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Advances and challenges in the treatment of Multiple Sclerosis: The role of disease-modifying therapies

Rebeca Tazo Miosso [1], Eduarda Fernanda da Silva Costa [1], Natã Pereira Mariano [1], Raquel Kato Loureiro [1], Júlia Onodera Shinohara [1], Rafaela Tinasso Castelo Branco [1], Yasmin Fernandes Abdelnur [1], Dioelen Virgínia Borges Souza de Aquino Coelho [2].

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REVISÃO DE LITERATURA

RESUMO

A esclerose múltipla (EM) é uma doença inflamatória crônica, autoimune e neurodegenerativa do sistema nervoso central, caracterizada pela desmielinização e progressiva incapacidade neurológica. Apesar de não possuir cura, avanços terapêuticos têm ampliado significativamente as possibilidades de controle da doença, especialmente por meio das terapias modificadoras da doença (DMTs), que atuam em diferentes mecanismos imunológicos. O presente estudo teve como objetivo analisar os avanços e desafios relacionados ao uso das DMTs no tratamento da esclerose múltipla, destacando seus mecanismos de ação, eficácia clínica, limitações e perspectivas futuras, com base em evidências recentes. Trata-se de uma revisão integrativa da literatura, orientada pela questão norteadora sobre quais são as terapias modificadoras da doença no contexto da EM e seus principais avanços e desafios. A busca foi realizada nas bases de dados PubMed, SciELO, MEDLINE e LILACS, utilizando descritores combinados pelo operador *booleano "AND"*. Foram incluídos artigos publicados nos últimos cinco anos, disponíveis na íntegra e com metodologia compatível com o objetivo do estudo. Os resultados evidenciam que terapias de alta eficácia, como os anticorpos monoclonais anti-CD20 e o natalizumabe, apresentam importante redução na atividade inflamatória e na progressão da incapacidade. No entanto, limitações relacionadas à segurança, individualização terapêutica e baixa penetração no sistema nervoso central ainda persistem. Novas abordagens, como os inibidores de BTK e o uso de biomarcadores e inteligência artificial, mostram-se promissoras para o futuro do tratamento. Conclui-se que, embora haja avanços significativos no manejo da EM, a escolha terapêutica deve ser individualizada, considerando características clínicas e resposta ao tratamento, sendo essencial o desenvolvimento de estratégias que integrem controle inflamatório, neuroproteção e medicina personalizada.

Palavras-chave: Esclerose múltipla; Terapias modificadoras da doença; Anticorpos monoclonais; Tratamento.

Advances and Challenges in the Treatment of Multiple Sclerosis: The Role of Disease-Modifying Therapies

ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune, and neurodegenerative disease of the central nervous system, characterized by demyelination and progressive neurological disability. Although it has no cure, therapeutic advances have significantly expanded disease control possibilities, especially through disease-modifying therapies (DMTs), which act on different immunological mechanisms. This study aimed to analyze the advances and challenges related to the use of DMTs in the treatment of multiple sclerosis, highlighting their mechanisms of action, clinical efficacy, limitations, and future perspectives based on recent evidence. This is an integrative literature review guided by the research question regarding the disease-modifying therapies in the context of MS and their main advances and challenges. The search was conducted in the PubMed, SciELO, MEDLINE, and LILACS databases using descriptors combined with the Boolean operator "AND." Articles published in the last five years, with full-text availability and compatible methodology, were included. The results indicate that high-efficacy therapies, such as anti-CD20 monoclonal antibodies and natalizumab, significantly reduce inflammatory activity and disease progression. However, limitations related to safety, therapeutic individualization, and low penetration into the central nervous system remain. Emerging approaches, such as BTK inhibitors and the use of biomarkers and artificial intelligence, show promise for future treatment strategies. In conclusion, despite significant advances in MS management, therapeutic decisions should be individualized, considering clinical characteristics and treatment response, and should integrate inflammatory control, neuroprotection, and personalized medicine.

Keywords: Multiple sclerosis; Disease-modifying therapies; Monoclonal antibodies; Treatment.

Instituição afiliada – Universidade Federal da Grande Dourados (UFGD)[1]; Universidade Estadual de Mato Grosso do Sul (UEMS)[2].

Autor correspondente*: Dra Dioelen Virgínia Borges Souza de Aquino Coelho dioelemn.coelho@uems.br*

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune disease with neurodegenerative features that affects the central nervous system (CNS) and can lead to the progressive accumulation of irreversible clinical disabilities. MS is an incurable disease, but several treatment options continue to be studied and applied, significantly improving the quality of life of people with multiple sclerosis. (Chmielewska et al., 2023).

According to the literature, the highest prevalence of multiple sclerosis is found in countries of the European continent and the Americas, with environmental factors, lifestyle, and availability of medical resources influencing the observed gradient in countries with higher socioeconomic status. MS mainly affects women and the diagnosis is typically made around the age of 32 years, while late-onset multiple sclerosis is diagnosed around the age of 50 years (Lorenzut et al., 2025).

Currently, MS can be classified according to the clinical course in which it presents and manifests in patients. The first type is Clinically Isolated Syndrome (CIS), in which there is the first manifestation of the inflammatory demyelination characteristic of an MS episode. The second form is Relapsing-Remitting Multiple Sclerosis (RRMS), in which new symptoms arise or an objective worsening of previous symptoms is observed (Brasil, 2024), characterized by episodes of neurological dysfunction followed by partial or complete recovery (Al Anber et al., 2026).

The progressive stages of MS can be differentiated into Secondary Progressive Multiple Sclerosis (SPMS) or Primary Progressive Multiple Sclerosis (PPMS). SPMS is the phase that occurs after an initial RRMS course, in which the disease begins to progress and there is a worsening of neurological function, with or without relapses. PPMS, in turn, is characterized by a continuous progression of the disease from the onset of symptoms, which develop gradually and progressively, with an accumulation of disabilities and without a prior phase of remission and recurrence (Brasil, 2024).

MS begins with an immune response triggered by various factors that, despite being widely studied, remain incompletely understood, such as viral, environmental, and genetic predisposing factors. The CNS relies on the blood–brain barrier to selectively regulate cell entry; in MS this control is disrupted, leading to an unwanted activation of antigen-specific B

and T lymphocytes and triggering auto-destructive inflammatory processes (Mohammed, 2024).

Activation of peripheral antigen-presenting cells—such as dendritic cells (DCs), monocytes, macrophages, and tissue-resident cells (including CNS microglia)—stimulates autoreactive T and B cells in the context of failed autotolerance mechanisms mediated by regulatory cells (Tregs and Bregs). The migration of these effector leukocytes into the CNS is orchestrated by chemokines and facilitated by the interaction of integrins with the vascular endothelium of the blood–brain barrier, the integrity of which is already compromised by inflammatory cytokines secreted by immune cells. Within the CNS, neuroinflammation is perpetuated by the activation of resident microglia and the recruitment of pro-inflammatory M1 macrophages, which, together with reactive astrocytes and neutrophils, determine the extent of damage to myelin and oligodendrocytes (Mohammed, 2024; Piehl, 2021).

Although MS is an incurable disease, the last decades have seen an increase in the range of available therapeutic options. Disease-modifying therapies (DMTs), known to improve disease outcomes, act on specific immunological mechanisms involved in the pathology of MS (Mohammed, 2024). So far, DMTs have proved highly effective not only in early treatment but also in delaying more advanced stages of the disease (Lambert et al., 2024).

In this scenario, the growing number of research works and clinical studies on immunosuppressive therapeutic approaches in patients with multiple sclerosis makes it necessary to analyze the existing evidence. In this context, the present article aims to gather and critically evaluate current therapies, as well as their advances and challenges, supporting evidence-based clinical decision-making and contributing to improved quality of life for patients.

METHODOLOGY

This study is characterized as an integrative review, guided by the research question: “What are the disease-modifying therapies in the context of MS and what are their advances and challenges?” The search was carried out using the following databases: PubMed, Scientific Electronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (MEDLINE), and Latin American and Caribbean Literature in Health Sciences (LILACS).

The search strategy followed the Boolean operator "AND," used to combine terms. The search terms included: "multiple sclerosis AND central nervous system," "multiple sclerosis AND disease-modifying therapy," and "multiple sclerosis AND immunological factors." The inclusion criteria consisted of articles published in the last five years, with priority given to those from 2023 to 2026, articles using a systematic or integrative review methodology, and those with full-text availability. Articles published more than five years ago, studies with a methodology opposite to the one under investigation, and incomplete texts were excluded. The results were presented in a table listing the author, year of publication, title, database, and key findings.

RESULTS AND DISCUSSION

To compile the results of this research, 10,152 articles were analyzed, of which 40 were selected according to the criteria defined in the methodology. All included articles were carefully analyzed, as all are relevant, and for the composition of the framework, 23 articles were used (Table 1).

Table 1: Summary of the main articles highlighted by author, year of publication, database, title, and abstract.

Autor/Ano	**Título**	**Achados Importantes**
Bar-Or et al., 2021	Clinical Perspectives on the Molecular and Pharmacological Attributes of Anti-CD20 Therapies for Multiple Sclerosis.	He thoroughly explored the pharmacological properties of anti-CD20 monoclonal antibodies (mAbs): rituximab, ocrelizumab, ofatumumab, and ublituximab. A clear distinction was identified in the mechanisms of B cell depletion among the mAbs, in addition to pharmacodynamically divergent B cell repopulation patterns and variations in immunogenicity according to the molecular structure.
Dumitrescu	Beta interferons as	It reassessed the role of beta interferons

et al., 2021	immunotherapy in multiple sclerosis: a new outlook on a classic drug during the COVID-19 pandemic	(IFN-B) in the context of the COVID-19 pandemic, highlighting their safety and protective potential. The authors evidenced that IFN-B restores the Type I innate immune response, promoting the upregulation of class I MHC molecules and the induction of enzymes that degrade viral RNA.
Contentti et al., 2022	Current Perspectives: Evidence to Date on BTK Inhibitors in the Management of Multiple Sclerosis	BTKis showed dose-dependent efficacy in reducing T1 lesions with a favorable safety profile and mild effects. They act doubly: they inhibit peripheral B cells and modulate microglia/macrophages in the CNS via BBB penetration. The central potential is the control of compartmentalized inflammation and silent progression in RRMS and PMS..
Rowles et al., 2022	Transitioning From S1P Receptor Modulators to B Cell–Depleting Therapies in Multiple Sclerosis	In real-life scenarios, switching from S1P modulators to anti-CD20 showed slow and unpredictable recovery of absolute lymphocyte count (ALC). Prolonged washout increased the risk of disease reactivation, while early initiation of anti-CD20 did not raise severe infections in the short term, favoring rapid transition instead of waiting for lymphocyte normalization.
Arisi et al., 2023	Cladribine and ocrelizumab induce differential miRNA profiles in peripheral blood mononucleated cells from relapsing–remitting multiple	He compared the microRNA (miRNA) expression profiles in patients treated with Cladribine and Ocrelizumab. He also investigated how these high-efficacy therapies modulate post-transcriptional

	sclerosis patients	gene expression. He revealed that, although both are highly effective, they induce distinct miRNA signatures, suggesting different biological pathways of action in immune regulation.
Calfunao et al., 2023	Siponimod (BAF312): Características generales e implicancias clínicas de la dosificación farmacogenómica en el tratamiento de la Esclerosis Múltiple secundaria progresiva	Analyzed siponimod highlighting the need for personalized medicine in SPMS, since its metabolism depends on the CYP2C9 polymorphism. A prior pharmacogenetic test is recommended, being contraindicated in patients carrying the CYP2C933 variant. Interactions with CYP2C9 inhibitors and CYP3A4 inducers should also be considered.
Hartung et al., 2023	Bioavailable central nervous system disease-modifying therapies for multiple sclerosis	It identified, as a central discovery, that current DMTs, especially monoclonal antibodies, have insufficient penetration of the BBB to reach the CNS. BTKis emerge as the most promising class to modulate B lymphocytes, microglia, and macrophages in situ. Controlling progression requires a paradigm shift to therapies that target innate mechanisms and combat latent inflammation in the CNS.
Kappos et al., 2023	Ocrelizumab exposure in relapsing–remitting multiple sclerosis: 10-year analysis of the phase 2 randomized clinical trial and its extension	Provided long-term (10 years) evidence on the use of Ocrelizumab in patients with relapsing-remitting MS, derived from the extension of a phase 2 clinical trial. It demonstrated that no new safety signals emerged and that the efficacy in preventing

		relapses and disability was sustained.
Monschein et al., 2023	Real-world use of natalizumab in Austria: data from the Austrian Multiple Sclerosis Treatment Registry (AMSTR)	It analyzed data from up to 14 years of natalizumab use, confirming high efficacy in reducing relapses and stabilizing disability (EDSS). The main cause of discontinuation was seropositivity for the JC virus, reinforcing the management of PML risk in clinical practice.
Piacentini et al., 2023	Cognitive impairment in multiple sclerosis:"classic" knowledge and recent acquisitions	It highlighted the association of multiple sclerosis with motor, sensory, and cognitive deficits. The most common cognitive changes involve attention, information processing, memory, and executive functions, and may also affect social skills and decision-making.
Queiroz et al., 2023	Plasma exchange in inflammatory demyelinating disorders of the central nervous system: reasonable use in the clinical practice	It systematized the role of plasmapheresis (PLEX) in severe MS relapses, highlighting that the benefit is maximized in cases refractory to corticosteroids, with improvement rates between 42–78% in MS. Greater benefit was noted when started early, especially in humoral mechanisms (e.g., anti-AQP4). Five to seven sessions were suggested, with possible combined use with methylprednisolone in severe attacks.
Saponaro et al., 2023	Treatments of paediatric multiple sclerosis: Efficacy and tolerance in a	It retrospectively compared new therapies with interferon beta-1a in children with MS, demonstrating greater efficacy of modern

	longitudinal follow-up study	therapies, especially natalizumab, in reducing relapses and radiological activity in the pediatric setting.
Bou Rjeily et al., 2024	Highly Effective Therapy Versus Escalation Approaches in Early Multiple Sclerosis	It compared escalation (Interferons and Glatiramer) versus early high-efficacy therapy (Ocrelizumab, Ofatumumab, Natalizumab, Cladribine). The critical analysis favors the early use of high-efficacy therapy to prevent long-term disability, challenging the traditional escalation approach based on clinical and radiological outcomes.
Coyle et al., 2024	Sphingosine 1-phosphate receptor modulators in multiple sclerosis treatment: A practical review	He described the evolution of S1P modulators, highlighting that second-generation selective agents have a better pharmacokinetic profile. The selectivity for S1P1 and S1P5, associated with dose titration, maintains relapse reduction and preservation of brain volume, as well as promotes adherence, personalization, and faster lymphocyte recovery.
Moccia et al., 2024	Utilization of peginterferon-β-1a in the real-world practice for relapsing-remitting multiple sclerosis	Real-world data compared Peginterferon beta-1a to other injectables (Glatiramer, Interferon beta-1a SC). Due to the lower frequency of doses, Peginterferon was associated with higher adherence, persistence, and lower rates of switching to more expensive therapies or efficacy escalation compared to traditional injectables.

Morales et al., 2024	Importancia de la predicción temprana de la atrofia cerebral en pacientes con esclerosis múltiple	He emphasized that brain atrophy is an early marker of progression in multiple sclerosis, associated with worse clinical and cognitive outcomes. Its early detection through neuroimaging allows for better risk stratification and can guide earlier therapeutic decisions.
Chisari et al., 2025	Effectiveness of Rituximab in relapsing Multiple Sclerosis previously treated with highly-active disease modifying thErapies (RENEGADE study)	It evaluated Rituximab (RTX) as a rescue in patients with RRMS who discontinued high-efficacy therapies (Natalizumab, Fingolimod, Alemtuzumab, Cladribine, Cyclophosphamide, or Mitoxantrone) due to safety or therapeutic failure. RTX proved to be effective and safe, controlling inflammatory activity and stabilizing disability in these cases.
Franceschini et al., 2025	Lesion Location and Functional Connections Reveal Cognitive Impairment Networks in Multiple Sclerosis	It investigated 596 patients with MS, associating cognitive deficits with specific lesion patterns. Verbal memory was related to the parahippocampus, temporal pole, and cerebellum; verbal fluency to the thalamus, putamen, caudate, anterior cingulate, and cerebellum. There was no defined pattern for visual memory, fatigue, or depression, suggesting that these symptoms do not depend on the same lesion pattern.

Maersk-Moller et al., 2025	A National Danish Effectiveness Study of Ocrelizumab Versus Natalizumab in Multiple Sclerosis	It compared the effectiveness of Ocrelizumab and Natalizumab in RRMS through a national population registry. Both proved to be highly effective, with no significant differences in the risk of relapses, disability progression, or MRI activity. The study concludes that the therapies have equivalent efficacy for disease control.
Martin et al., 2025	A drug evaluation narrative review of cladribine as a treatment for multiple sclerosis	It characterized oral cladribine as a high-efficacy immune reconstitution therapy, administered in short cycles, with transient lymphopenia and lasting immune reconstitution. Phase 3 and real-world studies showed consistent reduction of disease activity, with a good safety profile and low treatment burden.
Moradi et al., 2025	Neurofilament Light Chain Concentration in the Prediction of Treatment Response in Multiple Sclerosis	It was evaluated whether age-adjusted serum neurofilament light chain (NfL) improves the prediction of response to Interferon β, Fingolimod, or Natalizumab. High NfL levels in Natalizumab were associated with less improvement in disability. It was concluded that NfL has limited additional clinical utility compared to the demographic data already available in patients with MS.

Willard et al., 2025	Combined magnetic resonance imaging and serum analysis reveals distinct multiple sclerosis types	Developed an AI model that integrates MRI and sNfL to classify MS subtypes. Identified a profile with early sNfL and higher inflammatory activity, and another with late sNfL and gradual degeneration. The model outperformed MRI alone in predicting progression, lesion activity, and treatment response.
Weatherley et al., 2026	Therapeutic targeting of oligodendrocytes in an agent-based model of multiple sclerosis	An open-source model simulated lesions in MS (T cells, macrophages, oligodendrocytes). Modulating the stress response of oligodendrocytes stabilized lesions. Complete prevention occurred when combining the control of BBB permeability with this stress response. The platform aimed to generate hypotheses about neuroimmune mechanisms and therapeutic strategies in MS.

Source: Authors, 2026.

Corroborating Rowles et al. (2022) and Saponaro et al. (2023), the findings of Cencioni et al. (2021) provide evidence that B cells not only act in antibody production in the pathogenesis of MS, but also perform critical functions as antigen-presenting cells (APCs) and secretors of pro-inflammatory cytokines, in addition to forming tertiary lymphoid structures in the meninges, which are associated with cortical neurodegeneration.

In clinical practice, as discussed by Bou Rjeily et al. (2024), anti-CD20 therapies have shown high efficacy in reducing MS relapses through the depletion of peripheral memory B cells. This consolidation of mAbs—such as Rituximab, Ocrelizumab, Ofatumumab, and Ublituximab—as high-efficacy therapies highlights that selective depletion of CD20+ B cells results in an effective and sustained reduction of focal inflammatory activity. As analyzed by Kappos et al. (2023) and Chisari et al. (2025), the clinical success of these molecules confirms

the critical role of B cells in the inflammatory cascade, with Ocrelizumab being the only therapy to demonstrate statistically significant efficacy in reducing disability progression in Primary Progressive MS (PPMS). Furthermore, the transition from chimeric antibodies to humanized and fully human molecules was interpreted as essential to reduce immunogenicity and allow self-administration (Frisch et al., 2021; Margoni et al., 2022; De Sèze et al., 2023).

Regarding the therapeutic use of Natalizumab, the findings of Monschein et al. (2023) show that there is a significant reduction in relapse rate and stabilization of disability progression measured by the EDSS. Furthermore, the study demonstrates that the main limitation of the continuous use of this medication is not related to loss of efficacy, but to safety issues associated with PML and JC virus seropositivity. In this context, Jeantin et al. (2023) demonstrated that a therapeutic strategy of extended-interval dosing with Natalizumab (6-week dosing interval instead of 4 weeks in the standard regimen) maintains clinical and radiological efficacy compared to the standard regimen, while mitigating the risk of PML, as evidenced in the first study. Lereim et al. (2024), in turn, deepens the understanding of the drug's mechanism of action, showing that Natalizumab not only acts as a peripheral immunosuppressant but also promotes a reduction of intrathecal inflammation, favoring neural repair and reinforcing the clinical findings of disability stabilization described by Monschein et al. (2023).

Moreover, the study by Saponaro et al., (2023) demonstrates that high-efficacy therapies, particularly Natalizumab, outperform interferon beta-1a in pediatric patients, both in relapse reduction and in radiological inflammatory activity. From this perspective, Bou Rjeily et al., (2024) question the classic therapeutic escalation model, arguing that early initiation of high-efficacy therapies (such as Natalizumab) is associated with better long-term outcomes, especially in preventing disability progression.

However, Maersk-Moller et al., (2025) adds a relevant piece of information: Natalizumab has comparable efficacy to Ocrelizumab in terms of relapse, overturning the idea of clear superiority between these high-efficacy therapies. This scenario is corroborated by Wessels et al., (2023) when comparing the pharmacokinetics and pharmacodynamics of a biosimilar to Natalizumab (PB006), validating therapeutic alternatives that allow expanded access to treatment without loss of efficacy, impacting public health policies and access to treatment. Moreover, when compared to Fingolimod in patients with rapidly progressing

severe disease in the context of the United Kingdom, Natalizumab was not only clinically more effective but also less costly to patients with this Multiple Sclerosis profile, according to MSBase records and economic modeling data (Spelman et al., 2024).

The study by Dumitrescu et al., (2021) reassessed the role of beta-interferons in modulating the innate immune response, primarily through activation of the type I interferon pathway and increased expression of class I MHC. When this type of therapy is analyzed in light of clinical data, it is observed that it is inferior compared to high-efficacy therapies, as previously mentioned. However, Moccia et al., (2024) demonstrated higher therapeutic adherence and a lower discontinuation rate in patients who used therapies based on interferon beta-1a, due to its lower frequency of administration. Therefore, although not competitive in efficacy, interferons can remain useful in strategic contexts, such as in patients with lower disease activity, when there is greater concern for safety, or when simplified therapeutic regimes are needed.

Still under the perspective of therapeutic strategies, Arisi et al. (2023) demonstrated that, despite presenting similar clinical efficacy, cladribine and ocrelizumab induce different profiles of immune mechanisms. Martin et al. (2025) characterized cladribine as an immune reconstitution therapy (IRT), based on cycles that induce transient lymphopenia, followed by the reconstitution of a functionally modified immune system. Kappos et al. (2023), on the other hand, states that ocrelizumab acts through continuous B cell depletion, maintaining sustained suppression of inflammatory activity over time. Thus, although often grouped as high-efficacy therapies in the context of MS, these drugs imply different variations in contexts such as infectious risk and the duration of effect after discontinuation of the medication, reinforcing the need for individualized approaches in the therapeutic decision-making process.

This need for therapeutic individualization becomes even more evident in the findings of Calfunao et al., (2023), who demonstrated that the presence of the CYP2C9*3*3 variant of the siponimod-metabolizing enzyme constitutes an absolute contraindication in the prescription of this medication. Moradi et al., (2025), on the other hand, evaluated the role of the neurofilament light chain (NFL) as a predictor of therapeutic response, showing that, although elevated levels are associated with worse outcomes in patients treated with Natalizumab, its additional utility is limited when assessed in isolation.

With this, Willard et al. (2025) demonstrated in their study that this limit is partially overcome when artificial intelligence (AI) is associated with the integration of magnetic resonance imaging data and biomarkers, where AI helped predict lesion activities over time, disease progression, and treatment response. These data demonstrate the critical need for therapeutic personalization in each case, integrating knowledge about currently used therapies, known biomarkers, and integrated AI-based models.

Within the structural context of disease progression, the data found by Morales et al., (2024) establish that cerebral atrophy is an early marker of MS progression, often preceding clinical manifestations such as changes in memory, information processing, and executive alterations, mentioned by Piacentini et al. (2023), associated with lesions in structures such as the thalamus and cerebellum evidenced by Franceschini et al., (2025) in their study. Thus, MS progression should not be understood as merely a process of brain volume loss, but as a progressive dysfunction of neurological networks that can manifest in different ways and, consequently, require different approaches according to each case, each patient, and their response to therapeutic regimens.

With progressive dysfunction and atrophy, it becomes evident that inflammation control must be able to reach the intracerebral compartment. However, this is where the limitations of current therapies arise; Hartung et al., (2023) highlighted that monoclonal antibodies have intrinsic limitations regarding penetration into the Central Nervous System (CNS). In this regard, to fill the gap, Geladaris et al., (2022) and Saberi et al., (2023) found that the transformative potential of BTKis lies in their ability to inhibit B cell receptor signaling and myeloid cell activation. As corroborated by Contentti et al., (2022), this approach represents a paradigm shift by targeting the 'dual face' of the pathology: BTKis control peripheral adaptive inflammation and, at the same time, modulate resident innate immunity, which distinguishes them from mAbs. Complementarily, Weatherley et al., (2026) suggested that long-term therapeutic success also depends on the reparative capacity of oligodendrocytes, demonstrating that lesion stabilization is enhanced when inflammation control is combined with the strengthening of cellular resilience via the integrated stress response (ISR).

FINAL CONSIDERATIONS

The comparative analysis between therapies shows that there is no absolute superiority among high-efficacy agents, highlighting the need for therapeutic individualization

based on clinical factors, safety profile, adherence, and patient characteristics. In this context, traditional therapies, such as beta-interferons, still remain applicable in specific scenarios, while advances such as biomarkers and artificial intelligence-based tools contribute to a more precise and personalized approach. Additionally, the heterogeneity of mechanisms of action among drugs reinforces the complexity of clinical decision-making.

Finally, important limitations persist related to the insufficient action of current therapies in the intrathecal compartment, where a significant part of disease progression occurs. In this scenario, Bruton's tyrosine kinase inhibitors emerge as a promising strategy by integrating effects on both peripheral and central immunity, pointing to a paradigm shift in MS treatment. Thus, the future of disease management tends to consolidate into integrated approaches that combine inflammatory control, neuroprotection, and therapeutic personalization.

REFERENCES

AL ANBER, Arwa et al. Therapeutic outcomes of fingolimod and interferon beta-1a in relapsing–remitting multiple sclerosis: a real-world study from Jordan. **Medicina**, v. 62, p. 203, 2026.

ARISI, Ivan et al. Cladribine and ocrelizumab induce differential miRNA profiles in peripheral blood mononucleated cells from relapsing–remitting multiple sclerosis patients. **Frontiers in Immunology**, v. 14, 2023.

BAR-OR, Amit et al. Clinical perspectives on the molecular and pharmacological attributes of anti-CD20 therapies for multiple sclerosis. **CNS Drugs**, v. 35, p. 985–997, 2021.

BOU RJEILY, Nicole et al. Highly effective therapy versus escalation approaches in early multiple sclerosis. **Neurologic Clinics**, v. 42, n. 1, p. 185–201, 2024.

BRASIL, Ministério da Saúde.Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Esclerose Múltipla (EM). **Portaria Conjunta SAES/SECTICS nº 8, de 12 de setembro de 2024**. Brasília: Ministério da Saúde, 2024

CALFUNAO, Susan et al. Siponimod (BAF312): características generales e implicancias clínicas de la dosificación farmacogenómica en el tratamiento de la esclerosis múltiple secundaria progresiva. **Revista Médica de Chile**, v. 151, p. 1375–1384, 2023.

CENCIONI, Maria et al. B cells in multiple sclerosis — from targeted depletion to immune reconstitution therapies. **Nature Reviews Neurology**, v. 17, p. 399–414, 2021.

CHMIELEWSKA, Natalia et al**.** Targeting CD20 in multiple sclerosis — review of current treatment strategies. **Neurologia i Neurochirurgia Polska**, v. 57, n. 3, p. 235–242, 2023.

CHISARI, Clara Grazia et al. Effectiveness of rituximab in relapsing multiple sclerosis previously treated with highly active disease modifying therapies (RENEGADE study). **Journal of Neurology**, v. 273, n. 47, 2026.

CONTENTTI, Edgar Carnero et al. Current perspectives: evidence to date on BTK inhibitors in the management of multiple sclerosis. **Drug Design, Development and Therapy**, v. 16, p. 2249–2263, 2022.

COYLE, Patricia et al. Sphingosine 1-phosphate receptor modulators in multiple sclerosis treatment: a practical review. **Annals of Clinical and Translational Neurology**, v. 11, n. 4, p. 842–855, 2024.

DE SÈZE, Jérôme et al. Anti-CD20 therapies in multiple sclerosis: from pathology to the clinic. **Frontiers in Immunology**, v. 14, 2023.

DUMITRESCU, L. et al. Beta interferons as immunotherapy in multiple sclerosis: a new outlook on a classic drug during the COVID-19 pandemic. **QJM: An International Journal of Medicine**, v. 114, p. 691-697, 2021.

FRANCESCHINI, Alessandro et al. Lesion location and functional connections reveal cognitive impairment networks in multiple sclerosis. **Annals of Clinical and Translational Neurology**, v. 13, p. 242-255, 2025.

FRISCH, Esther et al. A milestone in multiple sclerosis therapy: monoclonal antibodies against CD20—Yet progress continues. **Neurotherapeutics**,v. 18, p. 1602-1622, 2021.

GELADARIS, Anastasia et al. Bruton's tyrosine kinase inhibitors in multiple sclerosis: pioneering the path towards treatment of progression? **CNS Drugs**, v. 36, p. 1019-1030 2022.

HARTUNG, Hans-Peter et al. Bioavailable central nervous system disease-modifying therapies for multiple sclerosis. **Frontiers in Immunology**, v. 14, e1290666, 2023.

JEANTIN, Lina et al**.** Natalizumab extended-interval dosing in a real-life setting. **Journal of the Neurological Sciences**, v. 450, e120689, 2023.

KAPPOS, Ludwig et al. Ocrelizumab exposure in relapsing–remitting multiple sclerosis: 10-year analysis of the phase 2 randomized clinical trial and its extension. **Journal of Neurology**, v. 271, p. 642–657, 2024.

LAMBERT, Clare McGarvey et al. Real-world infection risk in multiple sclerosis patients on long-term immunomodulatory treatments. **Multiple Sclerosis and Related Disorders**, v. 94, e106236, 2024.

LEREIM, Ragnhild Reehorst et al. Natalizumab promotes anti-inflammatory and repair effects in multiple sclerosis. **PLoS ONE**, v.19, e0300914.

LORENZUT, Simone et al. Exploring the Pathophysiology, Diagnosis, and Treatment Options of Multiple Sclerosis. **Journal of integrative neuroscience**, v. 24, n. 1, p. 25081, Spring 2025.

MAERSK-MOLLER, Camilla et al. A national Danish effectiveness study of ocrelizumab versus natalizumab in multiple sclerosis. **European Journal of Neurology**, n. 2, e70507, 2025.

MARGONI, Monica et al. Anti-CD20 therapies for multiple sclerosis: current status and future perspectives. **Journal of Neurology**, v. 269, n. 3, p. 1203–1217, 2022.

MARTIN, Sarah-Jane; ARSENAULT, Shane; OH, Jiwon. A drug evaluation narrative review of cladribine as a treatment for multiple sclerosis. **Neurodegenerative Disease Management**, v. 15, n. 6, p. 323–339, 2025.

MOCCIA, M. et al. Utilization of peginterferon-β-1a in the real-world practice for relapsing-remitting multiple sclerosis. **European Review for Medical and Pharmacological Sciences**, v. 28, p. 411–418, 2024.

MOHAMMED, Eiman et al. Understanding multiple sclerosis pathophysiology and current disease-modifying therapies: a review of unaddressed aspects. **Frontiers in Bioscience (Landmark Edition)**, v. 29, n. 11, 2024.

MONSCHEIN, Tobias et al. Real-world use of natalizumab in Austria: data from the Austrian Multiple Sclerosis Treatment Registry (AMSTR). **Journal of Neurology**, v. 270, p.3779-3786, 2023.

MORADI, Nahidi et al. Neurofilament Light Chain Concentration in the Prediction of Treatment Response in Multiple Sclerosis. **European Journal of Neurology**, v. 33, e70505, 2026.

MORALES, Yanet Valdés; MESA, Carlos Jorge Hidalgo; CABRERA, Yalina Beatriz Bravo. Importancia de la predicción temprana de la atrofia cerebral en pacientes con esclerosis múltiple. **Medicent Electrón**, v. 28, e4270, 2024.

PIACENTINI, Chiara et al. Cognitive impairment in multiple sclerosis: “classic” knowledge and recent acquisitions. **Arquivos de Neuro-Psiquiatria**, v. 81, p. 585–596, 2023.

PIEHL, F. Current and emerging disease-modulatory therapies and treatment targets for multiple sclerosis. **Journal of internal medicine**. v. 289, p. 771-791.

QUEIROZ, André Luiz Guimarães de et al. Plasma exchange in inflammatory demyelinating disorders of the central nervous system: reasonable use in the clinical practice. **Arquivos de Neuro-Psiquiatria**, v. 81, p. 296–307, 2023.

ROWLES, William et al. Transitioning from S1P receptor modulators to B cell–depleting therapies in multiple sclerosis: clinical, radiographic, and laboratory data. **Neurology: Neuroimmunology & Neuroinflammation**, v. 9, e1183, 2022.

SABERI, Darius et al. Bruton’s tyrosine kinase as a promising therapeutic target for multiple sclerosis. **Expert Opinion on Therapeutic Targets**, v. 27, n. 4-5, p. 347–359, 2023.

SAPONARO, Anne-Charlotte et al. Treatments of paediatric multiple sclerosis: efficacy and tolerance in a longitudinal follow-up study. **European Journal of Paediatric Neurology**, v. 45, p. 22–28, 2023.

SPELMAN, Tim et al. Comparative effectiveness and cost-effectiveness of natalizumab and fingolimod in rapidly evolving severe relapsing-remitting multiple sclerosis in the United Kingdom. **Journal of Medical Economics**, v. 27, n. 1, p. 109–125, 2024.

WEATHERLEY, Georgia et al. Therapeutic targeting of oligodendrocytes in an agent-based model of multiple sclerosis. **PLoS Computational Biology**, v. 22, n. 1, e1013273, 2026.

WESSELS, Hendrik et al. Pharmacokinetic and pharmacodynamic similarity of biosimilar natalizumab (PB006) to its reference medicine: a randomized controlled trial. **Expert Opinion on Biological Therapy**, v. 23, n. 12, p. 1287–1297, 2023.

WILLARD, Charles et al. Combined magnetic resonance imaging and serum analysis reveals distinct multiple sclerosis types. **Brain**, v. 148, p. 4578–4591, 2025.