiple sclerosis: A systematic review

Received: 16 Mar. 2020
Accepted: 13 May 2020

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Keywords
Multiple Sclerosis; Disease-Modifying Therapy; Systematic Review

Abstract

Background: Although widely used, first-line injectable medicines for the treatment of multiple sclerosis (MS) remain an issue of efficacy and adherence. Recently, new oral medications for MS have contributed to dramatic improvements in MS treatment. This study aims to evaluate the safety and efficacy of oral disease-modifying drugs (DMDs) used in relapsing-remitting MS (RRMS).

Methods: A systematic review was conducted on related databases including PubMed, Scopus, Cochrane, and Web of Science up to April 2020. The screening of the studies and their quality assessment was carried out independently by the two authors.

Results: Three studies fulfilled the predefined criteria of inclusion. One of them compared teriflonomide with subcutaneous interferon beta-1a (IFN β-1a), another compared oral fingolimod with intramuscular (IM) IFN β-1b, and the third article compared oral fingolimod with IM IFN β-1a. No eligible study was found for dimethyl fumarate (DMF). The results indicated that while the efficacy of fingolimod was more than IFN β (IM β-1a and β-1b), teriflunomide 7 mg had less efficacy than subcutaneous IFN β-1a. Regarding safety, the results indicated that the proportion of diabetic patients with adverse events (AEs) in the fingolimod group was higher than in the IFN β-1b group and the overall occurrence of AEs was similar between teriflunomide and IFN β-1a groups.

How to cite this article: Shahtaheri RS, Nikfar S, Khorasani E, Sabbagh-Baniazad M, Goudarzi Z, Emamikhah M. The efficacy and safety of oral disease-modifying therapies for relapsing-remitting multiple sclerosis: A systematic review. Curr J Neurol 2020; 19(3): 138-45.

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Conclusion: There is evidence for the effectiveness of fingolimod in reducing annualized relapse rates (ARRs) and improving magnetic resonance imaging (MRI) findings, but the evidence does not support the effectiveness of teriflunomide and further studies are required to determine its efficacy. Also, fingolimod is associated with more side effects than IFN β-1b, but there is no evidence to suggest any difference in side effects between teriflunomide and IFN β-1a.

Introduction

Over the previous two decades, treatments for multiple sclerosis (MS) have experienced a revolution.[1] Interferon beta-1b (IFN β-1b), the first medication for MS, has been shown to effectively transform the disease natural course since its introduction in 1993.[2] The next development of new therapeutic tools is developing rapidly.

Classical treatments using first-line injectable medications, although widely used, are worrisome in terms of adherence and therapeutic efficacy. IFNs, the first and (still) most medications used for MS, with injection site reactions, flu symptoms, and liver dysfunction, are associated with the risk of developing neutral antibodies that can limit their effectiveness.[1,3] Glatiramer acetate (GA) has a localized response to the site of injection and systemic reactions that can reduce the adherence of the patient to treatment. In addition to such discomforts, these injectable medications only reduce the relapse rate by about 30%; although this is a significant decrease, it is clear that better treatments are needed.[3]

There are significant therapeutic advances in new oral medicines that are approved for MS treatment. The oral route increases patient satisfaction. However, safety and tolerance issues may arise about injectable medications, and a thorough assessment of their risks and benefits is required. Fingolimod, teriflunomide, dimethyl fumarate (DMF), and cladribine (newly approved) are approved MS treatments.

Fingolimod: Fingolimod (also known as FTY720, Gilenya) was the first approved oral medication for MS therapy by the United States Food and Drug Administration (USFDA). It is a myriocin derivative, a metabolite of the ascomycete fungus Isaria sinclairii, used in Oriental medicine.[4] The FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis),[5] TRANSFORMS [TRial Assessing injectable interferoN vS. FTY720 Oral in Relapsing-remitting Multiple sclerosis (RRMS)],[6] and FREEDOMS II[7] studies are three large-scale trials that have assessed the long-term safety and efficacy of fingolimod and reported that patients taking fingolimod had significantly better MRI outcome measures.

Teriflunomide: Teriflunomide (Aubagio) is an effective leflunomide metabolite,[8] a disease-modifying drug (DMD) approved for mild and moderate rheumatoid arthritis (RA) therapy.[9] The medication's role in MS treatment was first assessed in the Dark Agouti rat model of experimental autoimmune encephalomyelitis; the medication has been shown to delay the onset of disease, decrease the frequency of relapse, and improve neurological results.[10] A randomized controlled trial (RCT) involving patients with RRMS and secondary progressive MS (SPMS) showed that teriflunomide (7 or 14 mg/day) reduced the brain active lesions over 36 weeks. Also, the TEMSO (TEriflunomide Multiple Sclerosis Oral),[11] TOPIC (TeriflunOmide vs. Placebo in patients with first Clinical symptom of multiple sclerosis),[12] TENERE (TErifluNomidE and REbif),[13] and TOWER (Teriflunomide Oral in people with relapsing multiplE scleRosis)[14] studies endorsed the favorable clinical profile of the medication.

DMF: A dimethyl ester of fumaric acid compound, DMF (BG-12, Fumaderm), which contains four separate fumaric acid esters, is a second-line agent for the treatment of severe psoriasis. However, similarities in the related inflammatory cascades resulted in the hypothesis that in patients with central nervous system (CNS) autoimmune disorders, Fumaderm could also have positive impacts and resulted in the subsequent acceptance of Fumaderm as a promising MS treatment. Biogen (now Biogen Idec) licensed BG00012 (BG-12, Tecfidera), a second-generation fumaric acid compound comprising only dimethyl fumarate in enteric-coated micro-tablets, exclusively in September 2003. Two phase 3 trials evaluated the long-term efficacy and safety of the medication and the findings – together with knowledge gained in using fumaric acid ester in patients with psoriasis – contributed to the latest FDA approval of the medication as the newest oral RRMS therapy. The findings of a study in 2006 indicated that the number of gadolinium (Gd)-enhanced lesions significantly reduced by DMF.[15] Since that time, this medication yielded further impressive results.[16-18]

Cladribine: FDA announced the approval of

Mavenclad (cladribine) oral tablets to treat adults with RRMS and SPMS in a news release dated March 29, 2019.[19] Cladribine is administered approximately a year apart as two tablet courses. In the first month, every course includes four to five treatment days, followed by a further four to five treatment days in the second month. Mavenclad's recommended dose is 3.5 mg/kg for two years, given in two treatment courses of 1 and 75 mg/kg/year. Consequently, the weight of the person is the key factor of determining the number of tablets given on each day of treatment.[20] Cladribine is an effective therapy for RRMS and decreases the annual rate of relapses.[21]

Materials and Methods

This systematic review was conducted based on the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Search strategy: The following 4 databases were searched from inception until April 2020: The Cochrane Library, PubMed, Scopus, and Web of Science. Searches were conducted by using predetermined keywords. The full search strategy is shown in table 1.

Selection of studies: Before the literature search, criteria for inclusion/exclusion of studies were established. All studies were initially screened by two reviewers based on their titles and abstracts. After excluding studies that were not acceptable based on inclusion criteria, the full texts of the remaining studies were assessed by both reviewers to understand whether inclusion and exclusion criteria were met or not. By discussion, disagreements were resolved.

RCTs which evaluated the efficacy [relapse rate, magnetic resonance imaging (MRI) results] and safety [adverse events (AEs)] (both efficacy and safety or one of them) of oral DMDs including teriflunomide, fingolimod, DMF for patients with MS and GA and IFN β for control group, which their full text was available in English, were included in this study.

Studies conducted in patients who switched their medication or received these medications as combination therapy, studies which considered other medications as the control group, or studies with incomplete criteria for inclusion, were excluded from the systematic review.

Data extraction: Information from each article was evaluated by two independent reviewers to answer the research questions [Population, Intervention, Comparison, Outcome (PICO)]. Data extracted included sample size, first author, year of publication, type of MS, name of medication and dose, mean Expanded Disability Status Scale (EDSS) score, annualized relapse rates (ARRs), adverse drug events (ADEs), and MRI test result.

Study quality assessment: The quality of each article was separately evaluated by both authors using the Jadad scale. The discussion settled any disagreement. The Jadad scale assesses the performance of RCTs; it assigns up to 2 points for randomization recorded, up to 2 points for double-blinding, and up to 1 point for the description of withdrawals and dropouts. A minimum Jadad score of 3 is considered high quality.[22]

Table 1. Search strategy

No	Databases
1	**PubMed**
	"Multiple Sclerosis" [Mesh] AND ("Fingolimod Hydrochloride" [Mesh] OR "Dimethyl Fumarate" [Mesh] OR "teriflunomide" [Mesh] OR "Aubagio" OR "Cladribine" [Mesh] OR "Mavenclad" OR" Leustatin DSC")
2	**Scopus**
	("Multiple Sclerosis" OR MS) AND (teriflunomide OR Aubagio OR HMR*1726 OR "Dimethyl Fumarate" OR Dimethylfumarate OR BG*12 OR "Fingolimod Hydrochloride" OR fingolimod OR Gilenya OR Gilenya OR FTY*720 OR "Cladribine" OR Mavenclad OR Leustatin DSC)
3	**Cochrane**
	#1 MeSH descriptor: [Multiple Sclerosis] explode all trees
	#2 MeSH descriptor: [Fingolimod Hydrochloride] explode all trees
	#3 MeSH descriptor: [Dimethyl Fumarate] explode all tree
	#4 teriflunomide or Aubagio or HMR
	#5 Cladribine or Mavenclad or Leustatin DSC*: ti,ab,kw
	#6 #2 or #3 or #4 or #5
	#7 #1 and #6
4	**Web of Science (ISI)**
	("Multiple Sclerosis" OR MS) AND (teriflunomide OR Aubagio OR HMR*1726 OR "Dimethyl Fumarate" OR Dimethylfumarate OR BG*12 OR "Fingolimod Hydrochloride" OR fingolimod OR Gilenya OR Gilenya OR FTY*720 OR "Cladribine" OR Mavenclad OR Leustatin DSC)

Results

Search: The search identified 6605 articles. After combining databases, we removed 2389 articles. Of the 4216 remaining articles, we removed 4202 articles after the title and abstract screening and 14 articles met the criteria for reviewing full-text, of which we excluded 11. The remaining 3 articles were the subject of this review (Figure 1).

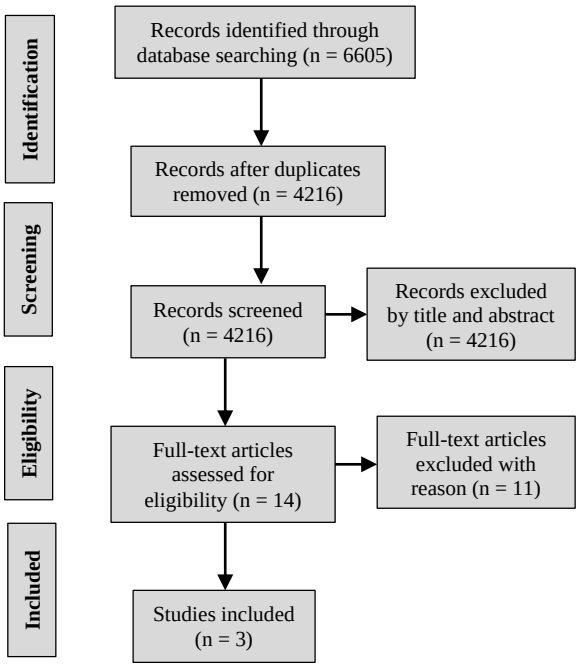

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart diagram

Study characteristics: In this study, three articles were reviewed. Comi et al.[23] in an 18-month, open-label, rater-blinded, randomized, multicenter study (the GOLDEN study) compared oral fingolimod with intramuscular (IM) IFN β-1b. Vermersch et al.[13] in a rater-blinded, randomized, controlled phase 3 trial compared oral teriflunomide with subcutaneous IFN β-1a and Cohen et al.[24] in a double-blind, randomized, controlled phase 3 trial (subgroups from TRANSFORMs study) compared oral fingolimod with IM IFN β-1a. The studies were published between 2013 and 2017. The main characteristics of the studies are presented in table 2.

Outcomes

Effects of oral medications on ARR: All studies evaluated the effect of oral medications on ARR. Results suggested that in patients with RRMS, fingolimod decreased ARR by 32-59 percent over 12 months compared to IFN β-1a.[24] Also, in the IFN β-1b group, ARR was higher than in the fingolimod group (0.39 vs. 0.12).[23] However, no difference between teriflunomide 14 mg (0.22 vs. 0.26, P = 0.600) and IFN β-1a was observed in the ARR, but with teriflunomide 7 mg (0.41, P = 0.030 vs. IFN β-1a), the ARR was significantly higher[13] (Table 2).

Summary: The two studies[23,24] provided some evidence that fingolimod was effective in reducing ARR, at least in the short term; further research is needed on the longer-term effect of the drug on the reduction of ARR based on these results. But, there is no evidence that teriflunomide 7 mg leads to a reduction in ARR when compared to IFN β-1a and no difference has been demonstrated between the effectiveness of teriflunomide 14 mg and IFN β-1a;[13] however, further studies are required to determine its efficacy.

Effects of oral medications on MRI findings: Two studies evaluated the effect of oral medications on MRI results. Cohen et al.[24] evaluated Gd-enhancing T1 lesions, new/newly-enlarged (active) T2 lesions, and brain volume change, and found that in the total population, fingolimod decreased the number of Gd-enhancing T1 lesions (15-82 percent) and new/newly-expanded T2 lesions (11-52 percent) versus IFN β-1a and also the loss of brain volume by 30-40 percent. Comi et al.[23] found that in the IFN β-1b group, T2 lesion volume (LV) was higher than in the fingolimod group (P = 0.177). At the end of the analysis, more new T2 lesions were presented in the IFN β-1b group (3.33 ± 4.44 vs. 1.25 ± 2.05) than in the fingolimod group (P = 0.0276 between groups). In patients treated with fingolimod, both the amount and volume of Gd-enhancing T1 lesions decreased (significant for the amount of lesions, P = 0.032). In the fingolimod group, brain volume loss was also decreased as opposed to the change in brain volume loss in the IFN β-1b group (P = 0.045) (Table 3).

Summary: In both of the comparisons between fingolimod and IFN β-1a and fingolimod and IFN β-1b, improvement in the MRI findings on treatment with fingolimod was observed.[23,24] However, further research is needed on the longer-term effect of the drug on MRI findings.

AEs: Two studies evaluated the AEs of MS medications on patients. The results of Comi et al.[23] study indicated that overall, 79.81% of patients under fingolimod therapy and 59.57% under IFN β-1b therapy were reported with AEs. During the study, no death was reported.

Table 2. Characteristics of included studies

References	Type of MS	Length of study	Intervention group dose and duration	Control group dose and duration	Number of participants		Mean number of relapses past year (time)		Mean EDSS score (at screening)		ARR		AEs
					I	C	I	C	I	C	I	C	
Comi et al.[23]	RRMS	18 months	Oral fingolimod (0.5 mg/day)	IFN β-1b (250 µg every other day)	97	30	1.45	1.18	2.78	2.90	0.12	0.39	83	28
Vermersch et al.[13]	RRMS	24 months	Oral teriflunomide (7 or 14 mg/day)	Subcutaneous IFN β-1a (with the dose titrated from 8.8 µg for the first 2 weeks to 22 µg for the next 2 weeks, and 44 µg until study completion)	7 mg = 109, 14 mg = 111	104	7 mg = 1.30, 14 mg = 1.40	1.20	7 mg = 2.00, 14 mg = 2.30	2.00	7 mg = 0.41, 14 mg = 0.26	0.22	7 mg = 103, 14 mg = 102	97
Cohen et al.[24]	RRMS	12 months	Oral fingolimod (0.5 mg or 1.25 mg/day)	IFN β-1a (30 µg weekly)	429	431	< 1 (261), ≥ 1 (168)	< 1 (157), ≥ 1 (274)	0-3.50 (362), > 3.50 (67)	0-3.50 (371), > 3.50 (60)	0.21	0.41	-	-

MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; EDSS: Expanded Disability Status Scale; ARR: Annualized relapse rate; AE: Adverse event; IFN β: Interferon beta; I: Intervention; C: Control

Table 3. Changing in magnetic resonance imaging (MRI) variables (P-value)

References	Intervention group dose and duration	Control group dose and duration	Total T2-LV (mm^3)	Number of T1 Gd+ lesions	The volume of T1 Gd+ lesions (mm^3)	Normalized brain volume
Comi et al.[23]	Oral fingolimod (0.5 mg/day)	IFN β-1b (250 µg every other day)	0.028	0.029	0.031	0.045
Vermersch et al.[13]	Oral teriflunomide (7 or 14 mg/day)	Subcutaneous IFN β-1a (with the dose titrated from 8.8 µg for the first 2 weeks to 22 µg for the next 2 weeks, and 44 µg until study completion)	NA	NA	NA	NA
Cohen et al.[24]	Oral fingolimod (0.5 mg or 1.25 mg/day)	IFN β-1a (30 µg weekly)	0.025	0.002	NA	0.004

Gd: Gadolinium; IFN β: Interferon beta; LV: Lesion volume; NA: Not available

In the fingolimod group, the proportion of patients with severe AEs was higher (8.65%) relative to the IFN β-1b group (2.13%). In the IFN β-1b group, the proportion of patients who discontinued the study because of AEs was higher (6.38% vs. 4.81%). Infection, infestation, blood cholesterol and transaminase increase for fingolimod and blood transaminase, triglyceride (TG), and cholesterol increase for IFN β-1b were the most widely-recorded AEs in both groups.

Study findings of Vermersch et al.[13] showed that the overall incidence of AEs between teriflunomide and IFN β-1a groups was similar. During the study, no death was reported. Diarrhea, paranesthesia, nasopharyngitis, thinning hair, and back pain were the AEs that were recorded with teriflunomide more frequently and influenza-like symptoms, increase in alanine transaminase (ALT), and headache were the AEs that reported more often with IFN β-1a. A similar incidence of severe AEs was also reported in the groups of IFN β-1a and teriflunomide 14 mg and a higher incidence in the group of teriflunomide 7 mg.

Summary: The results of evaluating the AEs of fingolimod on patients showed that fingolimod more adversely affected patients compared to IFN β-1b,[23] while the incidence of severe AEs was higher in teriflunomide 7 mg compared to IFN β-1a group.[13]

Study quality: According to the Jadad scale, the methodological quality of the included RCTs was high (Table 4) and all studies had a score of 4.

Discussion

Treating MS using first-line injection medications is a major concern for adherence and therapeutic efficacy. New oral drugs recently approved for treating MS have made substantial progress in the treatment of this disease. The oral route administration increases patient satisfaction. However, these medications may also have safety issues, and a thorough analysis of risks and benefits is needed. Fingolimod, teriflunomide, DMF, and cladribine are approved oral medications for treating MS.

After a systematic search of resources, three articles were finally included in the study.

About fingolimod, the results indicated that patients receiving fingolimod (0.5 or 1.25 mg) had a better clinical status and better MRI findings than patients receiving IFN (β-1a and β-1b). The number of relapses, the number and volume of brain lesions as well as the percentage of change in brain volume during the study were higher in the group taking IFN. The MRI findings and the rates of relapses were significantly better in the fingolimod group.[23,24] The proportion of patients suffering from AEs and serious AEs was higher in the fingolimod group than the IFN β-1b group, while in the IFN β-1b group, the proportion of patients discontinuing the study due to AEs was higher.[23]

About teriflunomide, the results indicated that there was no significant difference between 14 mg teriflunomide and subcutaneous IFN β-1a in ARR, while ARR with 7 mg teriflunomide was significantly higher. The incidence of AEs between the teriflunomide and IFN β-1a groups, overall, was similar.[13]

This review suggests that fingolimod is effective in reducing ARR and improving MRI findings and other clinical measures but leads to more adversely-affected patients compared to IFN β-1b, though, longer-term studies are required to determine its true value. Also, the results indicate that teriflunomide is not effective in reducing ARR but it has the same adverse effects on patients as IFN β-1a. Since there is only one RCT of teriflunomide in this study, further studies are required to determine its efficacy.

Results of efficacy and safety profiles of new oral agents are important to assess their role in the care of patients with MS. With the introduction of new treatments, the need for biomarkers to predict a patient's reaction to therapy is imperative. Further studies are required to improve treatments for stopping neurodegeneration and encouraging remyelination and neuronal repair.[25]

Table 4. Jadad scale

	Comi et al.[23]	Vermersch et al.[13]	Cohen et al.[24]
Described as randomized*	1	1	1
Described as double-blind*	1	1	1
Description of withdrawals*	1	1	1
Randomization method described and appropriate**	1	1	1
Double-blinding method described and appropriate**	0	0	1
Score	4	4	4

*A study receives a score of 1 for "yes" and 0 for "no"; **A study receives a score of 0 if no description is given, 1 if the method is described and appropriate, and -1 if the method is described but inappropriate

"The word "double-blind" was not used by the authors. However, according to the description of the blinding of the investigator, investigational site staff, and participants, one point was given for "described as double-blind"

MS disease-modifying treatments are long-term treatments for most patients. Therefore, treatment adherence is important, and many patients may also prefer oral treatment. It is therefore suggested to start with oral first-line medication. In the event of intolerability or undesirable side effects, consideration should be given to switching between oral medications or one of the injectable medications. Injectable drugs have been used for longer periods than oral drugs and thus, more long-term safety data are available.[26,27] It is necessary to constantly monitor the treatment regimen for optimum adherence, taking into account both the administration type and the side-effect profiles.

The review has some limitations. First, all three RCTs had used a head to head comparison and we excluded RCTs that used a comparison placebo-controlled group and compared the safety and efficacy of oral DMDs with placebo. Therefore, the number of included RCTs was limited and no clear conclusion can be drawn concerning the efficacy and safety of oral DMDs. And second, in this review, no eligible study was found for DMF and cladribine and therefore, there are no data on the efficacy and safety of these medications.

In view of the prevalence of MS, it is disappointing that published evidence base for the effectiveness of oral treatments is so poor. And we need to additional studies to better understand the efficacy and safety of oral DMDs for treating MS.

Conclusion

Approval of several new oral medications for patients with MS will be beneficial and provide more convenient ways. However, the lack of long-term data on the efficacy and AEs are of concern. Therefore, an assessment of the best treatment for each patient should include an overall assessment of its efficacy, safety, tolerance, monitoring need, and cost-effectiveness.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

The authors would like to thank the School of Pharmacy of Tehran University of Medical Sciences, Tehran, Iran, for their valued cooperation during the entire project.

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