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REVIEW ARTICLE **OPEN ACCESS**

EFFICACY AND SAFETY OF EVOBRUTINIB IN RELAPSING MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Background: Evobrutinib is a selective Bruton's tyrosine kinase (BTK) inhibitor that crosses the blood-brain barrier. BTK regulates B lymphocytes and myeloid cells, significantly contributing to multiple sclerosis (MS) inflammation. While current MS treatments alleviate relapses and disability, they have a limited impact on inflammation within the central nervous system.
Objective: We aim to evaluate the efficacy and safety of evobrutinib in relapsing MS.
Methods: A systematic search of databases, including PubMed, Elsevier, NEJM, BMJ Journals, and Neurology, was conducted. Inclusion criteria: Studies within 5 years, randomized controlled trials, and interventions with evobrutinib. Exclusion criteria: Incomplete reporting, non-phase two trials, and JADAD score < 3. The quality of the included studies was evaluated using the JADAD scale.
Results: The literature search yielded 552 studies, of which eight were included in the final analysis. All studies consistently demonstrated significant benefits in reducing disease activity. The efficacy of evobrutinib 75 mg BID showed a significant reduction in ARR (mean ARR = 0.10) and gadolinium-enhancing lesions compared to placebo (mean ARR = 0.37). SEL volume was significantly reduced, especially in patients with higher disability and longer disease duration. The safety profile of evobrutinib was comparable to that of a placebo, with similar rates of TEAEs. Liver enzyme elevations were noted in one study but were generally manageable. Stability in EDSS scores over extended treatment periods suggests effective disease control.
Conclusion: Evobrutinib is a promising therapeutic option for managing MS, particularly relapsing forms, due to its efficacy in reducing disease activity and favorable safety profile.

Keywords: efficacy, evobrutinib, multiple sclerosis, safety

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system, characterized by focal disturbances in the optic nerves, spinal cord, or brain. MS typically has a peak onset between the ages of 20 and 40, is progressive, and is the leading cause of disability in young adults.[1] MS lesions have varying predilections within the CNS, resulting in complex symptoms depending on their location. Typical clinical manifestations include motor disturbances such as weakness, tremors, dysarthria, coordination impairment, spasticity, and fatigue; sensory disturbances such as paresthesia, paraparesis, and profound sensation impairment; visual disturbances such as vision loss, diplopia, and nystagmus; and bladder dysfunction. At the initial onset, symptoms are often nonspecific, making diagnosis uncertain, mainly because the clinical manifestations may only refer to one locus of the nervous system, which may not even receive medical attention. As the disease progresses and recurs over 1

to 10 years or longer, spreading to other parts of the CNS, the diagnosis becomes more specific.[2,3]

MS can be categorized into relapsing-remitting form, secondary progressive form, primary progressive form, acute multiple sclerosis (Marburg disease and tumefactive multiple sclerosis), and diffuse cerebral sclerosis (Schilder disease and Balo's concentric sclerosis). In most cases, about 85-90% present with the relapsing-remitting form, while 10-15% present with the primary progressive form. Relapsing-remitting MS typically features periods of symptom exacerbation followed by incomplete remission, eventually leading to recurrences of the same abnormalities or new neurological manifestations in other parts of the nervous system. Primary progressive MS generally occurs in patients with onset after the age of 40 and presents with a steadily progressive clinical course. Additionally, secondary progressive MS begins with a relapsing course and then becomes steadily progressive, occurring in 50% of relapsing-remitting MS cases.[2,4]

Previous studies have shown a higher prevalence in patients with genetic factors, leading to the belief that there is a combination of genetic and environmental factors. Patients with first-degree family members have a 2-4% risk, while the general population only has a 0.1% risk.[2] Patsopoulos et al.in 2019 identified 233 genetic variants significantly associated with MS at the genome-wide level, with 32 of them found in the major histocompatibility complex (MHC) genome, one on the X chromosome, and the remaining 200 in the autosomal non-MHC genome. The genes involved are related to the development, maturation, and terminal differentiation of B cells, T cells, natural killer cells, and myeloid cells, contributing to MS variants.[5]

In MS, numerous scattered patches typically affect the white matter in the brain and spinal cord, with lesion diameters varying from less than 1 millimeter to several centimeters. Despite their widespread distribution, the lesions typically do not extend beyond the root entry zones in the cranial and spinal nerves. The underlying pathogenesis of MS involves both adaptive and innate immunity, particularly the focal infiltration of lymphocytes in the CNS, which damages myelin and axons, eventually forming plaques. Most MS plaques are driven by the humoral immune system, with oligoclonal immune protein antibodies produced by B lymphocytes in the CNS. Activated B cells can differentiate into memory or plasma cells, and in more than 90% of cases, autoantibodies are formed, contributing to antibody-dependent cytotoxicity (ADCC) and complement injury. B cells can also produce proinflammatory cytokines like TNF-α and lymphotoxin, further activating T cells via antigen-presenting cells (APCs).[2,3]

T cells, including CD4+ T cells and CD8+ T cells, also contribute to MS pathology, with CD4+ T cells being more frequently involved. In response to interleukin 12 (IL-12), naïve CD4+ T cells can differentiate into proinflammatory T helper type 1 (Th1) cells that express the transcription factor Tbet and produce interferon-gamma (IFN-γ). Additionally, in response to TGF-β1, IL-23, IL-6, and IL-21, CD4+ T cells can differentiate into Th17 cells that express RORγt and produce IL-17. CD8+ T cells contribute to CNS damage through the production of perforins, granzymes, Fas/FasL-mediated cytotoxicity, proinflammatory cytokines like IL-17 and lymphotoxin, and chemoattractants for CD4+ T cells such as IL-16 and IP-10. Furthermore, the pathology of MS is linked to a decrease in the number of Tregs, suppressed Treg activity, and T cell resistance to Treg regulation, leading to dysregulated autoimmune responses in MS.[2,3]

On the other hand, innate immunity also plays a role in MS pathology. Rather than acting independently, innate immune cells interact with others to amplify CNS pathology. Mast cells produce tryptase and histamine, which open the blood-brain barrier (BBB), recruit inflammatory cells into the CNS, and promote neurodegeneration through matrix metalloproteinase (MMP) cascades. Microglia and macrophages act as APCs and produce proinflammatory cytokines, chemokines, and metabolites that cause neurodegeneration. They also produce TNF-α, reactive oxygen species (ROS), and nitric oxide (NO), which have direct neurotoxic effects in MS. Astrocytes, glial cells in the CNS, contribute to neuroinflammation and neurodegeneration through the production of cytokines (such as IL-6, TNF), chemokines (such as CCL2), and neurotoxic metabolites (such as NO). Natural killer cells are also believed to have cytotoxic activity, though their role is complex and still under investigation. Overall, these interactions suggest potential targets for therapeutic intervention in MS.[2,3]

Inflammatory reactions in the brains of patients with progressive MS are mainly seen in the meninges and periventricular Virchow-Robin spaces, which are large connective tissue spaces. These sites predominantly contain CD8+ T cells, CD20+ B-cells, and varying numbers of plasma cells. These are associated with the slow expansion of demyelinated lesions bordered by a rim of activated microglia cells containing early myelin degradation products.[6]

Evobrutinib is a highly selective Bruton’s tyrosine kinase (BTK) inhibitor that penetrates the CNS and acts on immune cells on both sides of the blood-brain barrier (BBB). BTK is an enzyme from the Tec family of tyrosine kinases that plays a key role in regulating B lymphocytes and myeloid cells, including microglia, macrophages, and monocytes. BTK is crucial in

signaling, specifically in the B cell receptor (BCR) in B lymphocytes and the Fcγ receptor (FcγR) in myeloid cells. Given that the inflammatory process in MS is driven by autoantibodies and the overexpression of BTK in B lymphocytes, BTK inhibitors represent a promising therapeutic target for diseases involving the activation of B cells and macrophages, such as multiple sclerosis (MS). In relapsing-remitting MS and secondary-progressive MS, elevated BTK levels are found in B cells and the microglia within progressive MS lesions.[7] Ibrutinib, the first BTK inhibitor, showed efficacy against previously difficult-to-treat lymphomas but also caused side effects related to the epidermal growth factor receptor (EGFR), such as bleeding, rash, diarrhea, and atrial fibrillation. New BTK inhibitors are being developed to improve tolerability, such as acalabrutinib, a second-generation BTK inhibitor for oncology indications. Recently, there has been increased interest in developing BTK inhibitors for autoimmune and inflammatory diseases. Evobrutinib has demonstrated suitable pharmacokinetics and promising pharmacodynamics for treating autoimmune diseases such as multiple sclerosis. It also has excellent kinome selectivity, avoiding the off-target effects on EGFR, thus not significantly inhibiting EGFR or other kinases that could lead to unwanted side effects, distinguishing it from other BTK inhibitors.

In treating MS, currently, available therapies are divided into disease-modifying therapies (DMTs), which modulate the peripheral immune response; symptomatic therapies that address specific symptoms associated with MS, such as muscle spasms, fatigue, and bladder problems; and acute relapse therapies to manage flare-ups by reducing inflammation, such as corticosteroids or plasmapheresis. Current DMTs, like rituximab, ocrelizumab, and ofatumumab, are monoclonal antibodies that work by depleting CD20-positive B cells involved in immune-mediated damage in MS. While these therapies have shown clinical success in reducing relapses in relapsing MS (RMS), their primary action is limited to the peripheral immune system due to poor brain penetration. As a result, they have a limited impact on the CNS, which plays a critical role in progressive MS (PMS) and the accumulation of disability. Moreover, chronic B-cell depletion raises concerns about an increased risk of serious infections and possibly malignancy.[8,9]

Methods

We conducted a systematic literature search of electronic databases, including PubMed, Elsevier, NEJM, BMJ Journals, and Neurology, to find relevant literature on BTK inhibitors in relapsing multiple sclerosis patients. The keywords used in various combinations were: ("Evobrutinib") and ("Relapsing multiple sclerosis" or "Multiple sclerosis" or "MS").

Study Selection and Eligibility Criteria

The studies were collected using a PRISMA diagram, with one independent reviewer responsible for screening the titles and abstracts of each study (Figure 1). A second reviewer evaluated the selected studies to confirm inclusion decisions and ensure accuracy. Any discrepancies were discussed between the reviewers to achieve consensus. Full-text articles of the selected studies were then obtained and reviewed for eligibility using PICOS (Participants, Intervention, Comparisons, Outcome, Studies) analysis shown in Table 1. Following the initial database search, manual reference checking was conducted on the reference lists of all included studies to identify additional eligible studies. The criteria for including studies in this analysis were as follows: i) studies published within the last five years, ensuring that they remain current and relevant to recent advancements; ii) the study must be a randomized clinical trial (RCT), considered the gold standard in clinical trials for establishing cause-and-effect relationships; and iii) the intervention must include the use of evobrutinib, a selective BTK inhibitor.

Studies were excluded based on the following criteria: i) studies with incomplete outcome reporting, which limited their ability to contribute meaningful data to the analysis; ii) non-phase 2 or 3 clinical trials, as this study focused on evaluating the efficacy and side effects of treatment; iii) articles not available in English; and iv) studies with a JADAD score lower than 3, indicating lower quality evidence, were excluded to ensure the reliability and accuracy of the data included.

Table 1. Inclusion criteria in terms of PICOS

Category	Description
Participants	Patients of any age and gender are diagnosed with multiple sclerosis. Studies with any treatment duration and dosing were considered due to the limited data availability.
Interventions	Evobrutinib, a selective BTK inhibitor.
Comparison	Control groups are receiving a placebo.
Outcomes	The efficacy of evobrutinib is measured by its ability to reduce annualized relapse rate (ARR), the number of gadolinium-enhancing lesions, the volume of slowly expanding lesions, and its safety profile.
Study design	Randomized controlled trials (RCTs).

Data Extraction and Quality Assessment

The selected articles were collected, and duplicate papers were removed. Subsequently, the articles were screened based on the eligibility criteria and extracted into Microsoft Excel 2023. Data extracted included the

name of the study, study design, sample size, study location, period, and clinical findings of the study participants. We assessed the articles using the JADAD score to determine the quality of the clinical trials and Cochrane's risk-of-bias tools for RCTs.

Results

Of the 552 articles from the literature search, eight studies met the inclusion criteria and were used in this systematic review. The studies included from 2019 to 2024, consisting of seven phase 2 clinical trials and one phase 3 clinical trial. The phase 3 trial was included due to data limitations, as long as it provided the desired information for this systematic review. A summary of the characteristics of each study is presented in Table 2.

Nine of the included studies had double-blinded, randomized, controlled trial designs. The sample sizes ranged from 130 to 2,285 patients, with study durations ranging from 16 to 192 weeks. Three studies evaluated the efficacy of evobrutinib in reducing the annualized relapse rate (ARR), with mean ARR results of 0.10 in patients treated with evobrutinib 75 mg BID, 0.57 in evobrutinib 25 mg QD, and 0.37 in the placebo group. ARR is calculated by dividing the total number of relapses by the total number of patient-years at risk. A lower ARR indicates fewer relapses, suggesting better disease control and the effectiveness of a treatment in reducing disease activity.

Two studies assessed the impact of evobrutinib on gadolinium-enhancing lesions, a marker of active inflammation in MS, with a mean of 1.15 in patients treated with evobrutinib 75 mg BID, 0.13 in evobrutinib 60 mg, and 2.44 in the placebo group. Another study used neurofilament light chain levels (NfL) as a marker of neuroinflammation in MS, showing a reduction in patients treated with evobrutinib 75 mg BID to levels similar to those in the non-MS population.

One study evaluated the impact of evobrutinib 75 mg BID on the volume of slowly expanding lesions (SELs), which indicates chronic inflammation, with a reduction of -474.5 mm^3 ($p = 0.047$) vs. placebo (switched to evobrutinib 25 mg QD after week 24) and a reduction of -711.6 mm^3 ($p = 0.011$) vs. open-label dimethyl fumarate (DMF) 240 mg BID. Meanwhile, two other studies assessed the Expanded Disability Status Scale (EDSS), a method for quantifying disability in MS and monitoring changes in the level of disability over time, such as the ability to walk, sensory, bowel and bladder, visual, cerebral, and brainstem functions. The EDSS scale ranges from 0 to 10; 0 = normal neurological exam (no disability); 1-3.5 = mild disability; 4-6.5 = moderate disability (ambulation issues begin); 7-9.5 = severe disability (requiring assistance for mobility). A lower EDSS score indicates less disability, suggesting effective disease management and positive outcomes. In these two clinical studies, evobrutinib consistently showed a maintained EDSS score, indicating its significant impact on slowing disability progression. One study evaluated dosing strategies with evobrutinib 75 mg BID on an empty stomach vs. 45 mg BID with food, with similar efficacy observed in 93% of patients. Taking the drug on an empty stomach ensures effective concentration and response in most patients, providing dosing flexibility without reducing effectiveness.

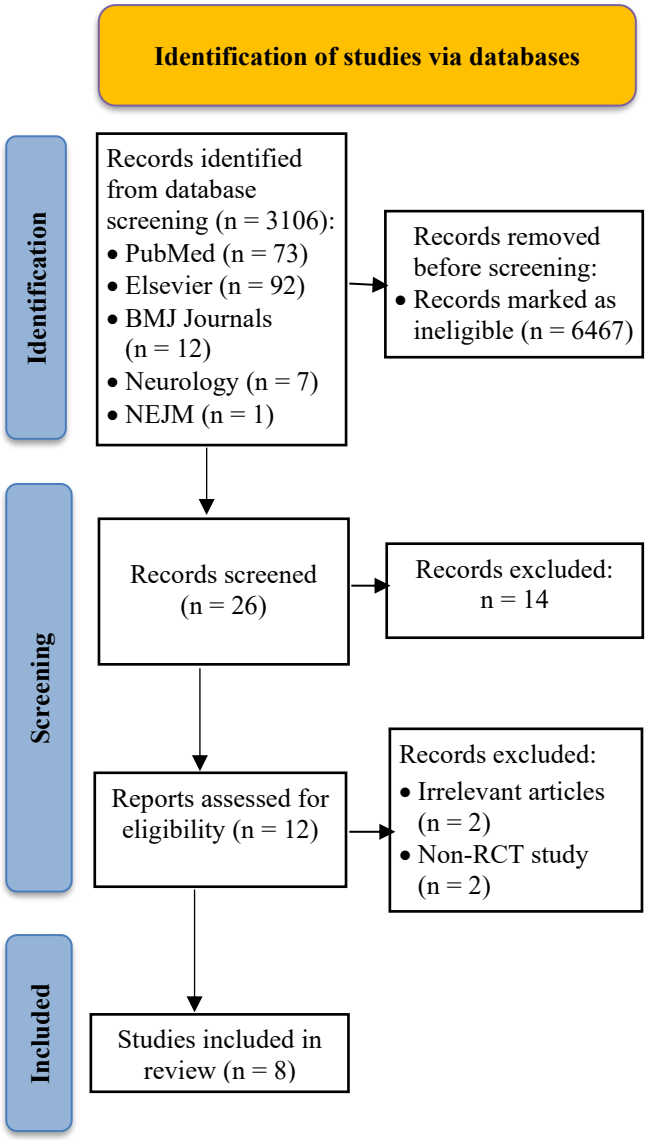

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection

Four studies reported on the safety profile and treatment-emergent adverse events (TEAEs) with evobrutinib. Two studies found that evobrutinib has a safety profile comparable to a placebo. One study reported a serious event due to an MS relapse in the 60 mg group, while 7% of other patients experienced headaches. Another study noted elevated liver enzyme levels.

Table 2. Characteristic of each study

First author, year	Study type	Cases (n)	Duration	Dose	Results	Side effects	Conclusion
Montalban, 2024[10]	Phase II RCT, double-masked	164	192 weeks	Evobrutinib 25 mg QD vs. evobrutinib 75 mg QD vs. evobrutinib 75 mg BID vs. placebo	1. ARR at Week 48: 0.11 (95% CI = 0.04-0.25) 2. ARR at Week 192: 0.11 (95% CI = 0.05-0.22) 3. EDSS remained stable over 192 weeks, indicating no significant progression in disability. 4. Neurofilament Light Chain Levels: Serum neurofilament light chain levels fell to levels similar to a non-MS population, indicating reduced neuronal damage. 5. T1 Gadolinium-Enhancing Lesions: Numbers remained low, indicating sustained control over new inflammatory lesions. 6. CSF Penetration: Evobrutinib was detected in the CSF of all sub-study patients, indicating its ability to reach the central nervous system effectively.	Safety profile	Safety profile and effective CNS penetration
Arnold, 2024[11]	Phase II RCT, double-masked	223	48 weeks	Evobrutinib 25 mg QD vs. evobrutinib 75 mg QD vs. evobrutinib 75 mg BID vs. placebo (switched to evobrutinib 25 mg QD after 24 weeks)	1. Mean SEL Volume Evobrutinib 75 mg BID: 2,099 mm^3 2. Mean SEL Volume Placebo/Evobrutinib 25 mg QD: 2,681 mm^3 3. Reduction with Evobrutinib 75 mg BID: -474.5 mm^3 (p = 0.047) vs. placebo 4. Reduction vs. DMF: -711.6 mm^3 (p = 0.011)	NA	Evobrutinib 75 mg BID significantly reduces SEL volume compared to lower doses and other treatments. This indicates its effectiveness in reducing chronic inflammation and potential neurodegeneration in MS patients, particularly in those with higher disability and longer disease duration.
Montalban, 2023[12]	Phase III RCT, double-blind	2285	156 weeks	Evobrutinib 45 mg BID (with food) vs. teri 14 mg QD (with food)	1. Mean(±SD) EDSS: 2.8(±1.3) 2. Mean(±SD) time since diagnosis was 4.7(±5.7) years, 96.1/3.9% of patients had RRMS/SPMS	NA	The baseline characteristics of the study population show a diverse and representative sample of MS patients, primarily with relapsing-remitting MS, and a significant portion being treatment-naïve. This provides a robust foundation for evaluating evobrutinib's effectiveness and safety.

First author, year	Study type	Cases (n)	Duration	Dose	Results	Side effects	Conclusion
Papasouliotis, 2022[13]	Phase II RCT, double-masked	207	48 weeks	Evobrutinib 75 mg BID (fasted) vs Evobrutinib 45 mg BID (with food)	1. AUC0-24, SS of 468 ng/ml h associated with T1 Gd+/T2 lesion reduction. 2. AUC0-24, SS ≥400 ng/ml h linked to ARR improvement. 3. Steady-state (SS) predose BTK occupancy (BTKO) ≥95% associated with these exposures	NA	Evobrutinib 75 mg BID while fasted and 45 mg BID with food effectively achieves target exposure levels, optimizing clinical responses in MS patients by maintaining high BTKO. This offers flexibility in dosing strategies while ensuring efficacy
Montalban, 2022[7]	Phase II RCT, double-masked	1083	48 weeks	Evobrutinib 25 mg or 75 mg QD vs. evobrutinib 75 mg BID vs. placebo	1. TEAEs (Events/100 Pt-Years): a. Evobrutinib: 247.6 (66.2%) b. Placebo: 261.4 (62.4%) 2. Serious Infections (EAIR): a. Evobrutinib: 2.7 events/100 pt-years b. Placebo: 2.1 events/100 pt-years 3. Elevated Liver Enzymes (Events/100 Pt-Years): a. Alanine Aminotransferase: 4.8 (Evobrutinib) vs. 2.8 (Placebo) b. Aspartate Aminotransferase: 3.5 (Evobrutinib) vs. 0.7 (Placebo)	Comparable safety profile between the groups across multiple conditions, with similar rates of adverse events	Evobrutinib shows a safety profile comparable to a placebo across multiple conditions, with similar rates of adverse events. Liver enzyme elevations were noted but were within an acceptable range. The safety profile suggests that evobrutinib is a viable option for long-term treatment across these conditions
Reich, 2021[14]	Phase II RCT, double-blind	130	16 weeks	Evobrutinib 5 mg, 15 mg, 30 mg, 60 mg	1. Mean Gadolinium-Enhancing Lesions at Week 12: a. Placebo: 1.03 ± 2.50 b. 5 mg: 1.39 ± 3.20 c. 15 mg: 0.77 ± 1.48 d. 30 mg: 0.76 ± 3.31 60 mg: 0.13 ± 0.43	One serious event (hospitalization due to MS relapse in the 60 mg group). The most common non-serious event was a headache (7% overall)	Evobrutinib demonstrates a dose-dependent reduction in gadolinium-enhancing lesions, supporting its efficacy at higher doses. The safety profile is acceptable, with manageable adverse events and no safety-related discontinuations

First author, year	Study type	Cases (n)	Duration	Dose	Results	Side effects	Conclusion
Montalban, 2021[15]	Phase II RCT, double-masked	213	108 weeks	Evobrutinib 75 mg BID	1. ARR at Week 48: 0.11 (95% CI = 0.04-0.25) 2. ARR at Week 108: 0.12 (95% CI = 0.06-0.22) 3. EDSS: No significant change from baseline in EDSS scores. 4. Cumulative Probability of First QR: a. Week 48: 0.08 (0.00, 0.16) b. Week 96: 0.20 (0.08, 0.31) c. Significant reduction in relapse risk for patients on 75 mg BID vs. other doses or placebo. 5. Time to 20% QR: Almost three times longer for patients initiated on 75 mg BID compared to placebo, indicating long-term effectiveness	NA	Evobrutinib 75 mg BID shows sustained efficacy in reducing relapse rates and delaying relapse onset over 108 weeks, confirming its long-term benefits in MS management
Montalban, 2019[16]	Phase II RCT, double-masked	267	24 weeks	Placebo vs. evobrutinib 25 mg, 75 mg QD, 75 mg BID	1. ARR at Week 24: a. Placebo: 0.37 b. Evobrutinib 25 mg: 0.57 c. Evobrutinib 75 mg once daily: 0.13 d. Evobrutinib 75 mg BID: 0.08 2. Mean Gadolinium-Enhancing Lesions during Weeks 12-24: a. Placebo: 3.85 ± 5.44 b. Evobrutinib 25 mg: 4.06 ± 8.02 c. Evobrutinib 75 mg once daily: 1.69 ± 4.69 d. Evobrutinib 75 mg BID: 1.15 ± 3.70 e. DMF: 4.78 ± 22.05 EDSS Scores: No significant effect on change from baseline	Elevations in liver aminotransferase values were observed with evobrutinib	**75 mg QD Dose:** Demonstrated a significant reduction in inflammation, indicating that this specific dosing regimen has a positive therapeutic effect in reducing MS lesions compared to doing nothing (placebo) **Other Doses:** The 25 mg once and 75 mg twice daily did not show significant differences from the placebo, suggesting these doses may not be as effective or require further investigation to understand the lack of significant results

AUC=area under the curve; ARR=annualized relapse rate; BID=bis in die (twice a day); BTKO=BTK occupancy; CNS=central nervous system; CSF=cerebrospinal fluid; DMF=dimethyl fumarate; EDSS=expanded disability status scale; Gd+=gadolinium-enhancing lesions; MS=multiple sclerosis; NA=not available; QD=queue die (once daily); QR=qualified relapse; RCT=randomized clinical trial; RRMS=relapsing-remitting multiple sclerosis; SELs=slowly expanding lesions; SPMS=secondary progressive multiple sclerosis; SS=steady state; TEAEs=treatment-emergent adverse events

Discussion

This systematic review examined the efficacy and safety of evobrutinib as a BTK inhibitor in managing relapse for multiple sclerosis patients. Based on eight included studies, all studies showed significant benefits and promising results in reducing disease activity.[7,10–16] In MS patients, elevated levels of activated BTK have been detected in circulating B cells and microglia. BTK is a member of the Tec family of non-receptor tyrosine kinases, primarily expressed in B lymphocytes, macrophages, and microglia. It is crucial in various immune processes, mainly regulating immune responses. BTK is involved in the signaling pathways that contribute to the development and progression of multiple sclerosis (MS). Its function in these immune cells makes it a key player in the pathogenesis of MS. By modulating BTK signaling, it can reduce both peripheral and CNS inflammation, thereby inhibiting neurodegeneration and demyelination, further preventing disability accumulation in MS patients.[10]

Efficacy in Reducing Annualized Relapse Rate (ARR)

The mean ARR values in patients treated with evobrutinib 75 mg BID were significantly lower (0.10) compared to 0.37 in the placebo group and 0.57 in the 25 mg dose group. Evobrutinib is an irreversible, highly sensitive, orally administered, and CNS-penetrant BTK inhibitor. Evobrutinib is a dose-dependent treatment that can inhibit B-cell maturation, block antigen-triggered activation, and reduce the release of pro-inflammatory cytokines. Ultimately, the severity of MS can be reduced.[17,18] Bhargava et al. in 2021 found that mice treated with evobrutinib showed significant improvement in meningeal inflammation ($p = 0.003$), with a 30% reduction compared to a 5% increase in the control group (treated with vehicle solution containing 20% kleptose in 100 µM sodium citrate buffer, pH 3).[19]

BTK is expressed in myeloid cells and is crucial in regulating myeloid cells, including brain-specific microglia and peripheral macrophages. In myeloid cells, BTK is activated through the Fcγ receptor and FcεRI signaling, where BTK signals through plc-γ2 to activate the NFκB and NFAT pathways, leading to the production of inflammatory cytokines. The release of pro-inflammatory cytokines leads to the differentiation of CD4+ T cells, which then release more pro-inflammatory cytokines, contributing to the autoimmune attack on the myelin sheath, ultimately leading to demyelination in MS.[17,18]

Evobrutinib works by inhibiting BCR receptor-mediated signaling in B cells and Fc receptor-mediated signaling in innate immune cells, such as monocytes and basophils. In addition to inhibiting BTK, kinase screening panel assays have shown that evobrutinib inhibits Bmx (95%) and Tec (82%). The inhibition of BCR and Fc receptor-mediated signaling demonstrates evobrutinib's efficacy in treating multiple sclerosis and autoimmune diseases. In several studies on 25 mg QD, 75 mg QD, and 75 mg BID, the 75 mg BID dose exhibited a significantly lower ARR than the placebo group. Furthermore, compared to other BTK inhibitors, such as ibrutinib, evobrutinib has a significantly less potent effect on BTK-dependent platelet aggregation, by 15 to 50 times less. Evobrutinib at 10 µM did not show increased bleeding risk; thus, no bleeding has been reported.[20]

Pharmacodynamically, evobrutinib has a half-life of 2 hours.[17] In a phase I study, Becker et al. in 2020 compared two groups, consisting of a single dose of evobrutinib (25 mg, 50 mg, 100 mg, 200 mg, 350 mg, and 500 mg) or placebo, and multiple doses of 25 mg, 75 mg, and 200 mg once daily for 14 days. The overall TEAEs were mild, and there was no relationship between the dose and the frequency or type of TEAEs. Evobrutinib was rapidly absorbed, with a time to reach maximum plasma concentration of 0.5 hours and a short half-life of 2 hours. The pharmacokinetics showed dose-proportionality but no time dependency on repeat dosing. In the single-dosing group, BTK occupancy (BTKO) was dose-dependent and long-lasting. Dose dependency was demonstrated by maximum occupancy of >90% within 4 hours after a single dose of 200 mg, 350 mg, and 500 mg. Long-lasting BTK inhibition was shown through >50% occupancy at 96 hours after ≥100 mg. In the multiple-dosing group, full BTKO was achieved with 25 mg, indicating slow turnover of the BTK protein in vivo, with no prolongation of the QT/QTc interval in healthy subjects, making it suitable for autoimmune diseases.[21]

Based on this data, phase II studies by Papasouliotis et al. in 2022 found that minimum BTKO increased dose-dependently, with bioavailability increasing by 49% with low-fat food compared to fasting, showing tolerability in both conditions. The BTKO profile of evobrutinib also showed irreversible binding at the active site of the BTK receptor. Papasouliotis et al. in 2022 concluded that BTKO ≥70% is required to achieve efficacy, with doses of 25 mg QD, 50 mg BID, or 75 mg BID achieving the desired BTKO. Higher doses (≥200 mg BID with food or under fasted conditions) were required to achieve higher BTKO levels (approaching 100%).[18] BTK could reduce astrocytosis in the adjacent cortex, suggesting that the effects on the meningeal infiltrate lead to reduced pathology in the surrounding tissue.[19] At pharmacological doses, evobrutinib produces high levels of BTKO both in the periphery and the brain due to covalent binding to the BTK receptor.[10]

Impact on Gadolinium-Enhancing Lesions and Neurofilament Light Chain

Evobrutinib has been shown to reduce the number of gadolinium-enhancing lesions effectively. Gadolinium-based contrast agents (GBCAs) are paramagnetic gadolinium complexes used in magnetic resonance imaging (MRI) clinical studies, especially for identifying specific tissues and abnormalities, such as active inflammation.[22] Gadolinium can enhance MS plaques, making it a well-established marker for MS and a reliable tool for detecting BBB breakdown.[23,24] Based on the structure of the organic chelators used, GBCAs are classified into linear and macrocyclic types, with studies showing that both types are generally safe and well tolerated in patients with normal renal function.[22] Kanda et al. demonstrated a relationship between the serial administration of linear GBCAs and gadolinium deposition in the CNS, visible as foci of increased signal intensity on unenhanced T1-weighted images in the dentate nucleus-to-pons and globus pallidus-to-thalamus regions.[25]

Rovira et al. in 2020 found that the presence of active T2 lesions does not indicate whether the activity is recent and may even represent other pathologies, such as vascular co-morbidity in addition to MS. Therefore, T1-weighted sequences are highly recommended for detecting disease activity in MRI scans, as they reveal recent inflammatory activity and help guide treatment management before initiating MS therapy.[22] While Gd+ lesions can identify CNS inflammation, the availability of MRI scans may be limited in some centers due to long scanning times and high costs.[26]

In addition to T1 Gd+ lesions, the neurofilament light chain (NfL) protein can be a biomarker for ongoing neuroaxonal damage. NfL is a class IV intermediate filament that forms part of axon scaffolding, facilitating structural stability and signal conduction in neurons. Evobrutinib works by inhibiting BTK signaling, which modulates B-cell function and alters the activity of macrophages and microglia, rather than depleting B-cells through cell lysis or apoptosis. In a study by Montalban et al. in 2024, the use of evobrutinib 75 mg BID for up to 144 weeks significantly reduced serum NfL levels to those similar to a non-MS control population. Even at week 12, a rapid reduction in NfL was observed, with a corresponding decline in the mean number of T1 Gd+ lesions, indicating that NfL can serve as a marker of disease activity.[10,26]

NfL can be detected in cerebrospinal fluid (CSF) and serum (sNfL). Rosso et al. in 2020 observed a 35% elevation in sNfL three months after detecting a Gd+ lesion compared to the remission group ($p < 0.0001$). Additionally, compared to the remission group, there was a 32.3% elevation in sNfL at the time of or before a Gd+ lesion ($p = 0.002$). These findings support sNfL as a promising biomarker for clinical relapse, Gd+ lesions, and neurological inflammation.[26] Schaller-Paule et al. (2024) reported strong evidence that patients with higher NfL concentrations have a higher rate of brain atrophy, placing them at greater risk for long-term disability and worse clinical outcomes. NfL levels also indicate the probability of a progressive disease course, are helpful for therapeutic response monitoring, and serve as a prognostic biomarker for future disease progression or accelerated gray matter brain volume loss. The study also found a strong association between NfL concentrations as a neuroaxonal damage marker and two or more gadolinium-enhancing lesions in serum and CSF.[27]

Effects on Slowly Expanding Lesions (SELs)

Evobrutinib effectively reduces the volume of slowly expanding lesions (SELs), with a mean SEL volume of 2,099 mm^3 in patients treated with Evobrutinib 75 mg BID, compared to 2,681 mm^3 in the placebo group. The reduction in slowly expanding lesion volume indicates that evobrutinib impacts brain lesions associated with microglial activity in chronic inflammation and tissue loss in the CNS.[10] Slowly expanding lesions are smoldering or mixed active/inactive demyelinating lesions and are the dominant lesion type in progressive multiple sclerosis, not found in the early relapsing-remitting stages of the disease.[28] Histopathologically, smoldering lesions are characterized by an inactive center with few or no macrophages, surrounded by a rim of activated microglia or macrophages that contribute to chronic axonal damage and demyelination, slowly evolving. Chronic inflammation, believed to be sheltered behind a partially or non-disrupted BBB, is a hallmark of progressive MS.[29]

Previous studies have also identified chronic active lesions through susceptibility-based imaging, showing that iron rim lesions are associated with a more aggressive disease course.[30] In identifying substantially enlarging T2 lesions, conventional MRI can only detect tissue changes during acute focal inflammation in MS. Still, it cannot capture subtler inflammation, such as chronic active lesions or smoldering plaques, in the progressive phase of MS.[29]

On the other hand, Preziosa et al. in 2022 found that the severity of SEL microstructural abnormalities could predict worsening EDSS scores and conversion to secondary progressive MS after a 9.1-year follow-up. The SEL abnormalities referred to the severity of clinical disability, T2 hyperintense lesion burden, and brain volume. Therefore, the number and volume of SELs may be promising biomarkers for predicting a more severe disease course.[30] Calvi et al. in 2022 also found that higher SEL volumes were associated with higher disability levels, as measured by an increase in

EDSS scores (p = 0.01), suggesting an active role for SELs in determining changes in clinical outcomes.[31] Elliott et al. in 2019 observed that SELs evolve independently of T1 Gd enhancement, indicating they could serve as a potential marker for progressive neural tissue damage and axonal loss accumulation [29]

Safety Profile

Evobrutinib has a safety profile comparable to a placebo, with some elevated liver enzyme levels observed. Montalban et al. in 2022 showed that phase II trials confirm evobrutinib is well tolerated in MS, RA, and SLE patients. A recent analysis of adverse events (AEs) related to evobrutinib illustrated that this BTK inhibitor is well tolerated in individuals with MS, using data from phase II trials for MS, RA, and SLE involving more than 1,000 participants. The proportion of participants across all autoimmune conditions experiencing AEs was comparable between the evobrutinib and placebo groups, with an incidence of 66.2% and 62.4%, respectively.[7]

There are at least 22 BTK inhibitors in clinical trials, with adverse effects varying depending on the inhibitor type (reversible or irreversible) and their off-target effects on other kinases with similar binding domains. Rash and diarrhea may occur due to off-target inhibition of the EGF receptor and BRK kinase, though these effects are not present with all BTK inhibitors. Cardiovascular adverse effects, such as atrial fibrillation and hypertension, can occur due to the inhibition of ERBB family members. Ibrutinib, a first-generation BTK inhibitor, has off-target effects that inhibit HER2 and HER4, potentially impacting cardiovascular health. Bleeding can occur as a result of effects on thrombocytes, disrupting platelet function, with approximately 40% of patients on ibrutinib experiencing bleeding, including significant hemorrhage (4%). Additionally, the incidence of infection increases with the use of ibrutinib due to its impact on phagocytes, such as macrophages and neutrophils. Research into BTK inhibitors continues to evolve, and evobrutinib has shown an overall favorable safety profile.[32]

Montalban et al. in 2024 also found no new safety signals with the long-term use of evobrutinib, even after more than 3.5 years. In their previous study from 2019, transient elevations in liver aminotransferases were observed in some patients during the first 24 weeks of treatment with evobrutinib. However, no clinically relevant liver enzyme elevations occurred after over 3.5 years, demonstrating that these side effects are tolerable and can subside over time.[10]

The limitations of this study primarily stem from the small number of articles included in this systematic review. The literature search was restricted to studies published in English. The reviewers in this study were not blinded to the identities of the articles' authors, journals, or publishers. The included studies did not use the same outcome parameters to generate a quantitative analysis. Moreover, not all studies provided safety profiles, indicating that further evaluations of the long-term adverse effects of evobrutinib are needed.

Conclusion

Evobrutinib, an oral, highly sensitive BTK inhibitor, effectively reduces the annualized relapse rate (ARR), with a significant reduction observed at 75 mg BID compared to placebo. Its ability to penetrate the CNS and inhibit BTK is crucial for reducing immune cell activation and neuroinflammation, which contribute to MS pathology, offering substantial benefits in reducing disease activity. Safety data also reveal that evobrutinib has a favorable profile, comparable to placebo, with some elevated liver enzymes but no significant long-term safety concerns. Overall, evobrutinib appears to be a promising treatment option for MS, particularly for the relapsing form, with effective disease control and a manageable safety profile. Further studies and long-term evaluations are needed to clarify its role in MS management and ensure patient safety.

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