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Review article

Fingolimod for the treatment of Relapsing Remitting Multiple Sclerosis: a revision of systematic reviews

Fingolimode para o tratamento de Esclerose Múltipla Remitente Recorrente: uma revisão de revisões sistemáticas

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ABSTRACT

Objective: This revision aimed to summarize the evidence of efficacy and safety of fingolimod in the treatment of Relapsing Remitting Multiple Sclerosis (RRMS). **Method:** A literature search was performed in Medline, the Cochrane Library, EMBASE, and LILACS on 18 February 2025. We included systematic reviews with meta-analyses on the use of fingolimod compared to other treatments in adults with low or moderate activity RRMS. Two authors performed study selection, data extraction, and quality assessment using Rayyan QCRI, AMSTAR-2, and GRADE tools. Three studies were included. **Results:** Regarding efficacy, two reviews showed that fingolimod significantly reduced the annualized relapse rate (by 26% to 48%), and one indicated a reduction of approximately 35% in relapses over 24 months. For disability progression at 24 months, no relevant difference was observed between fingolimod and comparators. Regarding safety profile, one review reported that serious adverse events were similar between fingolimod and most comparators, except for interferon β-1a. The methodological quality of the reviews ranged from "critically low" to "high", and the quality of the evidence ranged from "very low" to "moderate". **Conclusion:** Fingolimod demonstrated superiority over glatiramer acetate, interferons β-1a and β-1b, and teriflunomide in reducing the relapse rate, but not in preventing disability progression. Despite the favorable results, these findings should be interpreted cautiously, as the efficacy data come from short-term clinical trials and do not reflect long-term effectiveness throughout RRMS.

Keywords: Relapsing remitting multiple sclerosis; Fingolimod; Systematic review.

RESUMO

Objetivo: Sintetizar evidências sobre a eficácia e segurança do fingolimode no tratamento da Esclerose Múltipla Remitente Recorrente (EMRR). **Método:** Foi realizada uma busca nas bases Medline, Biblioteca Cochrane, EMBASE e LILACS em 18 de fevereiro de 2025. Incluíram-se revisões sistemáticas com metanálises que compararam o fingolimode a outros tratamentos em adultos com EMRR de baixa ou moderada atividade. A seleção dos estudos, extração dos dados e avaliação da qualidade metodológica foram feitas por dois autores independentes, com uso das ferramentas Rayyan QCRI, AMSTAR-2 e GRADE. Três estudos foram incluídos. **Resultados:** Em termos de eficácia, duas revisões mostraram que o fingolimode reduziu significativamente a taxa anual de surtos (26% a 48%), e uma apontou redução de cerca de 35% de surtos em 24 meses. Quanto à progressão da incapacidade em 24 meses, não houve diferença relevante entre o fingolimode e os comparadores. Em relação à segurança, uma revisão indicou que os eventos adversos graves foram semelhantes entre o fingolimode e a maioria dos comparadores, com exceção do interferon β-1a. A qualidade metodológica das revisões variou de "criticamente baixa" a "alta", e a qualidade das evidências, de "muito baixa" a "moderada". **Conclusão:** O fingolimode mostrou superioridade em relação ao acetato de glatirâmer, interferons β-1a e β-1b e à teriflunomida na redução da taxa de surtos, mas não na progressão da incapacidade. Apesar dos resultados favoráveis, estes devem ser interpretados com cautela, pois os dados de eficácia provêm de ensaios clínicos de curto prazo, sem refletir a efetividade ao longo do curso da EMRR.

Palavras-chave: Esclerose múltipla remitente recorrente; Fingolimode; Revisão sistemática

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune, neurodegenerative, and inflammatory disease that damages the myelin sheath, commonly affecting young adults.[1] The most common manifestations are optic neuritis, paresis or paresthesia of the limbs, coordination and balance disorders, myelitis, sphincter dysfunction, and cognitive-behavioral dysfunction, occurring in isolation or in combination.[1,2] Because these symptoms involve the nervous system, there is the possibility of neuropathic pain, spasticity, depressive disorder, paresis, ataxia, tremor, fatigue, erectile, bowel, and bladder dysfunction, as well as bladder infection.[5-7] Worldwide, 1.89 million people live with MS, with more than 62,000 new cases diagnosed in 2021 and a global prevalence of 23.9 cases per 100,000 inhabitants.[3] In Brazil, prevalence ranges from 8.7 to 15 cases per 100,000 inhabitants, with wide regional variation (from 1.36 to 27.2 per 100,000 inhabitants in the Northeast and South regions, respectively).[4]

MS presents with isolated neurological events that evolve to a relapsing remitting condition (RRMS) in most patients, impairing quality of life still during the productive years. These individuals are psychologically affected, with the possibility of social exclusion. Family members and society may also be impacted, since the disease generates direct and indirect costs for both the patient and the health sector.[2,5]

According to the Brazilian Committee for Treatment and Research in Multiple Sclerosis and the Ministry of Health Clinical Protocol and Therapeutic Guidelines (PCDT) for MS, there is no curative treatment, and the current therapeutic approach aims to reduce the risk of relapses and the progression of disability.[1,6] Drug therapy seeks clinical improvement, better functional capacity, reduction of comorbidities, and attenuation of symptoms.[7]

Several disease-modifying therapies are available for the treatment of patients with RRMS. According to the latest Brazilian Consensus for MS Treatment, in the absence of specific concerns related to high levels of disease activity, it is recommended to start treatment with interferon β-1a, interferon β-1b, glatiramer acetate, pegylated interferon β-1a, dimethyl fumarate, or teriflunomide, as these have a good safety profile and are more widely available.[6] For patients who meet criteria for relapsing and highly active RRMS or who present factors associated with a worse prognosis, alternative options are considered, such as alemtuzumab, cladribine, fingolimod, natalizumab, and ocrelizumab.

Studies have shown the potential of fingolimod as a first-line option for treating RRMS, although careful monitoring is recommended due to several safety issues, including bradycardia, macular edema, skin cancer, and infections.[8–10]

Systematic reviews play a fundamental role in health decision-making processes, especially in promoting evidence-based clinical practice. However, the growing availability of such reviews poses a challenge for health professionals and decision-makers, highlighting the importance of critically assessing their methodological quality before recommendations can be safely and effectively implemented in clinical practice.[11]

Currently, there is no published revision comparing fingolimod with other treatments in adults with RRMS. Therefore, this overview aimed to summarize evidence on the efficacy and safety of fingolimod in treating low- or moderately active RRMS and to critically assess the methodological quality of systematic reviews.

Methods

The protocol for this systematic review was registered in the *International Prospective Register of Systematic Reviews* (PROSPERO; CRD420251054494). This review followed the *Preferred Reporting Items for Overviews of Reviews* (PRIOR).[12]

Databases and search strategy

A comprehensive search for relevant literature was conducted in Medline (PubMed), the Cochrane Library, Embase, and the Latin American and Caribbean Health Sciences Literature (LILACS), on February 18, 2025. Grey literature was also examined for any additional relevant material, using Google Scholar up to the first 100 records (excluding patents and citations) through the Pub-

lish or Perish v.8 software.[13] No language or publication-date restrictions were applied. Search strategies used MeSH and EMTREE descriptor terms or words related to multiple sclerosis and fingolimod. Full search strategies for all databases are available in Appendix 1.

Study selection

Manuscripts were considered eligible if they met the following criteria: 1) adults diagnosed with low- or moderately active RRMS, without prior treatment (*treatment-naïve*); 2) evaluation of effect of fingolimod compared with interferon β-1a, interferon β-1b, glatiramer acetate, teriflunomide, or dimethyl fumarate; 3) report of at least one outcome of interest related to efficacy (Annualized Relapse Rate, Disability progression, Number of new and/or active lesions per year) and safety (serious adverse events); and 4) systematic reviews of randomized clinical trials (RCTs) with direct or indirect meta-analysis. It is worth noting that the most clinically relevant outcomes for patients were selected. Primary studies, technical reports, conference proceedings, other types of reviews, meta-analyses conducted without a systematic review, systematic reviews without meta-analysis, and systematic reviews with meta-analysis that included other populations, interventions, comparators, or outcomes were excluded. Manuscripts retrieved from databases were imported into the Rayyan QCRI web program14 for duplicate removal (Phase 1), title and abstract screening (Phase 2), and full-text assessment of previously selected abstracts (Phase 3). Two reviewers independently screened titles and abstracts of all identified studies and discussed disagreements until reaching consensus. When the full text could not be obtained, corresponding authors were contacted by email and through ResearchGate (www.researchgate.net).

Data extraction

Data were collected in a pre-formatted Microsoft Excel® spreadsheet, including author and year, bibliographic search and period, type of meta-analysis, target population, intervention and comparator with dosing regimen, outcome measures, statistical model used in the meta-analysis, effect size, publication bias, and funding source. Two independent reviewers extracted the data, and disagreements were resolved by a third reviewer. In addition, was used the online tool Elicit (https://elicit.org/) to complement this process.

Methodological quality

The methodological quality of systematic reviews was assessed using the Assessing the *Methodological Quality of Systematic Reviews version* 2 (AMSTAR-2) tool.[15] AMSTAR-2 consists of a 16-item questionnaire, with responses categorized as "yes," "partially yes," or "no." Overall ratings were based on weaknesses in critical domains (items: 2, 4, 7, 9, 11, 13, and 15) as follows: "high," no or one non-critical weakness; "moderate," more than one non-critical weakness but no critical flaws; "low," one critical flaw with or without non-critical weaknesses; and "critically low," more than one critical flaw with or without non-critical weaknesses. One investigator assessed the studies and another reviewed this assessment. Any disagreement was resolved by consensus.

Quality of evidence

The quality of evidence for each measured outcome was assessed using the *Grading of Recommendation Assessment, Development, and Evaluation* (GRADE) tool.[16] Evidence quality was classified into four levels: high, moderate, low, and very low, indicating confidence in the effect estimate. Initially, evidence quality starts as high when randomized clinical trials (RCTs) are analyzed. Factors such as risk of bias (methodological limitations), publication bias, indirectness, imprecision, and inconsistency can reduce the level of evidence for an outcome. Indirect meta-analyses were assessed considering the adjustments proposed by Salanti et al.[17] The evidence profile was created from an explicit assessment of each of these factors using GRADEpro software (https://gradepro.org/). One investigator assessed the studies and another reviewed this assessment. Any disagreement was resolved by consensus.

Data synthesis

Characteristics of the systematic reviews, the methodological quality assessment, and the quality of evidence were presented through narrative and structured tables. The original ideas and concepts of the included studies were respected. Effect size estimates from meta-analysis and confidence intervals were expressed as odds ratio (OR), relative risk (RR), or hazard ratio (HR), as reported by the authors.

Results

Database search

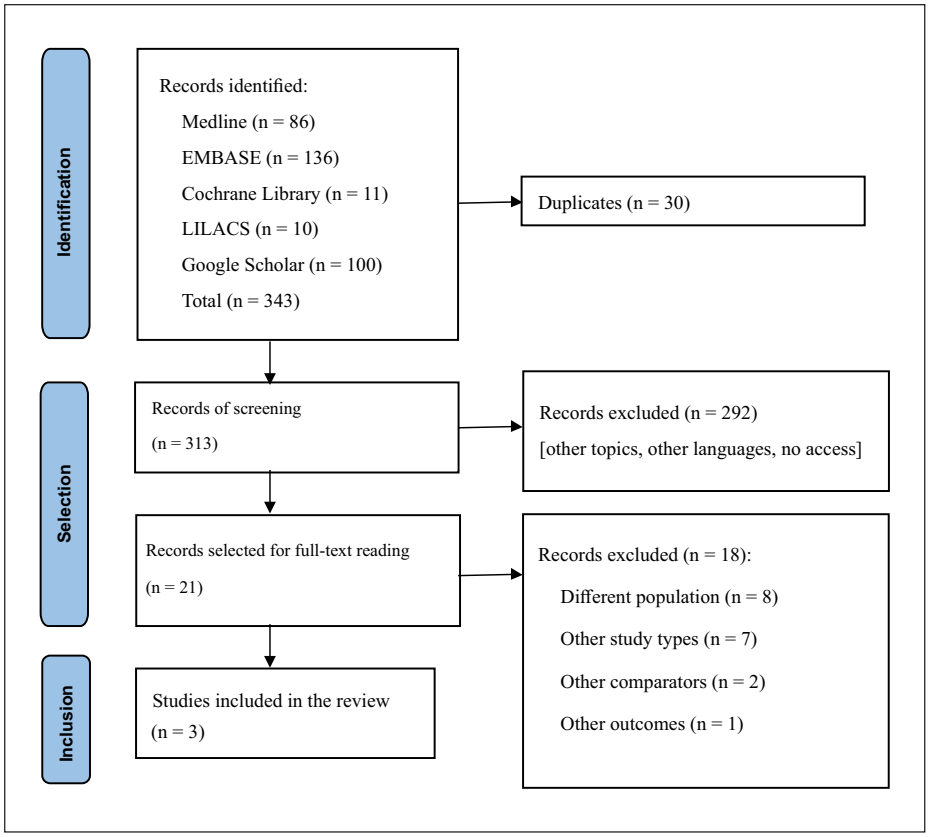
A total of 343 potentially relevant records were retrieved from the databases. After duplicate removal and title/abstract screening, 292 records were excluded. The full texts of the remaining 21 abstracts were assessed. Of these, only 3 systematic reviews with meta-analysis were included in this review.[18-20] The bibliographic search flowchart is presented in Figure 1.

Main characteristics of the included studies

The characteristics of the included systematic reviews are summarized in Table 1. All reviews performed indirect meta-analyses. All studies were published in English between 2012 and 2024 and were conducted through international collaborations. All reviews included primary studies that exclusively evaluated adult patients (≥18 years old) with RRMS, with the number of individuals ranging from 2,244 to 36,541.

Fingolimod at a dose of 0.5 mg/day was the most common intervention strategy in the reviews (n = 2).[18,19] One review did not describe information about the fingolimod dosing regimen.[20] The reviews included studies with different comparators, such as glatiramer acetate, interferon β-a, interferon β-1b, teriflunomide, and dimethyl fumarate. Only one review included studies that used dimethyl fumarate as the sole comparator.[19]

Figure 1. Flowchart of the selection of studies included in the systematic review



Source: Prepared by the authors.

Table 1. Characteristics of the systematic reviews with meta-analyses included

Author, year	Literature search (period)	Type of meta-analysis	Country	Target population (n)	Intervention (dosing regimen)	Comparator (dosing regimen)	Outcomes (time of measurement)	Funding source
Roskell et al., 2012[18]	April 2010	Indirect	United Kingdom and USA	Adult patients with RRMS (6,717)	Fingolimod (0.5 mg/day)	Beta interferons (22 mcg, 44 mcg, 30 mcg, 250 mcg); Glatiramer acetate (20 mg/day)	ARR (NR)	Novartis Pharmaceuticals US
Hutchinson et al., 2014[19]	January 1, 1960 to November 15, 2012	Indirect	Ireland, USA, and the Czech Republic	Adult patients aged 18–65 years with RRMS (2,244)	Fingolimod (0.5 mg/day)	Dimethyl fumarate (240 mg twice daily)	ARR (24 months) and disability progression (24 months)	Biogen Idec
Gonzalez-Lorenzo et al., 2024[20]	September 21, 2021, updated on August 8, 2022 Indirect	Indirect	NR	Adult patients ≥18 years with RRMS (36,541)	Fingolimode (NR)	Glatiramer acetate (NR); interferon beta-1a (NR); interferon beta-1b (NR); teriflunomide (NR); dimethyl fumarate (NR)	ARR (24 months), relapses (24 months), disability progression (24 months), and serious adverse events (NR)	"Ricerca Corrente" program of the Italian Ministry of Health.

Legend: AE (Adverse Event), RRMS (Relapsing–Remitting Multiple Sclerosis), USA (United States), NR (not reported), ARR (Annualized Relapse Rate).
Source: Prepared by the authors.

All reviews assessed efficacy outcomes, whereas only one evaluated the safety profile of fingolimod compared with other agents. One review did not report the timing of outcome measurements.[18]

All studies reported a source of research support; two received funding from the pharmaceutical industry[18,19] and one from the government.[20]

Efficacy results

All systematic reviews included in this overview assessed the Annualized Relapse Rate (ARR). Gonzalez-Lorenzo et al. (2024)[20] observed that fingolimod significantly reduced relapses at 12 months compared with glatiramer acetate (RR: 0.74 [95%: CI: 0.61–0.90]), interferon β-1a (RR: 0.63 [95%: CI: 0.53–0.75]), interferon β-1b (RR: 0.58 [95%: CI: 0.36–0.93]), and teriflunomide (RR: 0.72 [95%: CI: 0.56–0.93]). Roskell et al. (2012)[18] also reported a significant reduction in relapses at 12 months between fingolimod 0.5 mg/day and different doses of interferon β-1a, such as 22 mcg (RR: 0.60 [95%: CI: 0.48–0.76]), 30 mcg (RR: 0.52 [95%: CI: 0.43–0.63]), and 44 mcg (RR: 0.65 [95%: CI: 0.53–0.79]), as well as glatiramer acetate (RR: 0.70 [95%: CI: 0.56–0.86]). The study by Hutchinson et al. (2014)[19] did not show meaningful differences in relapse reduction at 12 months between fingolimod 0.5 mg/day and dimethyl fumarate 240 mg twice daily (RR: 1.19 [95%: CI: 0.97–1.46]).

Regarding disability worsening at 24 months, Gonzalez-Lorenzo et al. (2024)[20] considered the results similar between fingolimod and the other comparators: glatiramer acetate (RR: 0.93 [95%: CI: 0.70–1.22]), interferon beta-1a (RR: 0.74 [95%: CI: 0.55–1.00]), interferon beta-1b (RR: 0.89 [95%: CI: 0.67–1.19]), teriflunomide (RR: 0.90 [95%: CI: 0.67–1.20]), and dimethyl fumarate (RR: 1.05 [95%: CI: 0.81–1.36]). These findings were also similar in Hutchinson et al. (2014),[19] which compared fingolimod 0.5 mg/day with dimethyl fumarate 240 mg twice daily (RR: 0.74 [95%: CI: 0.49–1.12]).

Gonzalez-Lorenzo et al. (2024)[20] found that fingolimod significantly reduced relapses at 24 months compared with glatiramer acetate (RR: 0.64 [95%: CI: 0.55–0.75]), interferon β-1a (RR: 0.64 [95%: CI: 0.54–0.75]), interferon β-1b (RR: 0.64 [95%: CI: 0.56–0.73]), and teriflunomide (RR: 0.65 [95%: CI: 0.55–0.78]), except when compared with dimethyl fumarate (RR: 0.87 [95%: CI: 0.74–1.02]). The efficacy results are presented in Table 2.

Safety results

Gonzalez-Lorenzo et al. (2024)[20] did not identify significant differences between fingolimod and glatiramer acetate (OR: 0.91 [95%: CI: 0.65–1.29]), interferon β-1b (OR: 0.93 [95%: CI: 0.55–1.58]), teriflunomide (OR: 0.74 [95%: CI: 0.47–1.16]), or dimethyl fumarate (OR: 0.82 [95%: CI: 0.52–1.30]) regarding serious adverse events. The study indicated a significant reduction in the number of serious adverse events in patients treated with fingolimod compared with those who received interferon β-1a (OR: 0.71 [95%: CI: 0.51–0.99]). The safety results are presented in Table 2.

Table 2. Results of the outcomes assessed in systematic reviews with meta-analyses of fingolimod compared with other drug therapies.

Author, year	Comparator	Statistical model of the meta-analysis	Pooled effect [95% CI]	Publication bias	Quality of evidence*
ARR (12 months)					
Roskell et al., 2012	Interferon β-1a (22mcg, 3x week- SC)	Random-effects	RR: 0,60 [IC 95%: 0,48-0,76]	NR	Very low
Roskell et al., 2012	Interferon β-1a (30mcg, 1x week- IM)	Random-effects	RR: 0,52 [IC 95%: 0,43-0,63]	NR	Very low
Roskell et al., 2012	Interferon β-1a (44mcg, 3x week- SC)	Random-effects	RR: 0,65 [IC 95%: 0,53-0,79]	NR	Very low
Roskell et al., 2012	Glatiramer acetate (20 mg/day)	Random-effects	RR: 0,70 [IC 95%: 0,56-0,86]	NR	Very low
Hutchinson et al., (2014)	Dimethyl fumarate (240 mg 2x/daily)	Random-effects	RR: 1,19 [(IC 95%: 0.97 - 1.46]	NR	Very low
Gonzalez-Lorenzo et al., 2024	Interferon β-1a	Random-effects	RR: 0,63 [IC 95%: 0,53-0,75]	NA	Low
Gonzalez-Lorenzo et al., 2024	Interferon β-1b	Random-effects	RR: 0,58 [IC 95%: 0,36-0,93]	NA	Moderate
Gonzalez-Lorenzo et al., 2024	Glatiramer acetate	Random-effects	RR: 0,74 [IC 95%: 0,61-0,90]	NA	Moderate
Gonzalez-Lorenzo et al., 2024	Teriflunomide	Random-effects	RR: 0,72 [IC 95%: 0,56-0,93]	NA	Moderate
Gonzalez-Lorenzo et al., 2024	Dimethyl fumarate	Random-effects	RR: 0,87 [IC 95%: 0,74-1,02]	NA	Low
Disability progression (24 months)					
Hutchinson et al., (2014)	Dimethyl fumarate (240 mg 2x/daily)	Random-effects	RR: 1,05 [IC 95%: 0,81-1,36]	NA	Low
Gonzalez-Lorenzo et al., 2024	Interferon β-1a	Random-effects	RR: 0,74 [IC 95%: 0,55-1,00]	NA	Low
Gonzalez-Lorenzo et al., 2024	Interferon β-1b	Random-effects	RR: 0,89 [IC 95%: 0,67-1,19]	NA	Low
Gonzalez-Lorenzo et al., 2024	Glatiramer acetate	Random-effects	RR: 0,93 [IC 95%: 0,70-1,22]	NA	Low
Gonzalez-Lorenzo et al., 2024	Teriflunomide	Random-effects	RR: 0,90 [IC 95%: 0,67-1,20]	NA	Low
Gonzalez-Lorenzo et al., 2024	Dimethyl fumarate	Random-effects	RR: 1,05 [IC 95%: 0,81-1,36]	NA	Low
Relapses (24 months)					
Gonzalez-Lorenzo et al., 2024	Interferon β-1a	Random-effects	RR: 0,64 [IC 95%: 0,54-0,75]	NA	Low
Gonzalez-Lorenzo et al., 2024	Interferon β-1b	Random-effects	RR: 0,64 [(IC 95%: 0,56-0,73)	NA	Moderate
Gonzalez-Lorenzo et al., 2024	Glatiramer acetate	Random-effects	RR: 0,64 [IC 95%: 0,55-0,75]	NA	Moderate
Gonzalez-Lorenzo et al., 2024	Teriflunomide	Random-effects	RR: 0,65 [IC 95%: 0,55 a 0,78)]	NA	Moderate
Gonzalez-Lorenzo et al., 2024	Dimethyl fumarate	Random-effects	RR: 0,87 [IC 95%: 0,74-1,02)]	NA	Low
Serious AEs					
Gonzalez-Lorenzo et al., 2024	Interferon β-1a	Random-effects	OR: 0,71 [IC 95%: 0,51-0,99]	NA	Low
Gonzalez-Lorenzo et al., 2024	Interferon β-1b	Random-effects	OR: 0,93 [IC 95%: 0,55-1,58]	NA	Low
Gonzalez-Lorenzo et al., 2024	Glatiramer acetate	Random-effects	OR: 0,91 [IC 95%: 0,65-1,29]	NA	Low
Gonzalez-Lorenzo et al., 2024	Teriflunomide	Random-effects	OR: 0,74 [IC 95%: 0,47-1,16]	NA	Low
Gonzalez-Lorenzo et al., 2024	Dimethyl fumarate	Random-effects	OR: 0,82 [IC 95%:: 0,52-1,30]	NA	Low

**The Grading of Recommendations Assessment, Development, and Evaluation* (GRADE)
Legend: AE (adverse events), NA (not available), NR (not reported), OR (odds ratio), RR (relative risk).
Source: Prepared by the authors.

Methodological quality

All studies had an *a priori* design, indicating the existence of a protocol or ethical approval. Two studies performed study selection and data extraction in duplicate, resolving disagreements through discussion. All studies conducted a comprehensive literature review, including at least two electronic databases, search-strategy terms, and a supplementary search. All reviews included RCTs and described participants' characteristics and the interventions; only one study provided a list of studies excluded after full-text assessment.[20] The quality of the studies included in all systematic reviews was assessed and documented using validated tools. All reviews explained the risk of bias of individual studies when discussing review results or provided a satisfactory explanation for any observed heterogeneity. Only one review assessed publication bias for the main outcomes, but did not present the data in the manuscript.[20] Only one study explicitly disclosed potential conflicts of interest, and all of them provided information on the funding source for the systematic review.[20]

This revision found that two systematic reviews had a critically low overall quality rating, whereas one had a high overall quality rating. The methodological quality of the reviews is presented in Table 3.

Quality of evidence

In the comparison between fingolimod and interferon β-1a, the certainty of evidence was rated as low for the outcomes annualized relapse rate without dosing specification, relapses at 24 months, disability progression at 24 months, and serious adverse events. For ARR outcomes with specific interferon β-1a doses—22 mcg (three times per week, subcutaneous), 30 mcg (once per week, intramuscular), and 44 mcg (three times per week, subcutaneous)—the certainty of evidence was rated as very low.

In the comparison between fingolimod and interferon β-1b, glatiramer acetate, and teriflunomide, the certainty of evidence was rated as moderate for the outcomes annualized relapse rate and relapses at 24 months. However, it was considered very low for disability progression at 24 months and serious adverse events.

When comparing fingolimod and dimethyl fumarate, the certainty of evidence was rated as very low for all assessed outcomes: annualized relapse rate, relapses at 24 months, disability progression at 24 months, and serious adverse events. The quality of evidence of the reviews is presented in Table 2.

Table 3. Results of the quality assessment of the systematic reviews with meta-analyses using the AMSTAR-2 tool

	AMSTAR-2 item																Overall quality
	1	2*	3	4*	5	6	7*	8	9*	10	11*	12	13*	14	15*	16	
Roskell et al., 2012	Y	PY	Y	Y	Y	N	N	Y	PY	N	Y	Y	Y	Y	N	N	Critically low
Hutchinson et al., 2014	Y	PY	Y	PY	Y	Y	N	Y	PY	N	Y	Y	Y	Y	N	N	Critically low
Gonzalez-Lorenzo et al., 2024	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Free translation: 1. The research questions and inclusion criteria for the review included the components of PICO; 2. the report contained an explicit statement that the methods were established prior to conducting the review and justified any significant deviations from the protocol; 3. the review authors justified the selection of the study designs included; 4. the review authors used a comprehensive literature search strategy; 5. the review authors performed study selection in duplicate; 6. the review authors performed data extraction in duplicate; 7. the review authors provided a list of excluded studies and justified the exclusions; 8. the review authors described the included studies in adequate detail; 9. the review authors used a satisfactory technique for assessing the risk of bias in the individual studies included in the review; 10. the review authors reported the sources of funding for the studies included in the review; 11. if a meta-analysis was performed, the review authors used appropriate methods for statistically combining results; 12. if a meta-analysis was performed, the review authors assessed the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis; 13. the review authors accounted for risk of bias in individual studies when interpreting/discussing the results of the review; 14. the review authors provided a satisfactory explanation for and discussed any heterogeneity observed in the review results; 15. if a quantitative synthesis was performed, the review authors carried out an adequate investigation of publication bias and discussed its likely impact on the results of the review; and 16. the review authors reported any potential sources of conflict of interest, including any funding they received to conduct the review.

Interpretation: critically low (more than one critical failure), low (one critical failure), moderate (more than one non-critical failure), and high (none or one non-critical failure). * Critical items.

Legend: N (no), PY (partially yes), Y (yes).
Source: Prepared by the authors

Discussion

No other review articles were identified that proposed a review of systematic reviews with meta-analyses of RCTs evaluating fingolimod compared to other drug therapies for RRMS. This is the first revision of systematic reviews with RCT meta-analyses evaluating fingolimod compared with other drug therapies for RRMS. Fingolimod showed superior efficacy and safety relative to most comparators for relapses at 12 and 24 months. However, only three systematic reviews have been published on the topic up to the date of this publication. In addition, the quality of evidence for the main efficacy and safety outcomes was generally rated from very low to moderate, highlighting the need for further research to increase confidence in the effect estimates.

Fingolimod may be an alternative therapy option for adult patients diagnosed with low- or moderately active RRMS who are treatment-naïve. The National Institute for Health and Care Excellence (NICE),[21] the Canadian Agency for Drugs and Technologies in Health (CADTH),[22] and New Zealand's Pharmaceutical Management Agency (PHARMAC)23 have recommended the use of fingolimod for treating RRMS patients under well-established and differentiated criteria. However, a systematic review on cost-effectiveness and cost-utility of RRMS disease-modifying drugs reported that fingolimod was not considered cost-effective, in addition to being associated with lower with a smaller gain in quality-adjusted life years (QALYs) compared with other alternatives, such as dimethyl fumarate.[24] This review emphasizes that cost-effectiveness results often have country-specific characteristics, since treatment and healthcare cost data may differ substantially across countries and QALYs may vary among contexts. Thus, it is important to consider the budget impact on the health system for financing treatment, as well as the existence of clearly defined clinical criteria for its use.

All systematic reviews included in this revision conducted indirect (network) meta-analyses, allowing simultaneous comparison of the efficacy or safety of multiple interventions.[25] Nevertheless, concerns regarding network meta-analysis should be considered, such as heterogeneity among included studies, violation of the transitivity principle, and potentially biased indirect estimates, which may reduce the robustness and reliability of results.[26] Therefore, studies that assess direct comparisons for the main efficacy and safety outcomes are recommended.

Two systematic reviews included in this revision were rated as critically low and one as high methodological quality according to the AMSTAR-2 critical appraisal criteria. It is important to note that the two reviews rated as critically low were published (in 2012 and 2014) before the AMSTAR-2 tool was updated. In contrast, the review rated as high quality was published in 2024 and followed Cochrane Collaboration recommendations, widely recognized as a reference for methodological excellence.[28]

Among the aspects that need improvement in the reviews rated as critically low quality, the absence of a list of excluded studies after full-text reading was observed (item 7 from the AMSTAR-2 tool). This information is essential to ensure transparency and reproducibility of the review process,[28] and could easily be included as electronic supplementary material. In addition, neither of the two reported the funding sources of the included primary studies (item 10 from the AMSTAR-2 tool) nor declared potential conflicts of interest or funding for conducting the review (item 16 from the AMSTAR-2 tool). This raises concerns about undeclared conflicts of interest that may compromise the impartiality of results, since studies funded by the pharmaceutical industry tend to report results and conclusions more favorable to efficacy than those not funded or funded by other sources.[29,30] Finally, publication bias was not reported and/or assessed, which may distort the available body of evidence.[31]

This revision showed that there is room to improve future studies on the use of fingolimod in RRMS patients. Long-term RCTs are essential to provide evidence on the efficacy and safety of these treatments beyond the currently studied 12 to 24 months. The inclusion of humanistic outcomes, such as quality of life, may contribute to a more comprehensive view of clinical benefits associated with therapy. Stratified analyses in specific patient subgroups, such as those with different levels of disease

severity, would also be valuable to identify who may benefit most from each treatment. Finally, more systematic reviews on the topic are needed, with greater methodological rigor in conduct and reporting, in order to strengthen the evidence base and support clinical decision-making.

This revision some limitations. Some studies may not have been identified because they were not indexed in the searched databases or because they were published on the websites of Health Technology Assessment institutions or agencies. In addition, the exclusion criteria applied to systematic reviews without meta-analysis and to other clinical outcomes may have led to the omission of reviews on this topic. Lastly, it was not possible to perform a quantitative analysis due to heterogeneity among the populations, interventions, and outcomes of the included reviews.

Conclusion

The findings of this revision show fingolimod to be superior to glatiramer acetate, interferons β-1a and β-1b, and teriflunomide in reducing relapse rates at 12 and 24 months, but not in RRMS disability progression. No significant differences in efficacy outcomes were observed between fingolimod and dimethyl fumarate. Regarding serious AEs, fingolimod showed a safety profile similar to the other compared therapies, except relative to interferon β-1a, which was associated with a higher frequency of these events.

Despite the favorable results, they should be interpreted with caution, since efficacy data come from short-term clinical trials and may not reflect effectiveness over the course of RRMS.

Authors' contributions:
All authors had full access to all the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. CMMV, GBGM, and TML: study planning. TFGSB and TML: collected the study data. TFGSB and TML: analyzed and interpreted the data. TML: wrote the first draft of the manuscript. All authors reviewed the manuscript and approved its publication.

Conflicts of interest
The authors declare that there are no conflicts of interest.

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Data availability statement
The underlying contents of the research text are contained in the manuscript.

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Appendix 1. Search strategies used in the databases searched.

PubMed:
#1 "Multiple Sclerosis"[Mesh] OR "Multiple Sclerosis" OR MS OR "Disseminated Sclerosis" OR "Multiple Sclerosis, Relapsing-Remitting"[Mesh] OR "Relapsing-Remitting Multiple Sclerosis" OR "Relapsing Remitting Multiple Sclerosis" OR "Remitting-Relapsing Multiple Sclerosis" OR "Remitting Relapsing Multiple Sclerosis" OR "Acute Relapsing Multiple Sclerosis" OR "insular sclerosis" OR "sclerosis multiplex" OR "RR-multiple sclerosis" OR RRMS

#2 "Fingolimod Hydrochloride"[Mesh] OR Fingolimod OR FTY-720 OR FTY720 OR "FTY 720" OR Gilenya OR Gilenia OR imusera OR lognif

#3 ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR (((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]

#4 #1 AND #2 AND #3

EMBASE
#1 'multiple sclerosis'/exp OR 'chariot disease' OR 'disseminated sclerosis' OR 'insular sclerosis' OR MS OR 'sclerosis multiplex' OR 'sclerosis, disseminated' OR 'sclerosis, insular' OR 'sclerosis, multiple' OR 'multiple sclerosis' OR 'relapsing remitting multiple sclerosis'/exp OR 'multiple sclerosis, relapsing-remitting' OR 'RR multiple sclerosis' OR 'relapsing-remittent MS' OR 'relapsing-remittent multiple sclerosis' OR 'relapsing-remitting MS' OR 'relapsing-remitting multiple sclerosis' OR 'remittent-relapsing MS' OR 'remittent-relapsing multiple sclerosis' OR 'remitting-relapsing MS' OR 'remitting-relapsing multiple sclerosis' OR 'RR-multiple sclerosis' OR RRMS OR 'relapsing remitting multiple sclerosis'

#2 'fingolimod'/exp OR '2 (4 octylphenethyl) 2 aminopropane 1, 3 diol' OR '2 amino 2 (4 octylphenethyl) propane 1, 3 diol' OR '2 amino 2 [2 (4 octylphenyl) ethyl] 1, 3 propanediol' OR '2 amino 2 [2 (4 octylphenyl) ethyl] 1, 3 propanediol hydrochloride' OR '2 amino 2 [2 (4 octylphenyl) ethyl] propane 1, 3 diol' OR '2 amino 2 hydroxymethyl 4 (4 (octyl) phenyl) butanol' OR 'bonaxon' OR 'chantico' OR 'efigalo' OR 'fenoxa' OR 'fimodigo' OR 'fingod' OR 'fingolimod hydrochloride' OR 'fingolimod lauryl sulfate' OR 'fty 720' OR 'fty720' OR 'gilenia' OR 'gilenya' OR 'golpimec' OR 'imusera' OR 'inzolfi' OR 'lognif' OR 'ro 7079904' OR 'ro7079904' OR 'tascenso' OR 'tascenso odt' OR 'tdi 132' OR 'tdi132' OR 'fingolimod'

#3 'systematic review'/de OR 'systematic review (topic)'/de OR (('comprehensive':ti,ab,kw OR 'mapping':ti,ab,kw OR 'methodology':ti,ab,kw OR 'scoping':ti,ab,kw OR 'systematic':ti,ab,kw) AND ('search':ti,ab,kw OR 'searched':ti,ab,kw OR 'searches':ti,ab,kw OR 'studies':ti,ab,kw) AND ('cinahl':ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'psycinfo':ti,ab,kw OR 'pubmed':ti,ab,kw

OR 'medline':ti,ab,kw OR 'scopus':ti,ab,kw OR 'web of science':ti,ab,kw OR 'bibliographic review':ti,ab,kw OR 'bibliographic reviews':ti,ab,kw OR 'literature review':ti,ab,kw OR 'literature reviews':ti,ab,kw OR 'literature search':ti,ab,kw OR 'literature searches':ti,ab,kw OR 'qualitative review':ti,ab,kw OR 'qualitative reviews':ti,ab,kw OR 'quantitative review':ti,ab,kw OR 'quantitative reviews':ti,ab,kw)) OR 'comprehensive review':ti,ab,kw OR 'comprehensive reviews':ti,ab,kw OR 'comprehensive search':ti,ab,kw OR 'comprehensive searches':ti,ab,kw OR 'critical review':ti,ab,kw OR 'critical reviews':ti,ab,kw OR (('electronic database':ti,ab,kw OR 'electronic databases':ti,ab,kw OR (databases NEAR/3 searched)) AND (eligibility:ti,ab,kw OR excluded:ti,ab,kw OR exclusion:ti,ab,kw OR included:ti,ab,kw OR inclusion:ti,ab,kw)) OR 'evidence assessment':ti,ab,kw OR 'evidence review':ti,ab,kw OR 'exploratory review':ti,ab,kw OR 'framework synthesis':ti,ab,kw OR 'mapping review':ti,ab,kw OR 'meta-review':ti,ab,kw OR 'meta-synthesis':ti,ab,kw OR 'methodology review':ti,ab,kw OR 'mixed methods review':ti,ab,kw OR 'mixed methods synthesis':ti,ab,kw OR (overview NEAR/4 reviews) OR 'prisma':ab OR ('preferred':ti,ab,kw AND reporting:ti,ab,kw) OR 'prognostic review':ti,ab,kw OR 'psychometric review':ti,ab,kw OR 'rapid evidence assessment':ti,ab,kw OR 'rapid literature review':ti,ab,kw OR 'rapid literature search':ti,ab,kw OR 'rapid realist':ti,ab,kw OR 'rapid review':ti,ab,kw OR 'rapid reviews':ti,ab,kw OR 'realist review':ti,ab,kw OR 'review of reviews':ti,ab,kw OR 'scoping review':ti,ab,kw OR 'scoping reviews':ti,ab,kw OR 'scoping study':ti,ab,kw OR 'systematic evidence map':ti,ab,kw OR 'systematic evidence mapping':ti,ab,kw OR 'systematic literature':ti,ab,kw OR 'systematic medline':ti,ab,kw OR 'systematic pubmed':ti,ab,kw OR 'systematic review':ti,ab,kw OR 'systematic reviews':ti,ab,kw OR 'systematic search':ti,ab,kw OR 'systematic searches':ti,ab,kw OR 'systematical literature review':ti,ab,kw OR 'systematical review':ti,ab,kw OR 'systematical reviews':ti,ab,kw OR 'systematically identified':ti,ab,kw OR 'systematically review':ti,ab,kw OR 'systematically reviewed':ti,ab,kw OR 'umbrella review':ti,ab,kw OR 'umbrella reviews':ti,ab,kw OR '13616137':is OR 'cochrane database of systematic reviews'/jt OR 'meta analysis'/de OR 'network meta-analysis'/de OR 'meta analysis (topic)'/de OR 'meta analyses':ti,ab,kw OR 'meta analysis':ti,ab,kw OR 'meta analytic':ti,ab,kw OR 'meta analytical':ti,ab,kw OR 'meta analytics':ti,ab,kw OR 'meta analyze':ti,ab,kw OR 'meta analyzed':ti,ab,kw OR 'meta regression':ti,ab,kw OR 'metaanalyses':ti,ab,kw OR 'metaanalysis':ti,ab,kw OR 'metaanalytic':ti,ab,kw OR 'metaanalyze':ti,ab,kw OR 'metaanalyzed':ti,ab,kw OR 'metaregression':ti,ab,kw OR 'network meta analyses':ti,ab,kw OR 'network meta analysis':ti,ab,kw OR 'indirect treatment comparison':ti,ab,kw OR (('indirect':ti,ab,kw OR 'indirectly':ti,ab,kw OR 'mixed':ti,ab,kw) AND ('treatment':ti,ab,kw OR 'treatments':ti,ab,kw OR 'intervention':ti,ab,kw OR 'interventions':ti,ab,kw OR 'therapeutic':ti,ab,kw OR 'therapeutics':ti,ab,kw) AND ('comparison':ti,ab,kw OR 'comparisons':ti,ab,kw) AND ('bayesian':ti,ab,kw AND 'statistical':ti,ab,kw OR 'bayesian statistics':ti,ab,kw)) OR 'adaptive clinical trial (topic)'/de OR 'adaptive clinical trial'/de OR 'clinical trial (topic)'/de OR 'clinical trial'/de OR 'controlled clinical trial (topic)'/de OR 'controlled clinical trial'/de OR 'double blind procedure'/de OR 'early termination of clinical trial'/de OR 'equivalence trial (topic)'/de OR 'equivalence trial'/de OR 'intention to treat analysis'/de OR 'multicenter study (topic)'/de OR 'multicenter study'/de OR 'non-inferiority trial'/de OR 'phase 1 clinical trial (topic)'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial (topic)'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial (topic)'/de OR 'phase 4 clinical trial'/de OR 'pragmatic trial'/de OR 'randomized controlled trial (topic)'/de OR 'randomized controlled trial'/de OR 'superiority trial'/de OR 'multicenter study':ti,ab,kw OR 'phase i':ti,ab,kw OR 'phase ii':ti,ab,kw OR 'phase iii':ti,ab,kw OR 'phase iv':ti,ab,kw OR 'phase 1':ti,ab,kw OR 'phase 2':ti,ab,kw OR 'phase 3':ti,ab,kw OR 'phase 4':ti,ab,kw OR ((randomised OR randomized) NEAR/7 trial*) OR (controlled NEAR/3 trial*) OR (clinical NEAR/2 trial*) OR ((single:ti,ab,kw OR doubl*:ti,ab,kw OR tripl*:ti,ab,kw OR treb*:ti,ab,kw) AND (blind*:ti,ab,kw OR mask*:ti,ab,kw)) OR '4 arm':ti,ab,kw OR 'four arm':ti,ab,kw

#4 [embase]/lim NOT ([embase]/lim AND [medline]/lim)

#5 #1 AND #2 AND #3 AND #4
LILACS
#1 MH:"Multiple Sclerosis" OR "Multiple Sclerosis" OR MS OR "Disseminated Sclerosis" OR MH:"Multiple Sclerosis, Relapsing-Remitting" OR "Relapsing-Remitting Multiple Sclerosis" OR "Relapsing Remitting Multiple Sclerosis" OR "Remitting-Relapsing Multiple Sclerosis" OR "Remitting Relapsing Multiple Sclerosis" OR "Acute Relapsing Multiple Sclerosis" OR "insular sclerosis" OR "sclerosis multiplex" OR "RR-multiple sclerosis" OR RRMS

#2 MH:"Fingolimod Hydrochloride" OR Fingolimod OR FTY-720 OR FTY720 OR "FTY 720" OR Gilenya OR Gilenia OR imusera OR lognif

Cochrane Library
#1 MeSH descriptor: [Multiple Sclerosis] explode all trees
#2 MeSH descriptor: [Multiple Sclerosis, Relapsing-Remitting] explode all trees
#3 ("multiple sclerosis" OR MS OR "sclerosis disseminated" OR "disseminated sclerosis" OR "acute fulminating multiple sclerosis" OR "relapsing remitting multiple sclerosis" OR "remitting relapsing multiple sclerosis" OR "acute relapsing multiple sclerosis"):ti,ab,kw
#4 #1 OR #2 OR #3
#5 MeSH descriptor: [Fingolimod Hydrochloride] explode all trees
#6 (fingolimod OR "fingolimod hydrochloride" OR FTY-720 OR FTY720 OR "FTY 720" OR Gilenya OR Gilenia OR imusera OR lognif):ti,ab,kw
#7 #5 OR #6
#8 #4 AND #7
#9 Filter Cochrane Review AND Cochrane Protocols

Google Acadêmico
("Multiple Sclerosis" OR MS OR "Disseminated Sclerosis" OR "insular sclerosis" OR "sclerosis multiplex" OR "RR-multiple sclerosis" OR RRMS) AND (Fingolimod OR Gilenya OR Gilenia) AND (review)