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MULTIPLE SCLEROSIS: NEW THERAPEUTIC HORIZONS

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory and autoimmune disease that affects the central nervous system, resulting in demyelination and progressive axonal degeneration. This study presents a narrative review of recent literature (2019-2024), focusing on therapeutic advances in MS, including disease-modifying therapies, neuromotor rehabilitation strategies and symptomatic management. Robust evidence indicates that early initiation of high-efficacy therapies (HETA) is associated with reduced relapse rates, less disability progression and better functional outcomes, even in patients with low initial lesion burden. In addition, rehabilitation based on innovative technologies and a multidisciplinary approach has had a positive impact on quality of life. The paradigm shift, which prioritizes early and more aggressive interventions, reflects the current understanding of MS pathophysiology, particularly the central role of B cells in perpetuating the inflammatory process. It is concluded that therapeutic personalization, combined with the early adoption of highly effective strategies, represents the best approach to modifying the course of the disease and preserving neurological function.
Keywords: Multiple sclerosis; Disease-modifying therapies; High therapeutic efficacy; Neuromotor rehabilitation; B cells; Early management.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune, demyelinating and neurodegenerative disease of the central nervous system, characterized by inflammatory processes, neuronal loss and gliosis, culminating in progressive neurological disability. Considered the leading cause of non-traumatic disability in young adults, its pathogenesis involves the autoreactive activation of T helper cells (CD4+), particularly pro-inflammatory sub-

types, which trigger the destruction of the myelin sheath and axons. T lymphocytes, as well as B cells, are selectively recruited during the inflammation generated by MS to an antigen expressed **only** in the central nervous system (CNS). This immune cascade, initially attributed exclusively to T cells, has recently been re-evaluated, with evidence highlighting the critical role of B cells in modulating the inflammatory response and disease progression (HAKI et al., 2024; HAUSER; CREE, 2020).

The traditional therapeutic approach, based on the initial use of low-efficacy agents (LETA), has been questioned by studies showing superior benefits with the early introduction of high-efficacy therapies (HETA). Randomized clinical trials and long-term population analyses reveal that HETA significantly reduces the annualized relapse rate (ARR) and disability progression, even in patients with low lesion burden on MRI. In addition, the improved safety profiles of the new HETA minimize historical risks associated with immunosuppressive drugs, in line with patients' growing preference for therapies that combine symptomatic control and prevention of degeneration (HAUSER; CREE, 2020; SELMAJ et al., 2024).

At the same time, advances in neuromotor rehabilitation have redefined the management of MS. Technologies such as transcranial magnetic stimulation, virtual reality and robot-assisted walking show potential for mitigating functional deficits such as spasticity, ataxia and dysphagia, improving quality of life and reducing socio-economic costs. These interventions, associated with physiotherapy and telerehabilitation protocols, broaden therapeutic options, especially in advanced stages where pharmacology alone is insufficient (DUAN et al., 2023).

Symptomatic treatment has also evolved, integrating multifaceted strategies. For spasticity, baclofen or gabapentin is combined with physiotherapy, while anticholinergics and intermittent self-catheterization address urinary incontinence. The management of psychological and cognitive comorbidities, coupled with high-fibre diets and lifestyle modifications, reinforces the need for therapeutic personalization. This holistic approach reflects the complexity of MS and the importance of early interventions to preserve neurological function. (HAKI et al., 2024)

Given this scenario, contemporary medicine emphasizes the critical therapeutic window in the early stages of MS, where vigorous inflammatory suppression can alter the course of the disease. The transition to HETA as first line, backed by robust evidence, represents a paradigm shift, prioritizing the prevention of disability over reactive models. However, continued research into pathogenic mechanisms and the development of even safer and more precise therapies remain imperative (HAKI et al., 2024; SELMAJ et al., 2024).

METHODOLOGY

This paper consists of a narrative literature review designed to synthesize recent evidence on therapeutic advances in multiple sclerosis (MS), with an emphasis on publications from the last five years (2019-2024). The search strategy was conducted in the PubMed database, using the controlled descriptors *Medical Subject Headings (MeSH)*: *"Multiple Sclerosis"*, *"Diagnosis"*, *"Treatment"* and *"Management"*. Filters were applied to human articles published in English or Portuguese and available in full text. The inclusion criteria prioritized original articles, systematic reviews and meta-analyses that addressed pathophysiological mechanisms, diagnosis, disease-modifying therapies, rehabilitation or symptomatic management of MS, as well as clinical (randomized, cohort, case-control) or pre-clinical studies with translational relevance. Exclusion criteria were case reports, case series, editorials, letters to the editor, non-peer-reviewed

studies, studies outside the thematic scope, duplicates or with insufficiently described methodology, as well as articles not indexed in PubMed or published outside the delimited period.

RESULTS AND DISCUSSION

The findings of this study consolidate the premise that early therapeutic intervention in relapsing-remitting multiple sclerosis (RRMS) is decisive in mitigating the progression of disability. Evidence derived from randomized clinical trials and long-term population cohorts, such as the Swedish STOP--MS project, showed that patients who started disease-modifying therapies (DMT) within one year of symptom onset had a 2.64 times lower risk of reaching EDSS 4 compared to those with late onset (after three years). These results were replicated in analyses of the Big Multiple Sclerosis Data (BMSD) network, with a cohort of 11,871 patients, where the group treated early (within 1.2 years) showed a statistically significant reduction in the risk of disabling outcomes ($p<0.0004$). Additionally, data from MSBase, involving 14,717 individuals, revealed that early treatment reduced relapses by 41% ($p=10-9$) and progression of EDSS by 19% ($p=0.043$), reinforcing the sustained efficacy of TMDs. Notably, these benefits were observed in both patients with relapse-dependent progression (RDW) and those with relapse-independent progression (PIRA), indicating that the early therapeutic window is universally relevant, regardless of disease subtype. (SELMAJ et al., 2024)

In the management of acute relapses, corticosteroids remain a fundamental intervention, acting to suppress inflammatory cytokines, inhibit the activation of T and B lymphocytes and reduce the infiltration of immune cells in the central nervous system. Comparative studies have confirmed that oral regimens of prednisone (1,250 mg/day) or methylprednisolone (1,000-1,250 mg/day) have equivalent efficacy to intravenous formulations, offering practicality and cost savings. However, adverse effects such as gastrointestinal disorders, hyperglycemia and osteoporosis require close monitoring. For refractory cases, plasma exchange (5-7 sessions over 14 days) has emerged as an alternative, although its application is limited by high costs and inconclusive evidence (HAKI et al., 2024).

The evolution of disease-modifying therapies has redefined the treatment paradigm, with the introduction of oral agents (dimethyl fumarate, fingolimod) and infusion drugs (natalizumab, ocrelizumab) that offer greater efficacy and adherence. Recent guidelines recommend high efficacy therapies (HETA) as first line for patients with active disease, while options such as interferon-β and glatiramer acetate remain indicated for less aggressive profiles. The transition to HETA after therapeutic failure is associated with better inflammatory control, as evidenced by clinical trials and observational studies. The stratification of disease aggressiveness into stages, combined with the evaluation of clinical markers (relapses, EDSS) and magnetic resonance imaging (new lesions or lesions with gadolinium enhancement), makes it possible to personalize strategies and optimize outcomes (HAKI et al., 2024).

The article by Selmaj et al. (2024) reinforces the paradigm shift in the treatment of relapsing-remitting multiple sclerosis (RRMS), by demonstrating that initiating high-efficacy therapies (HETA) from diagnosis results in superior benefits compared to the stepwise approach based on lower-potency drugs (LETA). Data derived from randomized and real-world studies, including propensity score analyses and marginal structural modeling, reveal that early use of HETA is associated with a lower annualized relapse rate, less disability accumulation and better maintenance of functional independence over time. The earlier and more inten-

se suppression of inflammation in the central nervous system provided by HETA makes it possible to reduce axonal loss and prevent irreversible clinical progression, especially when started in the "window of opportunity" of the first years of the disease. This growing body of evidence underpins the current recommendation to prioritize highly effective therapies as first line for most patients with RMS, regardless of initial lesion load or prognostic profile (SELMAJ et al., 2024).

Although stratification by prognostic factors is a useful tool in clinical practice, Selmaj et al. (2024) point out that multiple sclerosis remains a highly unpredictable disease, which makes therapeutic decisions based exclusively on predictive models difficult. Natural history studies show that variables such as age of onset, gender, type of initial symptom and lesion load on MRI have limited association with long-term outcomes, and that predictive models explain only part of the clinical variability. In addition, the concept of "benign" multiple sclerosis has been increasingly questioned, since many patients with an apparently indolent course in the first few years end up converting to progressive forms of the disease after long periods of follow-up. This degree of uncertainty justifies the adoption of more aggressive therapeutic strategies from the outset, in order to more effectively prevent irreversible axonal loss and the silent accumulation of disability (SELMAJ et al., 2024).

In recent years, understanding of the pathophysiology of multiple sclerosis has advanced significantly, especially in relation to the role of B cells. Previously seen only as an adjunct to the immune response, it is now known that these cells play a central role in the progression of the disease, such as the presentation of antigens, the production of autoantibodies and the activation of pro-inflammatory T cells. Based on this discovery, therapies aimed at B-cell depletion - such as ocrelizumab and ofatumumab - have gained prominence, especially in the relapsing-remitting form of the disease, with consistent results in reducing inflammatory lesions and slowing down the progression of disability. Although the effects are more discreet in the primary progressive form, the data suggest important benefits, consolidating these therapies as pillars in the current management of MS (HAUSER; CREE, 2020).

Alongside pharmacological advances, neurological rehabilitation has become increasingly essential in the treatment of MS, especially in the more advanced stages, when symptomatic control alone is not enough. The use of technologies such as repetitive transcranial magnetic stimulation, virtual reality and robotic gait aids has expanded therapeutic possibilities, promoting neuroplasticity and functional improvement. These resources, combined with physiotherapy and telerehabilitation programs, have contributed not only to the recovery of mobility and cognition, but also to the reduction of the inflammatory burden, as demonstrated by studies that observed a decrease in pro-inflammatory cytokines after rehabilitative interventions (DUAN et al., 2023).

Furthermore, another field that is expanding is the use of biomarkers to monitor the disease. Serum neurofilament light (NfL), for example, has been studied as a possible indicator of axonal damage, with a positive correlation with relapses, brain atrophy and the accumulation of lesions on magnetic resonance imaging. Although clinical use is still in the validation phase, the incorporation of markers such as NfL signals a promising path towards personalizing treatment, allowing for more precise therapeutic decisions. In addition, the combination of clinical, genetic and imaging data by means of predictive algorithms may, in the future, make risk stratification more efficient and favor the early adoption of highly effective therapies (SELMAJ et al., 2024).

CONCLUSION

Multiple sclerosis is a highly complex clinical challenge whose inflammatory, demyelinating and neurodegenerative nature requires early, individualized interventions based on solid scientific evidence. Advances in the elucidation of immunopathological mechanisms, notably the identification of the central role of B cells in mediating the inflammatory response, have catalyzed a restructuring of therapeutic strategies, with increasing emphasis on the early adoption of highly effective disease-modifying therapies (HETA). Consistent data from randomized clinical trials and real-world longitudinal registries support the idea that early institution of these therapies is associated with a significant reduction in relapse rates, attenuation of disability progression and more effective preservation of neurological function, even in patients with a low initial lesion burden.

At the same time, the incorporation of innovative neuromotor rehabilitation technologies and the implementation of integrated symptom management strategies have broadened the therapeutic scope, contributing substantially to improving quality of life and mitigating the social and economic costs associated with the disease. In this context, the adoption of a holistic approach - which takes into account physical, cognitive, emotional and social dimensions - is essential, especially given the marked phenotypic heterogeneity of MS.

In this way, a new paradigm of care is being consolidated, based on early identification of inflammatory activity, intensive intervention and personalization of therapeutic approaches, with a focus on preventing irreversible axonal damage. However, it remains imperative to continually invest in translational research and prospective studies to deepen our understanding of the determinants of therapeutic response, improve risk stratification models and expand the therapeutic arsenal with safer and more specific options. Only through this interdisciplinary and sustained effort will it be possible to make effective progress in reducing the individual and collective burden imposed by multiple sclerosis.

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