Review Article

The Efficacy of Fingolimod and Interferons in Controlling Disability and Relapse Rate in Patients with Multiple Sclerosis: A Systematic Review and Meta-Analysis

Abstract

Background: Fingolimod and interferons are used in the relapse form of multiple sclerosis (MS). The goal of this systematic review and meta-analysis was to evaluate the efficacy of fingolimod versus interferon in patients with MS. The systematic search was done in PubMed, Scopus, Embase, Web of Science, and Google Scholar. **Methods:** The references of included studies as well as conference abstracts were searched up to July 2021. The literature search revealed 8211 articles, and after deleting duplicates 5594 remained. For the meta-analysis, four studies were included. The standardized mean difference (SMD) of the Expanded Disability Status Scale (EDSS) after treatment (interferon vs fingolimod) was −0.06 (95% CI: −0.28, 0.17) (I^2 = 80.2%, P = 0.002). **Results:** The SMD of the annual relapse rate (ARR) after treatment (interferon – fingolimod) was −0.08 (95% CI: −0.53, 0.36) (I^2 = 95.5%, P < 0.001). The SMD of the ARR after treatment and before treatment in the interferon group was − 1.45, (95% CI: −1.55, −1.36) (I^2 = 0, P = 0.3). The SMD of ARR after treatment and before treatment in the fingolimod group was − 1.3, (95% CI: −1.94, −0.65) (I^2 = 97.4%, P < 0.001). **Conclusions:** The results of this systematic review show that efficacy of interferon and fingolimod in controlling relapse rate and disability is similar.

Keywords: *Disability, multiple sclerosis, relapse, systematic review*

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Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, with a wide range of complications.[1-4] The type of the disease in near 85% of affected cases is relapsing-remitting (RR) which is characterized by worsening of neurological manifestations and then remission of clinical symptoms.[5]

The first-line treatments include glatiramer acetate (GA) and interferons (IFNs), which are injectable with partial effectiveness and tolerability.[6]

Dimethyl fumarate (DMF), fingolimod, and teriflunomide were introduced as oral disease-modifying therapies (DMTs) and dramatically the treatment of MS.[7] The advantages of oral therapies are more convenience and compliance.[7] Fingolimod is lipophilic and crosses the blood–brain barrier easily and is considered to have neuroprotective or reparative effects.[8,9] Fingolimod is the first oral medication that has been approved for the RR form of the disease.[10]

Up to now, some randomized clinical trials were conducted to assess the efficacy and safety of fingolimod versus interferons but there is no systematic review of it in this field. There are controversies regarding the efficacy of these two types of medications in treating patients with MS.[11-13]

Thus, we designed this systematic review and meta-analysis to evaluate the efficacy of fingolimod versus interferon in patients with MS.

Methods

Search strategy

The systematic search was done in PubMed, Scopus, Embase, Web of Science, and Google Scholar databases. The references of included studies as well as conference abstracts were searched up to July 2021.

The search strategy for PubMed was as follows:

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("Multiple Sclerosis" OR "MS" OR "Relapsing-Remitting Multiple Sclerosis" OR (Multiple Sclerosis AND Relapsing-Remitting) OR "Chronic Progressive Multiple Sclerosis" OR (Multiple Sclerosis AND Chronic-Progressive) OR "demyelinating diseases" OR "demyelinating disorders" OR (autoimmune AND demyelinating) OR "autoimmune demyelinating disease" OR (autoimmune AND cerebral) OR (autoimmune AND "spinal cord") OR (autoimmune AND "central nervous system") OR (autoimmune AND "peripheral nervous system") OR "demyelination" OR (autoimmune AND demyelination)) AND (fingolimod OR gilenya OR Fingolimod OR Gilenya OR "FTY720" OR "fty720" OR "Fingolimod Hydrochloride")

Inclusion criteria

Inclusion criteria were randomized clinical trials or cohort studies in which fingolimod was compared with interferon in patients with MS; and studies which provided information regarding annual relapse rate (ARR) and the Expanded Disability Status Scale (EDSS).

Exclusion criteria

Exclusion criteria were letters to the editor, case–control studies, case reports, and cross-sectional studies that had no clear data regarding ARR and EDSS.

Data extraction

Two researchers independently reviewed the complete texts of the included studies, and extracted and entered data into Microsoft Excel spreadsheets. In the case of discrepancy, a third researcher solved the problem.

We extracted data regarding the first author, publication year, the country of origin, sample size in INF group, sample size in fingolimod group, duration of follow-up, mean age, annual relapse rate (ARR), Expanded Disability Status Scale (EDSS), and adverse effects.

Risk of bias assessment

We evaluated the risk of potential bias by the Cochrane Collaboration's tool for assessing the risk of bias.[14]

Statistical analysis

All statistical analyses were performed using Stata (version 14.0; Stata Corp LP, College Station, TX, USA).

To determine heterogeneity, inconsistency (I^2) was calculated. When I^2 was more than 50%, we used the random effects model; otherwise we used the fixed effects model.

Standardized mean difference (SMD) was calculated as an effect size.

Results

The literature search revealed 8211 articles, and after deleting duplicates 5594 remained. For the meta-analysis, four studies were included [Figure 1].

Finally, four full-text articles were assessed. In one study (Cohen *et al*.),[17] authors evaluated 1.25- and 0.5-mg doses of fingolimod with interferon. So, we included data separately. Two studies were from Italy and two were from USA. The publication year ranged between 2010 and 2018, and the mean age ranged between 33 and 40 years [Table 1].

The SMD of EDSS after treatment (interferon – fingolimod) was − 0.06 (95% CI: −0.28, 0.17) (I^2 = 80.2%, P = 0.002) [Figure 2].

The SMD of ARR after treatment (interferon – fingolimod) was − 0.08 (95% CI: −0.53, 0.36) (I^2 = 95.5%, P < 0.001) [Figure 3].

The SMD of ARR after and before treatment in the interferon group was − 1.45 (95% CI: −1.55, −1.36) (I^2 = 0, P = 0.3) [Figure 4].

The SMD of ARR after and before treatment in the fingolimod group was − 1.3 (95% CI: −1.94, −0.65) (I^2 = 97.4%, P < 0.001) [Figure 5].

The SMD of EDSS after and before treatment in the interferon group was 0.02 (95% CI: −0.07, 0.11) [Figure 6].

The SMD of EDSS after and before treatment in the fingolimod group was − 0.08 (95% CI: −0.16, 0.11) [Figure 7]. The risk of bias assessment is summarized in Table 2.

Discussion

To our knowledge, this is the first study that has evaluated the efficacy and safety of intramuscular interferons versus fingolimod in patients with relapsing-remitting MS. Our results show that the SMD of the ARR after treatment was − 0.08 (−0.53, 0.36) (interferon – fingolimod) and the SMD of EDSS (interferon – fingolimod) was − 0.06 (−0.28, 0.17) which could show that the ARR and EDSS after treatment were lower in the interferon group. We also found that the SMD of the ARR (after treatment – before treatment) was − 1.45 in both groups which was significant in both arms. This could indicate that both interferon and fingolimod treatments are effective in reducing relapses in MS patients. On the other hand, although not significant the SMD of EDSS reduction was 0.02 in the interferon group versus − 0.08 in the fingolimod group. This could indicate that fingolimod was more effective in disability reduction than interferons.

Signoriello *et al*.[10] enrolled 103 MS patients in the interferon and 103 in the fingolimod group and found that fingolimod was more effective in reducing relapse rate and disability than interferon. They suggested that binding to S1P-R receptors in CNS by fingolimod will result in its anti-inflammatory effects that influence central immunity and modulation of synaptic plasticity.

Administration of fingolimod causes tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β level reduction and promotes remyelination.[9] Fingolimod inhibits lymphocyte egress from the lymph node, leading to inhibition of lymphocyte infiltration into the CNS.[18,19]

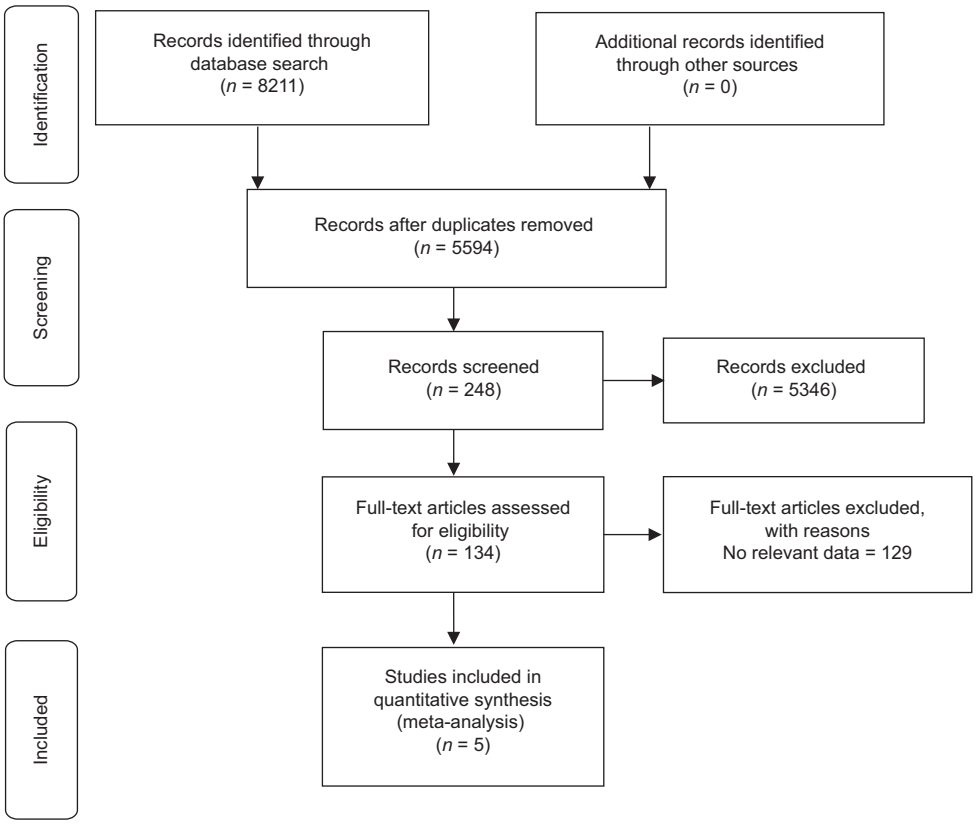

Figure 1: Flow diagram of studies included

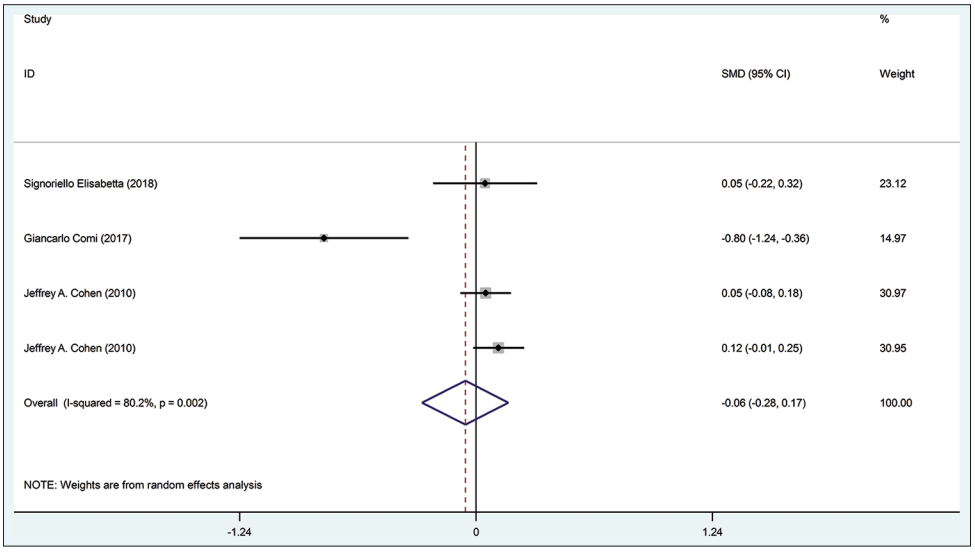

Figure 2: The SMD of EDSS after treatment

Comi *et al*.[16] enrolled 28 cases in the interferon group and 80 in the fingolimod group and reported higher ARR in the interferon group than the fingolimod group.

comparing different doses of fingolimod(1.25, o.5 mg), Cohen *et al* found that both doses were superior to interferon in controlling relapses.[17] They recommended that the dose of 1.25 mg was fully effective and the dose of 0.5 mg had submaximal effects on lymphocyte recirculation.

The results also showed that the rates of infection, lymphopenia, and musculoskeletal disorders were higher in the fingolimod group (urinary/and or respiratory infection) while flu-like syndromes were higher in the interferon group.

Interferons are the first-line treatment for MS that reduce production of pro-inflammatory cytokines and anti-inflammatory molecules with partial effectiveness and tolerability.[6] Although they cause lymphopenia, the rate of infection is rare.

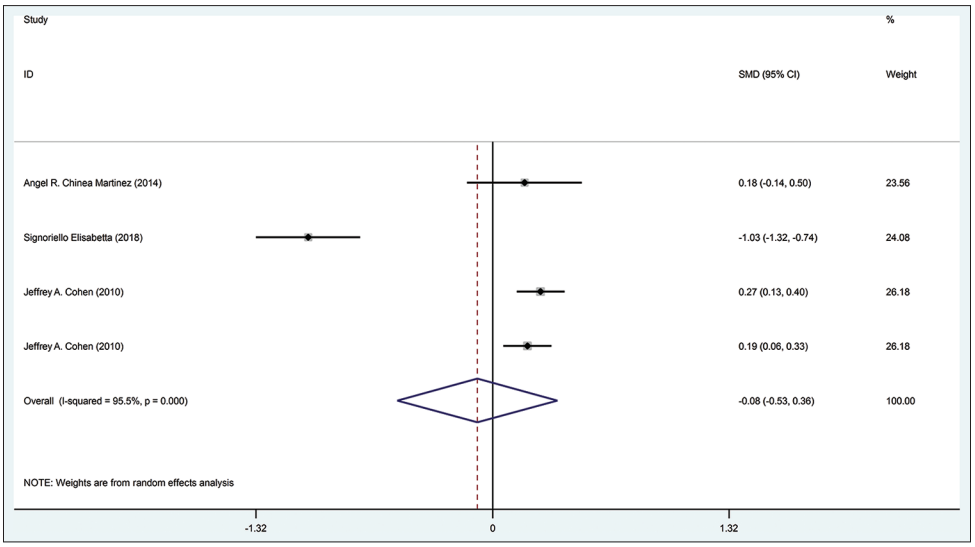

Figure 3: The ARR of EDSS after treatment

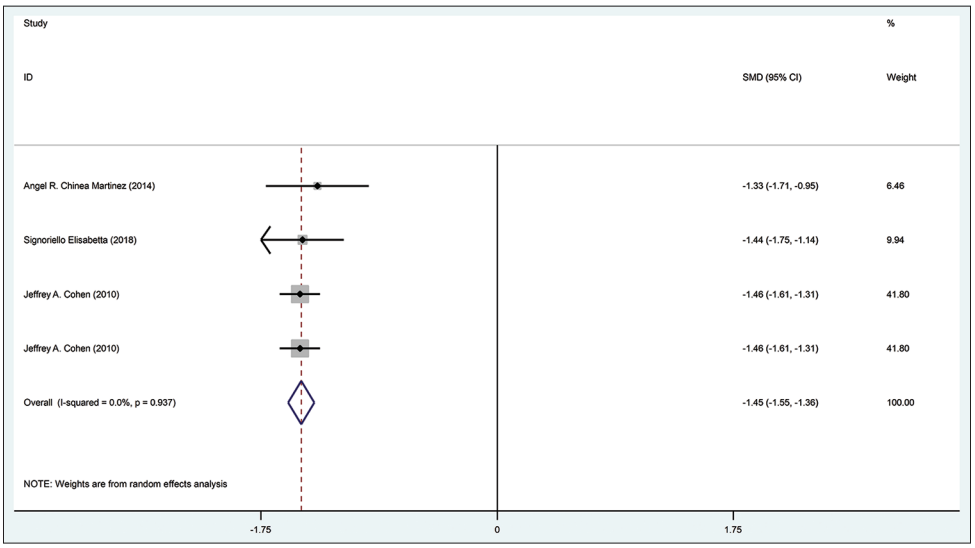

Figure 4: The SMD of ARR after and before treatment in the interferon group

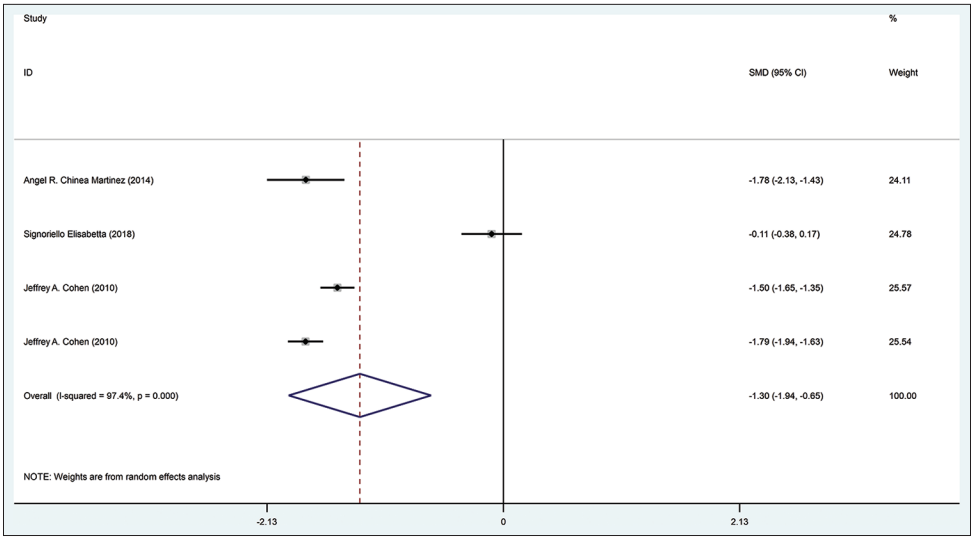

Figure 5: The SMD of ARR after and before treatment in the fingolimod group

Table 1: Basic characteristics of the included studies

Author	Country	Publication Year	Dose of Interferon (E.g., 2 mg daily)	Dose of Fingolimod (E.g., 2 mg daily)	Sample Size-Interferon	Sample Size-Fingolimod	Mean Age of Sample Size-Interferon	Mean Age of Sample Size-Fingolimod
Angel R. Chinea Martinez[15]	USA	2014	30 mg weekly	0.5 mg daily	65	89	33.4 (8.1)	37.6 (9.1)
Signoriello Elisabetta	Italy	2018			103	103		
Giancarlo Comi[16]	Italy	2017	250 µg every other day	0.5 mg daily	28	80	37.64 (9.29)	40.23 (9.09)
Jeffrey A. Cohen[17]	USA	2010	30 µg weekly	0.5 mg daily	435	431	36.0 (8.3)	36.7 (8.8)
Jeffrey A. Cohen[17]	USA	2010	30 µg weekly	1.25 mg daily	435	426	36.0 (8.3)	35.8 (8.4)

Author	Disease Duration-Interferon	Disease Duration-Fingolimod	Follow-up Duration	ARR-Interferon (Before)	ARR-Interferon (After)	ARR-Fingolimod (Before)	ARR-Fingolimod (After)
Angel R. Chinea Martinez[15]	7.3 (5.8)	9.3 (7.5)	24	1.4 (0.7)	0.34 (0.18-0.63)	1.5 (0.9)	0.22 (0.14-0.35) CI95
Signoriello Elisabetta	3.14 (1.6)	3.14 (1.6)	12	0.41 (0.32)	0.04 (0.17)	0.41 (0.32)	0.37 (0.42)
Giancarlo Comi[16]	4.71 (6.47)	4.97 (6.67)	18	1.18 (0.48)	0.39	1.45 (0.79)	0.12
Jeffrey A. Cohen[17]			12	1.5 (0.8)	0.33 (0.26-0.42)	1.5 (1.2)	0.16 (0.12-0.21)
Jeffrey A. Cohen[17]			12	1.5 (0.8)	0.33 (0.26-0.42)	1.5 (0.9)	0.20 (0.16-0.26)

Author	EDSS-Interferon (Before)	EDSS-Interferon (After)	EDSS-Fingolimod (Before)	EDSS-Fingolimod (After)	Adverse Events-Interferon	Adverse Events-Fingolimod
Angel R. Chinea Martinez[15]	2.2 (1.3)		2.2 (1.2)		New ECG events at 6 h post dose: 6	New ECG events at 6 h post dose: 10
					Any AEs: 62	Any AEs: 78
					AEs leading to treatment discontinuation: 1	AEs leading to treatment discontinuation: 7
					Serious adverse events: 1	Serious adverse events: 7
					Influenza-like illness: 37	Influenza-like illness: 4
					Nasopharyngitis: 7	Nasopharyngitis: 17
					Headache: 9	Headache: 17
					Urinary tract infection: 7	Urinary tract infection: 12
					Dizziness: 1	Dizziness: 6
					Upper respiratory tract infection: 5	Upper respiratory tract infection: 10 (11.2)
					Migraine: 2	Migraine: 4
					Cough: 1	Cough: 2
					Pyrexia: 8	Pyrexia: 5
					Nausea: 3	Nausea: 8
					Cystitis: 0	Cystitis: 1
					Neck pain: 3	Back pain: 6
					Dyspnea: 0	Neck pain: 3
					Diarrhea: 2	Dyspnea: 1
					Depression: 2	Diarrhea: 9
						Depression: 9

Contd...

Table 1: Contd...

Author	EDSS-Interferon (Before)	EDSS-Interferon (After)	EDSS-Fingolimod (Before)	EDSS-Fingolimod (After)	Adverse Events-Interferon	Adverse Events-Fingolimod
Signoriello Elisabetta	1.79 (1.17)	1.86 (1.18)	1.99 (1.32)	1.80 (1.29)		
Giancarlo Comi[16]	2.09 (1.05)	2.28 (0.54)	2.78 (1.34)	2.9 (0.84)	Number of patients with at least one AE: 28 Number of patients with at least one SAE: 1 Number of patients with at least one AE suspected to be: 10 Number of patients with at least one AE leading to discontinuation: 3 Number of patients with at least one AE: 28 Blood and lymphatic system disorders: 0 Eye disorders: 1 Gastrointestinal disorders: 5 General disorders and administration site conditions: 10 Infections and infestations: 9 Injury, poisoning, and procedural complications: 3 Investigations: 9 Metabolism and nutrition disorders: 2 Musculoskeletal and connective tissue disorders: 5 Nervous system disorders: 12 Psychiatric disorders: 6 Renal and urinary disorders: 4 Respiratory, thoracic, and mediastinal disorders: 3 Skin and subcutaneous tissue disorders: 0 Vascular disorders: 1	Number of patients with at least one AE: 83 Number of patients with at least one SAE: 9 Number of patients with at least one AE suspected to be: 37 Number of patients with at least one AE leading to discontinuation: 5 Number of patients with at least one AE: 83 Blood and lymphatic system disorders: 7 Eye disorders: 8 Gastrointestinal disorders: 22 General disorders and administration site conditions: 17 Infections and infestations: 29 Injury, poisoning, and procedural complications: 6 Metabolism and nutrition disorders: 8 Musculoskeletal and connective tissue disorders: 11 Nervous system disorders: 19 Psychiatric disorders: 13 Renal and urinary disorders: 6 Respiratory, thoracic, and mediastinal disorders: 6 Skin and subcutaneous tissue disorders: 11 Vascular disorders: 6

Contd...

Table 1: Contd...

Author	EDSS-Interferon (Before)	EDSS-Interferon (After)	EDSS-Fingolimod (Before)	EDSS-Fingolimod (After)	Adverse Events-Interferon	Adverse Events-Fingolimod
Jeffrey A. Cohen[17]	2.19 (1.26)	2.20 (0.78)	2.24 (1.33)	2.16 (0.79)	Any event: 395 Any event leading to discontinuation of a study drug: 16 Nasopharyngitis: 88 Upper respiratory tract infection: 27 Influenza: 32 Urinary tract infection: 22 Herpesvirus infection: 12 Headache: 88 Dizziness: 21 Fatigue: 45 Pyrexia: 77 Influenza-like illness: 159 Diarrhea: 21 Nausea: 29 Back pain: 23 Limb pain: 28 Arthralgia: 24 Myalgia: 44 Cough: 16 Dyspnea: 7 Melanocytic nevus: 24 Depression: 32 Hypertension: 8 Alanine aminotransferase increase: 8 Lymphocytopenia: 0	Any event: 369 Any event leading to discontinuation of a study drug: 24 Nasopharyngitis: 88 Upper respiratory tract infection: 31 Influenza: 29 Urinary tract infection: 26 Herpesvirus infection: 9 Headache: 99 Dizziness: 24 Fatigue: 44 Pyrexia: 18 Influenza-like illness: 15 Diarrhea: 32 Nausea: 40 Back pain: 26 Limb pain: 21 Arthralgia: 12 Myalgia: 14 Cough: 20 Dyspnea: 8 Melanocytic nevus: 28 Depression: 21 Hypertension: 16 Alanine aminotransferase increase: 28 Lymphocytopenia: 1

Contd...

Table 1: Contd...

Author	EDSS-Interferon (Before)	EDSS-Interferon (After)	EDSS-Fingolimod (Before)	EDSS-Fingolimod (After)	Adverse Events-Interferon	Adverse Events-Fingolimod
Jeffrey A. Cohen[17]	2.19 (1.26)	2.20 (0.78)	2.21 (1.31)	2.1 (0.90)	Any event: 395	Any event: 380
					Any event leading to discontinuation of a study drug: 16	Any event leading to discontinuation of a study drug: 42
					Nasopharyngitis: 88	Nasopharyngitis: 93
					Upper respiratory tract infection: 27	Upper respiratory tract infection: 36
					Influenza: 32	Influenza: 28
					Urinary tract infection: 22	Urinary tract infection: 24
					Herpesvirus infection: 12	Herpesvirus infection: 23
					Headache: 88	Headache: 96
					Dizziness: 21	Dizziness: 23
					Fatigue: 45	Fatigue: 59
					Pyrexia: 77	Pyrexia: 15
					Influenza-like illness: 159	Influenza-like illness: 15
					Diarrhea: 21	Diarrhea: 35
					Nausea: 29	Nausea: 28
					Back pain: 23	Back pain: 27
					Limb pain: 28	Limb pain: 20
					Arthralgia: 24	Arthralgia: 17
					Myalgia: 44	Myalgia: 14
					Cough: 16	Cough: 30
					Dyspnea: 7	Dyspnea: 22
					Melanocytic nevus: 24	Melanocytic nevus: 42
					Depression: 32	Depression: 18
					Hypertension: 8	Hypertension: 21
					Alanine aminotransferase increase: 8	Alanine aminotransferase increase: 24
					Lymphocytopenia: 0	Lymphocytopenia: 4

The SMD of EDSS after treatment (interferon - fingolimod) was − 0.06 (95% CI: −0.28, 0.17) (I2 = 80.2%, $P = 0.002$) [Figure 2].

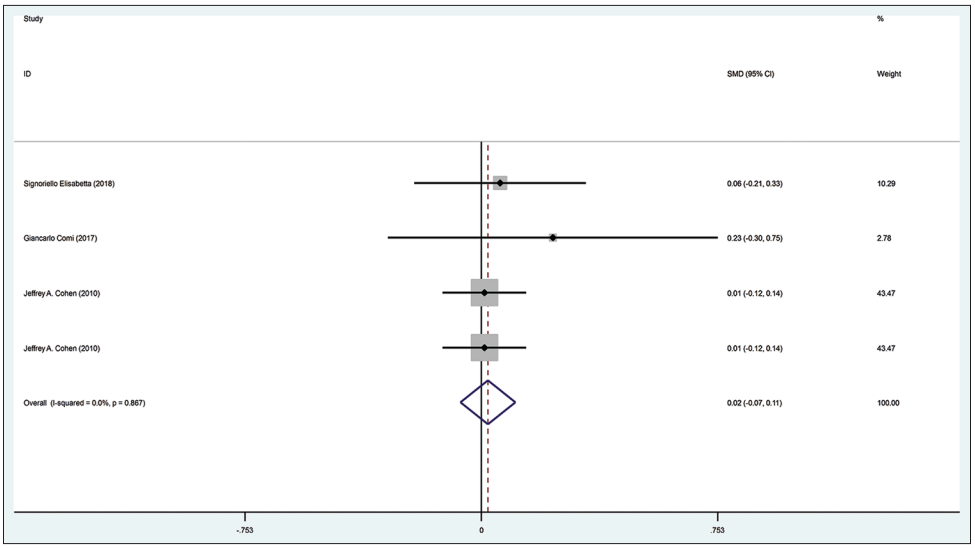

Figure 6: The SMD of EDSS after and before treatment in the interferon group

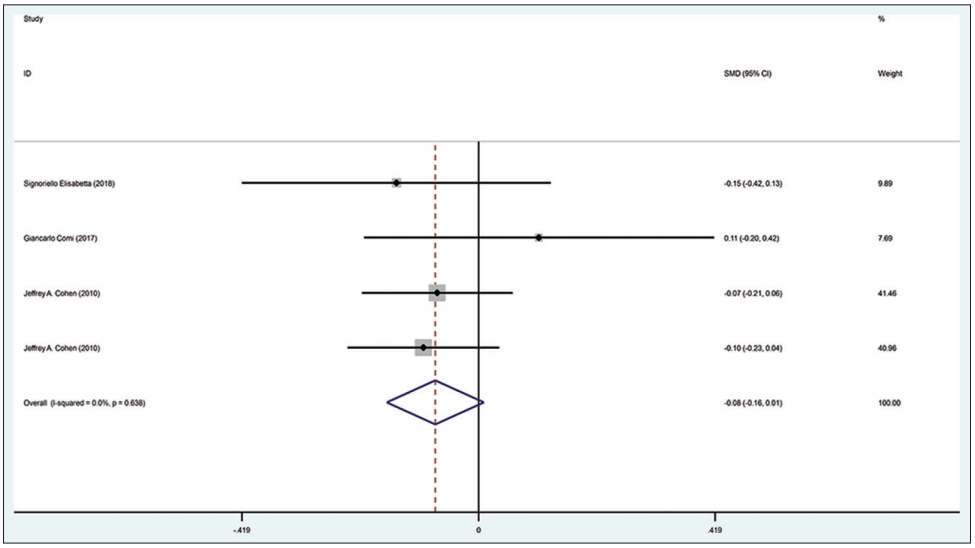

Figure 7: The SMD of EDSS after and before treatment in the fingolimod group

Table 2: Risk of bias assessment of clinical trials

	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Researchers (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)
Angel R. Chinea Martinez, 2014	LRB	LRB	LRB	HRB	URB	URB
Signoriello Elisabetta, 2018	LRB	LRB	HRB	URB	LRB	LRB
Giancarlo Comi, 2017	LRB	URB	HRB	URB	LRB	LRB
Jeffrey A. Cohen, 2010	LRB	LRB	LRB	LRB	LRB	LRB
Jeffrey A. Cohen, 2010	LRB	LRB	LRB	LRB	LRB	LRB

LRB: Low risk of bias. URB: Unclear risk of bias. HRB: High risk of bias

Fingolimod could prevent T cell trafficking which increases the risk of respiratory tract and urinary tract infections, as well as varicella zoster virus infection while there is no clear relationship between lymphopenia and infection.[17,20]

Although the efficacy of two medications in our study seems the same, the long-term administration of interferons is not pleasant for some cases due to needle phobia, injection site reaction, and flue-like syndrome.[21] By contrast, adherence to oral medications is higher.

This systematic review and meta-analysis has some limitations. First, the number of included studies is limited. Second, the dose of fingolimod was different in the two studies.

Conclusion

The results of this systematic review show that efficacy of interferon and fingolimod in controlling relapse rate and disability is similar.

Acknowledgment

None.

Data Accessibility

None.

Ethical Considerations

N/A.

Code of Ethics

N/A.

Authors' Contributions

VS:Study conception, data gathering, article writing OM:data gathering, article writing SB:data gathering, article writing PS:data gathering, article writing MG:Study design , data analysis, article writing and editing.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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