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Meta-Analysis

Comparative Therapeutic Strategies for Secondary Progressive Multiple Sclerosis: A Systematic Review and Network Meta-Analysis

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Clinical Question Box

What is the comparative effectiveness of disease-modifying therapies in adults with secondary progressive multiple sclerosis?

Moderate-certainty evidence suggests that siponimod may offer a favorable balance of efficacy and safety for delaying disability progression. Tolebrutinib appears promising but requires further investigation due to safety concerns. Interferon beta-1b remains a reasonable option, offering consistent benefits. Future head-to-head trials are needed to optimize treatment strategies for secondary progressive multiple sclerosis.

Abstract

Introduction: Secondary progressive multiple sclerosis (SPMS) represents a disabling stage of multiple sclerosis with limited treatment options. The evidence regarding the effectiveness of disease-modifying therapies (DMTs) in SPMS remains uncertain. This study evaluated the comparative efficacy and safety of DMTs in SPMS using a network meta-analysis (NMA). **Methods:** A systematic search of PubMed, Embase, Web of Science, and Cochrane databases was conducted from January 2000 to May 2025 to identify randomized controlled trials (RCTs) involving adults with SPMS. The outcomes of interest were confirmed disability progression (CDP) and serious adverse events (SAEs). A frequentist random-effects NMA was performed to estimate odds ratios (ORs) and rank treatments using surface under the cumulative ranking (SUCRA) values. **Results:** Seven RCTs involving 5,872 patients with SPMS were included in the final analysis. Approximately 60% of participants were women, with a mean age ranging from 39.9 to 48.9 years and a baseline Expanded Disability Status Scale score between 3.0 and 6.5. Tolebrutinib (OR 0.66, 95% confidence interval [CI] 0.50–0.87; SUCRA 0.713) and siponimod (OR 0.72, 95% CI 0.57–0.92; SUCRA 0.606) significantly reduced 6-month CDP compared with placebo. At 3 months, interferon beta-1b (IFN-β-1b; OR 0.64, 95% CI 0.43–0.97;

SUCRA 0.663), tolebrutinib (OR 0.73, 95% CI 0.56–0.96; SUCRA 0.554), and siponimod (OR 0.76, 95% CI 0.61–0.96; SUCRA 0.497) showed significant benefits. In terms of safety, tolebrutinib was associated with a higher risk of SAEs (OR 1.53, 95% CI 1.04–2.25), whereas the other agents had safety profiles comparable to placebo. **Conclusion:** This NMA found that tolebrutinib, IFN-β-1b, and siponimod delay disability progression in SPMS, with IFN-β-1b and siponimod remaining the most practical options. The conclusions should be interpreted cautiously given the risk of bias, moderate evidence certainty, limited safety data, and clinical heterogeneity.

Keywords: Secondary progressive multiple sclerosis, tolebrutinib, interferon beta-1b, siponimod, network meta-analysis

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated demyelinating disease of the central nervous system, affecting nearly 1 million people in the United States and approximately 2.9 million people globally.[1] Among its clinical phenotypes, secondary progressive multiple sclerosis (SPMS) represents a particularly disabling stage that typically follows an initial relapsing-remitting phase (RRMS).[2] SPMS is characterized by gradual and irreversible neurological decline, with or without relapses, marking a shift from predominantly inflammatory to neurodegenerative pathology. Common symptoms include gait disturbances, spasticity, progressive motor impairment, and cognitive decline.[3] The transition from RRMS to SPMS is often slow and difficult to diagnose early. It usually requires retrospective confirmation based on sustained progression. This diagnostic uncertainty hinders timely intervention, despite evidence suggesting that early detection and therapeutic escalation may improve long-term outcomes.[4] Recent advances in imaging techniques, such as volumetric magnetic resonance imaging (MRI) and spinal cord analysis, along with emerging biomarkers like neurofilament light chain, are improving the early recognition of disease progression.[5,6]

SPMS imposes a significant burden on both healthcare systems and individuals. A study conducted in Spanish neurology centers reported a mean annual cost of approximately €41,500 per patient with SPMS. Indirect costs—such as lost productivity, early retirement, and reduced leisure time—accounted for the majority of this amount. Direct medical expenses averaged €11,300, while nonmedical costs, including home adaptations, totaled €8,800. In this cohort, over 90% of patients were unemployed, nearly 80% had taken early retirement, and caregivers lost more than 8 hours of work each week. Costs increased with the severity of disability, reaching €46,300 annually at an Expanded Disability Status Scale (EDSS) score of 6.5, compared to €34,850 at an EDSS score of 3 to 3.5, primarily due to higher indirect costs.[7] These findings highlight the substantial economic, personal, and social impact of SPMS on both patients and healthcare systems.

Historically, SPMS, particularly its non-active form, was considered largely untreatable due to the absence of overt inflammatory activity. However, recent approvals of disease-modifying therapies (DMTs) for active SPMS, characterized by ongoing relapses or new or enhancing MRI lesions, have transformed clinical management.[8] A major milestone was the approval of siponimod, a selective sphingosine 1-phosphate receptor modulator, following the EXPAND trial, which demonstrated significant reductions in confirmed disability progression (CDP), brain volume loss, and relapse rates.[9] More recently, other oral agents such as ozanimod and ponesimod have expanded the range of treatment options, each with distinct safety and efficacy profiles.[10] Ofatumumab, a CD20-targeting monoclonal antibody approved for PPMS and RRMS, has also shown promise in active SPMS, particularly among patients transitioning from RRMS.[11] Meanwhile, investigational therapies such as tolebrutinib, a Bruton's tyrosine kinase inhibitor, are being studied in non-active SPMS. These therapies aim to target microglial-driven neurodegeneration and intrathecal inflammation, which are key features of late-stage disease.[12]

Ocrelizumab, cladribine, ofatumumab, and ponesimod are approved for the treatment of RMS. Ocrelizumab, ofatumumab, and ponesimod received approval based on trials conducted in RMS populations, whereas cladribine was approved following results from a study focused on RRMS. Evidence supporting their efficacy in SPMS is limited and primarily derived from post hoc analyses of small subgroups, typically comprising no more than 15% of trial participants. As a result, the approval of

these DMTs for RMS, including active SPMS, is largely based on the assumption that relapse reduction observed in RRMS also applies to SPMS. However, the actual effectiveness of these therapies in SPMS remains uncertain. This systematic review and network meta-analysis (NMA) aim to comprehensively evaluate the efficacy and safety of current and emerging treatments for SPMS, using data exclusively from RCTs conducted in SPMS populations. The goal is to support evidence-based decision-making in the management of this complex phase of the disease.

Methods

Study Design and Registration

This systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. The review protocol was prospectively registered in the Open Science Framework database (osf.io/jhr6t).

Eligibility Criteria

We included studies that met the following criteria: (1) population: adult patients aged 18 years or older diagnosed with SPMS; (2) study design: randomized controlled trials (RCTs); (3) intervention/comparator: any pharmacological treatment compared with placebo or other active therapies; and (4) outcomes: reporting at least one of the following: CDP (at 3 or 6 months) or serious adverse events (SAEs). Studies were excluded if they (1) presented only subgroup analyses without new, relevant data; (2) had non-extractable or insufficient outcome data; (3) included fewer than 50% SPMS participants; (4) had a small sample size ($n < 50$) for SPMS participants; or (5) were non-randomized studies, conference abstracts, case reports, reviews, or animal studies.

Databases

We searched PubMed, Embase, Web of Science, and the Cochrane Library from January 1, 2000, to May 31, 2025. In addition, we reviewed the reference lists of relevant articles and systematic reviews. A comprehensive search strategy was developed using the following search string: "((Randomized clinical trials) OR (RCT)) AND ((Secondary progressive multiple sclerosis) OR (SPMS))".

Selection Process

Two independent reviewers (Y.Y. and G.Z.) screened all retrieved titles and abstracts. Full texts of potentially relevant articles were assessed for eligibility. Discrepancies were resolved by discussion or by a third reviewer (D.Z.). A standardized data extraction form was used by two reviewers to independently collect the following: study design, sample size, participant demographics, diagnostic criteria for SPMS, treatment arms, duration of follow-up, and reported outcomes (CDP and SAEs). Authors were contacted when essential data were missing or unclear.

Synthesis Methods

All statistical analyses were conducted using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). Pairwise meta-analyses were performed using the "meta" package, and NMAs were conducted with the "netmeta" package, both based on frequentist methods. For binary outcomes (CDP and SAEs), odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Consistency between direct and indirect evidence was assessed using node-splitting methods and global inconsistency tests. Treatment ranking was evaluated using P-scores, a frequentist analogue of the surface under the cumulative ranking (SUCRA) curve, which estimates the probability of each treatment being the most effective or safest. Between-study heterogeneity was quantified using the I^2 statistic for pairwise comparisons and τ^2 for network models. A two-sided p-value < 0.05 was considered statistically significant.

Bias Assessment and Certainty of Evidence

The risk of bias for all included RCTs was assessed using the Cochrane Risk of Bias 2.0 tool. Two reviewers conducted the assessments independently, and any disagreements were resolved through consensus. Publication bias was evaluated using funnel plots and Egger's regression test. Selective reporting was assessed by comparing published outcomes with study protocols and registry entries, when available. The certainty of evidence for the primary outcomes was assessed using the GRADE framework adapted for NMA. This evaluation considered five domains: study limitations, inconsistency, indirectness, imprecision, and publication bias.

Result

A total of 2,013 unique records were identified through systematic searches of the Cochrane, Embase, PubMed, and Web of Science databases. After initial screening, 188 full-text articles were assessed for eligibility. Of these, 181 were excluded for the following reasons: lack of an RCT design (n = 78), irrelevance to SPMS (n = 57), review articles (n = 34), unavailable data (n = 10), and small sample size (n = 2). Ultimately, seven studies met the inclusion criteria and were included in the final systematic review (Fig. S1). These seven RCTs, comprising a total of 5,872 patients with SPMS, were included in the NMA (Table 1).[13–19] The studies evaluated various DMTs, including low- and high-dose mitoxantrone (5 and 10 mg/m^2), interferon beta-1a (IFN-β-1a), interferon beta-1b (IFN-β-1b) with both standard and adjusted dosages, natalizumab, siponimod, and tolebrutinib. Placebo arms served as comparators. The mean age of participants ranged from 39.9 to 48.9 years, with women accounting for approximately 60% of each study population. Most trials enrolled patients with EDSS scores between 3.0 and 6.5, indicating moderate to severe disability. Mitoxantrone was excluded from the NMA due to its known risks of cardiotoxicity and leukemia.

Six-Month CDP Outcomes

The network graph of the included studies is presented in Fig. 1A. Two studies compared placebo with IFN-β-1b, while each of the other treatments was assessed in a single study. The direct comparisons are shown in Fig. 2A. Among the interventions, low-dose mitoxantrone demonstrated the lowest OR for 6-month CDP at 0.28 (95% CI: 0.09–0.82), followed by tolebrutinib at 0.66 (95% CI: 0.50–0.87), IFN-β-1b at 0.68 (95% CI: 0.45–1.04), siponimod at 0.72 (95% CI: 0.57–0.92), IFN-β-1a at 0.85 (95% CI: 0.56–1.29), and natalizumab at 0.87 (95% CI: 0.62–1.22).

The results of the NMA are summarized in Table 2. Both tolebrutinib and siponimod demonstrated statistically significant superiority over placebo, with ORs consistent with those observed in direct comparisons. No other treatments showed superiority over one another. The relative efficacy of each treatment, based on SUCRA values, is illustrated in Fig. S2: tolebrutinib (0.713), IFN-β-1b (0.645), siponimod (0.606), IFN-β-1a (0.403), IFN-β-1b with adjusted dosage (0.357), natalizumab (0.351), and placebo (0.176). There was no notable heterogeneity ($I^2 = 0\%$), and no evidence of publication bias was detected using Egger's test (p = 0.90).

Three-Month CDP Outcomes

The results for 3-month CDP outcomes were generally consistent with those observed at 6 months (Fig. 1A). The direct comparisons are shown in Fig. 2B. Low- and high-dose mitoxantrone demonstrated the lowest ORs for 3-month CDP, at 0.30 (95% CI: 0.10–0.90) and 0.63 (95% CI: 0.25–1.59), respectively. These were followed by IFN-β-1b at 0.64 (95% CI: 0.43–0.97), tolebrutinib at 0.73 (95% CI: 0.56–0.96), siponimod at 0.76 (95% CI: 0.61–0.96), adjusted-dose IFN-β-1b at 0.81 (95% CI: 0.40–1.64), IFN-β-1a at 0.96 (95% CI: 0.27–3.36), and natalizumab at 1.02 (95% CI: 0.47–2.23).

The results of the NMA are presented in Table 2. IFN-β-1b, tolebrutinib, and siponimod showed statistically significant superiority over placebo, with ORs consistent with those from the direct comparisons. No other agents demonstrated superiority over one another. The relative efficacy of each treatment, based on SUCRA values, is shown in Fig. S3: IFN-β-1b (0.663), tolebrutinib (0.554), siponimod (0.497), adjusted-dose IFN-β-1b (0.428), IFN-β-1a (0.356), natalizumab (0.261),

Table 1. Characteristics and background of enrolled studies

Study	Cases	Age (years)	Female (%)	Treatment	Route	Diagnosis	EDSS score	Progression criteria	FU
Hartung et al. 2002	188	39.9 (7.7)	98 (52.1%)	Mitoxantrone (L), Mitoxantrone (H), placebo	IV	Worsening RRMS or SPMS	3.0–6.0	≥1.0 EDSS point in past 18 months; stepwise or gradual progression; with/without relapses	2y
Andersen et al. 2004	364	45.8 (7.8)	224 (61.5%)	IFN-β-1a, placebo	SC	SPMS	<7.0	≥1.0 EDSS point in past 4 years (0.5 if EDSS 6.0 or 6.5); ≥1 year MS duration; prior RRMS; ≥6 months worsening; with/without relapses	3y
Panitch et al. 2004	939	46.8 (0.5)	588 (62.6%)	IFN-β-1b (a), IFN-β-1b, placebo	SC	MS	3.0–6.5	≥1.0 EDSS point in past 2 years (0.5 if EDSS 6.5); ≥2 years MS duration; ≥1 relapse followed by ≥6 months progression	3y
Kappos et al. 2001	718	41.0 (7.2)	439 (61.1%)	IFN-β-1b, placebo	SC	SPMS	3.0–6.5	≥2 relapses or ≥1.0 EDSS increase in past 2 years	3y
Kapoor et al. 2018	887	47.3 (7.6)	550 (62.0%)	Natalizumab, placebo	IV	SPMS	3.0–6.5	MSSS ≥4; progression unrelated to relapses in past year	3y
Kappos et al. 2018	1,645	48.1 (7.9)	992 (60.3%)	Siponimod, placebo	PO	SPMS	3.0–6.5	Prior RRMS; no relapse in past 3 months; EDSS progression in past 2 years	3y
Fox et al. 2025	1,131	48.9 (8.0)	696 (61.5%)	Tolebrutinib, placebo	PO	SPMS	3.0–6.5	Progression in past 12 months; no relapse in past 24 months	2y

Note: EDSS: Expanded Disability Status Scale; FU: follow-up; IFN-β-1b (a): 5 million units/m^2; IV: intravenous; mitoxantrone (L): 5 mg/m^2; mitoxantrone (H): 10 mg/m^2; MS: multiple sclerosis; MSSS: Multiple Sclerosis Severity Score; PO: oral; SC: subcutaneous; SPMS: secondary progressive multiple sclerosis; y: year.

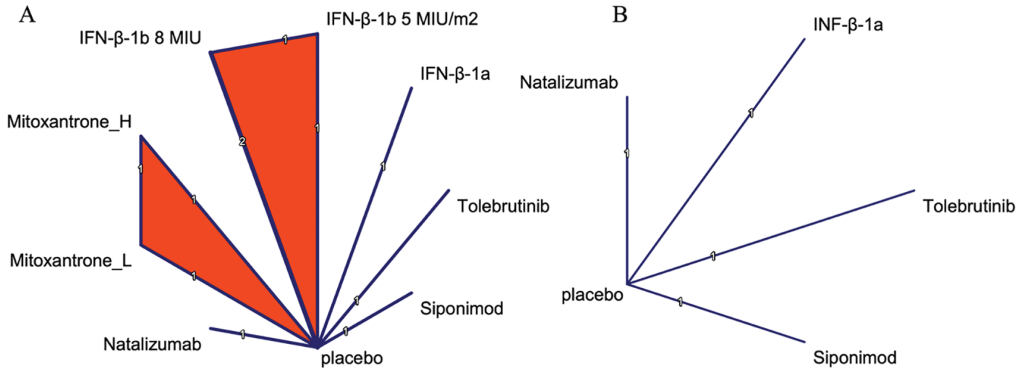

Figure 1. Network graph of enrolled studies. (A) Studies CDP at 3 and 6 months and (B) studies on serious adverse events.

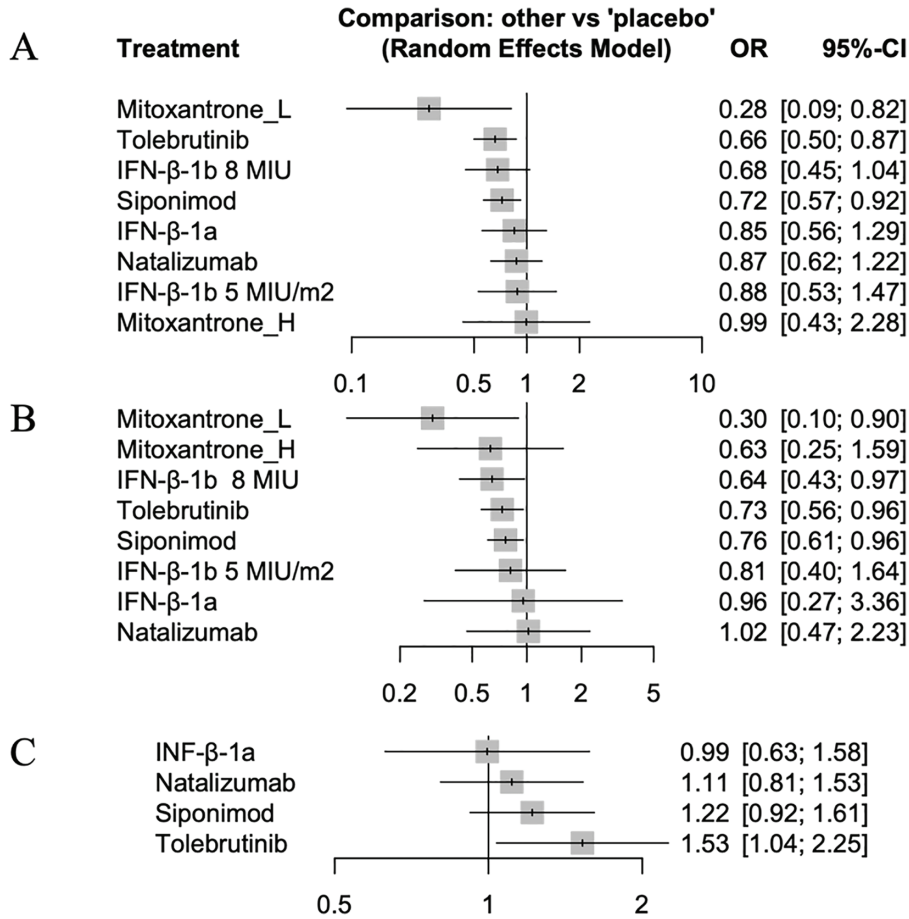

Figure 2. Direct comparison of various treatments. (A) Direct comparison of CDP at 6 months; (B) direct CDP progression at 3 months; (C) direct comparison of the risk of SAEs.

Table 2. Network meta-analysis of various treatments for confirmed disability progression at 3 and 6 months

Confirmed Disability Progression at 6 months						
Tolebrutinib						
0.97 [0.58; 1.60]	**INF-β-1b**					
0.91 [0.63; 1.32]	0.94 [0.58; 1.53]	**Siponimod**				
0.78 [0.47; 1.29]	0.80 [0.44; 1.46]	0.85 [0.52; 1.39]	**IFN-β-1a**			
0.76 [0.49; 1.17]	0.78 [0.46; 1.34]	0.83 [0.55; 1.25]	0.97 [0.57; 1.67]	**Natalizumab**		
0.75 [0.42; 1.34]	0.77 [0.45; 1.32]	0.82 [0.46; 1.44]	0.96 [0.49; 1.87]	0.99 [0.54; 1.82]	**IFN-β-1b (a)**	
0.66 [0.50; 0.87]	0.68 [0.45; 1.04]	0.72 [0.57; 0.92]	0.85 [0.56; 1.29]	0.87 [0.62; 1.22]	0.88 [0.53; 1.47]	**Placebo**
Confirmed Disability Progression at 3 months						
IFN-β-1b						
0.88 [0.54; 1.43]	**Tolebrutinib**					
0.84 [0.53; 1.35]	0.96 [0.68; 1.36]	**Siponimod**				
0.79 [0.38; 1.63]	0.90 [0.43; 1.90]	0.94 [0.45; 1.96]	**IFN-β-1b (a)**			
0.67 [0.18; 2.53]	0.77 [0.21; 2.77]	0.80 [0.22; 2.86]	0.85 [0.20; 3.58]	**IFN-β-1a**		
0.63 [0.26; 1.52]	0.72 [0.31; 1.64]	0.75 [0.33; 1.68]	0.80 [0.28; 2.27]	0.94 [0.21; 4.11]	**Natalizumab**	
0.64 [0.43; 0.97]	0.73 [0.56; 0.96]	0.76 [0.61; 0.96]	0.81 [0.40; 1.64]	0.96 [0.27; 3.36]	1.02 [0.47; 2.23]	**Placebo**

Note: IFN-β-1b (a): 5 million units/m^2 IV.

and placebo (0.196). There was no evidence of heterogeneity ($I^2 = 0\%$) and no publication bias was detected using Egger's test ($p = 0.58$).

SAEs

The network graph of the enrolled studies is shown in Fig. 1B. Only four agents reported data on SAEs. The results of the direct comparisons are presented in Fig. 2C. IFN-β-1b showed an OR of 0.99 (95% CI: 0.63–1.58), natalizumab had an OR of 1.11 (95% CI: 0.81–1.53), siponimod showed an OR of 1.22 (95% CI: 0.92–1.61), and tolebrutinib had an OR of 1.53 (95% CI: 1.04–2.25).

The results of the NMA are presented in Table 3. Tolebrutinib was associated with a significantly higher risk of SAEs compared to placebo, with ORs consistent with those from the direct comparisons. No other agents showed significant differences from each other. The relative safety of each treatment, based on SUCRA values, is shown in Fig. S4. The SUCRA values, rounded to three decimal places, were as follows: placebo (0.782), IFN-β-1a (0.709), natalizumab (0.548), siponimod (0.361), and tolebrutinib (0.101). Due to the small number of included studies, assessments of heterogeneity and publication bias using Egger's test are not considered reliable.

Table 3. Network meta-analysis of various treatments for serious adverse events

Placebo				
1.01 [0.63; 1.59]	**IFN-β-1a**			
0.90 [0.65; 1.24]	0.90 [0.51; 1.57]	**Natalizumab**		
0.82 [0.62; 1.09]	0.82 [0.48; 1.40]	0.91 [0.60; 1.40]	**Siponimod**	
0.65 [0.44; 0.96]	0.65 [0.36; 1.19]	0.73 [0.44; 1.20]	0.80 [0.49; 1.29]	**Tolebrutinib**

Risk of Bias and Certainity of Evidence

Risk of bias assessments (Fig. S5) showed that four studies were rated as having some concerns, while the remaining three were judged to have a low risk of bias. The evaluated outcomes included CDP at 3 and 6 months. Overall, the risk of bias was considered to be of some concern. The certainty of evidence for the treatment rankings was rated as moderate, downgraded due to risk of bias.

Discussion

This NMA synthesized evidence from seven RCTs evaluating DMTs for SPMS. The results indicate that tolebrutinib, IFN-β-1b, and siponimod demonstrated significant benefits in delaying CDP at both 3 and 6 months compared to placebo. Notably, tolebrutinib was more effective than IFN-β-1b at 6 months, whereas IFN-β-1b showed greater benefit at 3 months. These findings are consistent with previous reports supporting the efficacy of IFN-β-1b and siponimod,[20] while also highlighting the emerging potential of tolebrutinib. In contrast, IFN-β-1a and natalizumab exhibited more modest effects, in line with earlier studies suggesting limited benefits in delaying disability progression.[17] This review offers a comprehensive comparison of both established and newer agents by using an NMA framework to rank their relative effectiveness and safety.

Tolebrutinib, a next-generation BTK inhibitor, demonstrated encouraging results with significant benefits at 3 and 6 months.[21] Its dual mechanism of action, targeting peripheral immune cells and CNS-resident microglia, offers a promising approach for SPMS, where compartmentalized inflammation drives progression. Nevertheless, concerns remain due to the higher risk of SAEs and the short follow-up, which limits understanding of its long-term safety and efficacy. Real-world evidence from observational cohorts, registries, and post-marketing surveillance will be valuable in assessing durability of benefit, safety, and treatment persistence in broader patient populations. Furthermore, the inclusion of participants without active relapses in several trials may restrict generalizability. Despite these limitations, the findings highlight tolebrutinib's potential and underscore the need for longer-term studies.

Regarding IFN agents, IFN-β-1b ranked slightly higher than IFN-β-1a, with lower ORs for CDP at both time points. This suggests a somewhat greater immunomodulatory effect, although the overall benefit remains modest and is unlikely to significantly influence long-term outcomes. Similarly, natalizumab demonstrated limited benefit, with ORs close to unity, indicating no significant advantage in delaying disease progression. Mitoxantrone demonstrated the most pronounced short-term efficacy among the evaluated agents; however, its clinical utility is severely limited by a well-documented toxicity profile.[22] Notably, the risks of cumulative dose-dependent cardiotoxicity and therapy-related secondary acute myeloid leukemia significantly outweigh its benefits in most settings, thereby precluding its routine use in long-term disease management.[23]

From a clinical perspective, these findings suggest that siponimod remains the most practical treatment option due to its consistent efficacy and acceptable safety profile, as supported by current guidelines. Tolebrutinib appears promising, particularly for patients with active SPMS, but further evidence is needed to confirm its long-term benefits and safety. In contrast, IFN-based studies relied on older trial designs and outcome measures, which limit their applicability to contemporary clinical practice. Future research should prioritize head-to-head trials comparing tolebrutinib and siponimod in patients with active SPMS to clarify their relative effectiveness in slowing disease progression and

preserving quality of life. Longer-term studies are also essential to assess sustained benefits, cognitive outcomes, and patient-reported measures. Additionally, improved standardization of trial criteria is necessary to enhance the generalizability of findings.

Several limitations of this review should be acknowledged. The risk of bias in the included studies raised some concern, and the certainty of evidence was moderate, which limits the strength of the conclusions. The small sample size and inclusion of multiple agents limited safety comparisons and precluded sensitivity analyses. While statistical heterogeneity was low, clinical heterogeneity, including differences in disease activity status, baseline EDSS, and trial durations, should be considered when interpreting the generalizability of these findings. Lastly, although no publication bias was detected, its presence cannot be entirely ruled out.

Conclusion

This systematic review and NMA demonstrated that tolebrutinib, IFN-β-1b, and siponimod are effective in delaying disability progression in SPMS. Although tolebrutinib shows promise, further research is needed to confirm its long-term efficacy and safety. IFN-β-1b and siponimod, with their consistent effectiveness and favorable safety profiles, remain the most practical treatment options. Future head-to-head trials will be critical to refining therapeutic strategies for SPMS.

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Author Contributions

Y.Y. contributed to the study design and manuscript drafting. Y.Y. and G.Z. performed the literature search, quality assessment, data extraction, and analysis. S.M. and D.Z. contributed to data interpretation and revision. All authors have reviewed the manuscript and agree with its content and data.

Data Availability

The corresponding author will provide the datasets used in this study upon reasonable request.

Ethical Statement

Institutional Review Board approval was waived due to the nature of the meta-analysis.

Conflict of Interest

The authors report no conflicts of interest related to this work.

Supplemental Information

Supplemental information for this article can be found online at https://sup.jclinque.com/api/articles/88/download-suppl.

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