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From inflammation to repair: emerging therapeutic strategies for multiple sclerosis progression

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Abstract

Multiple sclerosis is an inflammatory, demyelinating, and neurodegenerative disease of the central nervous system for which therapeutic options have expanded considerably over recent decades. Although current disease-modifying therapies effectively suppress relapses and focal inflammatory activity in many patients, disability may continue to accumulate through progression independent of relapse activity (PIRA), highlighting the contribution of persistent compartmentalized CNS inflammation, axonal injury, and insufficient repair mechanisms that remain incompletely addressed. This narrative review aims to present and analyze the main therapeutic strategies targeting mechanisms involved in multiple sclerosis progression. For each of these directions, the available clinical results are discussed, together with the main limitations that currently prevent their widespread implementation in clinical practice. The studies reviewed indicate that several promising strategies may target disease mechanisms that are insufficiently influenced by current treatments. However, favorable effects on biological or imaging markers have not consistently translated into meaningful reductions in disability progression, highlighting the gap between measurable biological effects and clinical efficacy. Future treatment strategies may therefore require an integrated, mechanism-based approach combining control of peripheral and compartmentalized CNS inflammation with strategies aimed at limiting axonal injury and promoting remyelination and repair, supported by biomarker-guided patient selection.

Keywords: multiple sclerosis, emerging therapies, BTK inhibitors, remyelination, PIRA, compartmentalized CNS inflammation, biomarkers, precision medicine

Abbreviations: aHSCT – autologous hematopoietic stem cell transplantation; BTK – Bruton tyrosine kinase; CAR-T – chimeric antigen receptor T-cell; CNS – central nervous system; EBV – Epstein–Barr virus; EDSS – Expanded Disability Status Scale; GFAP – glial fibrillary acidic protein; ICANS – immune effector cell-associated neurotoxicity syndrome; MRI – magnetic resonance imaging; MS – multiple sclerosis; PIRA – progression independent of relapse activity; RRMS – relapsing-remitting multiple sclerosis; sGFAP – serum glial fibrillary acidic protein; sNfL – serum neurofilament light chain; SPMS – secondary progressive multiple sclerosis; TSPO – translocator protein.

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating, and neurodegenerative disease of the central nervous system characterized by a heterogeneous clinical course and the simultaneous involvement of immunological and neurodegenerative mechanisms. Despite major advances in controlling acute inflammation, the long-term accumulation of disability has not been fully addressed, and therapeutic options remain more limited when progressive disease mechanisms predominate [1, 2].

The understanding of MS progression has evolved with the development of the concept of progression independent of relapse activity (PIRA). PIRA represents an important component of disability accumulation and may occur across the spectrum of traditional MS phenotypes [3]. These observations support the concept that mechanisms responsible for progression may already be present during the early stages of the disease and challenge the strict distinction between relapsing and progressive phases.

The mechanisms underlying progression are complex and remain incompletely understood. Persistent and compartmentalized inflammation within the central nervous system, microglial and astrocytic activation, oxidative stress, metabolic and mitochondrial dysfunction, axonal loss, and insufficient endogenous repair mechanisms appear to contribute collectively to progressive neurological deterioration [1, 4]. Unlike the acute inflammation associated with relapses, these processes may persist within the CNS compartment and contribute to a form of chronic inflammation sometimes referred to as "smouldering inflammation" [4].

The aim of this narrative review is to analyze the main therapeutic strategies targeting key mechanisms involved in MS progression, including persistent CNS inflammation, axonal damage, and impaired repair mechanisms. Available evidence on BTK inhibitors, strategies aimed at limiting axonal damage and promoting remyelination and neural repair, modulation of compartmentalized CNS inflammation, cell-based therapies and immune reconstitution, Epstein–Barr virus targeting, selective immunotherapies, and biomarkers of disease progression and treatment response is discussed. Particular attention is given to the distinction between promising biological or imaging effects and the demonstration of a clinically meaningful benefit on disability progression.

Material and methods

This article was designed as a narrative review to analyze the main emerging therapeutic approaches in MS, particularly strategies targeting mechanisms involved in disease progression, neurodegeneration, and nervous tissue repair. The literature selection focused on relevant studies addressing Bruton tyrosine kinase (BTK) inhibitors, strategies aimed at limiting axonal damage and promoting remyelination and neural repair, modulation of microglia and compartmentalized CNS inflammation, cell-based therapies and immune reconstitution, Epstein–Barr virus targeting, selective immunotherapies, and biomarkers of disease progression and treatment response.

Relevant literature was identified through searches of the PubMed/MEDLINE bibliographic database. ClinicalTrials.gov was consulted to identify and verify information regarding clinical trials, including study design, endpoints, and reported results. Search terms used individually or in combination included "multiple sclerosis", "emerging therapies", "future therapies", "BTK inhibitors", "remyelination", "axonal regeneration", "microglia", "CNS inflammation", "hematopoietic stem cell transplantation", "CAR-T", "Epstein–Barr virus", "antigen-specific tolerance", "neurofilament light chain", "GFAP" and "precision medicine". Reference lists of relevant publications were also examined to identify additional studies.

Priority was given to clinical studies published in peer-reviewed journals, particularly randomized controlled trials and phase I–III clinical trials investigating the efficacy, safety, or biological effects of the therapeutic strategies analyzed. Recent reviews and synthesis articles were used to support the biological mechanisms and contextualize findings from original studies.

The study selection was not intended to constitute an exhaustive systematic search, but rather to identify representative publications for each therapeutic direction. For each strategy, the mechanism of action, main efficacy and safety findings, study limitations, and potential for translation into clinical practice were analyzed.

Given the narrative nature of the review, no meta-analysis or formal risk-of-bias assessment was performed. Nevertheless, the interpretation of the evidence sought to distinguish changes in biomarkers or imaging parameters from the demonstration of clinical benefits on relapses, disability progression, or neurological functional recovery. This approach allowed critical comparison of strategies with different levels of clinical evidence and therapeutic maturity and highlighted the major questions that remain open for future research.

Bruton tyrosine kinase (BTK) inhibitors

Bruton tyrosine kinase (BTK) inhibitors represent an emerging therapeutic approach in multiple sclerosis (MS), owing to their potential to

modulate both peripheral immune responses and inflammatory processes within the central nervous system (CNS). BTK is an intracellular non-receptor tyrosine kinase expressed predominantly in B lymphocytes and in cells of the myeloid lineage, including macrophages and microglia, where it plays an important role in receptor-mediated signaling and cellular activation. This broad expression pattern has generated interest in BTK inhibition as a potential strategy for targeting both B-cell–mediated immune responses in the periphery and myeloid-cell–driven inflammatory mechanisms within the CNS [5, 6].

Interest in this therapeutic class is particularly related to the role of B cells and microglia in maintaining compartmentalized CNS inflammation. Unlike anti-CD20 monoclonal antibodies, which deplete circulating B cells, BTK inhibitors primarily modulate B-cell signaling and function without directly depleting B cells. Moreover, because they are small molecules, some BTK inhibitors can cross the blood–brain barrier, potentially allowing them to influence inflammatory mechanisms directly within the CNS [5, 6]. However, CNS penetration, selectivity, and pharmacological properties differ among individual molecules; therefore, results obtained with one inhibitor cannot automatically be extrapolated to the entire class.

Early clinical evidence for BTK inhibition in MS was provided by evobrutinib, an oral selective BTK inhibitor. In the randomized phase II trial published by Montalban et al. in 2019, patients with relapsing MS were assigned to placebo, evobrutinib 25 mg once daily, 75 mg once daily, or 75 mg twice daily, while a reference group received dimethyl fumarate. The primary endpoint was the cumulative number of gadolinium-enhancing T1 lesions detected by MRI during weeks 12–24 [7].

Evobrutinib at a dose of 75 mg once daily significantly reduced MRI-detected inflammatory activity. The mean cumulative number of gadolinium-enhancing T1 lesions during weeks 12–24 was 3.85±5.44 in the placebo group, compared with 4.06±8.02 with evobrutinib 25 mg once daily, 1.69±4.69 with 75 mg once daily, and 1.15±3.70 with 75 mg twice daily. After adjustment for baseline disease activity, the rate ratio *versus* placebo was 0.30 for the 75-mg once-daily dose (95% CI 0.14–0.63; p=0.005), corresponding to an approximately 70% relative reduction in lesion number [7]. No significant difference *versus* placebo was demonstrated with the 25-mg once-daily dose, while the difference observed with 75 mg twice daily did not remain significant after adjustment for multiple comparisons.

Another BTK inhibitor of particular relevance is tolebrutinib, an oral covalent BTK inhibitor with CNS penetration. The phase IIb trial published by Reich *et al.* in 2021 evaluated once-daily doses of 5, 15, 30, and 60 mg in patients with relapsing MS. The study used a randomized, double-blind, placebo-controlled, dose-finding design, with the primary objective of evaluating the dose–response relationship for the number of new gadolinium-enhancing brain lesions [8].

The results demonstrated a clear dose–response relationship for MRI inflammatory activity, with the greatest effect observed at 60 mg/day. The mean number of new gadolinium-enhancing T1 lesions was 1.39 with 5 mg, 0.77 with 15 mg, 0.76 with 30 mg, and 0.13 with 60 mg, compared with 1.03 during the placebo period [8]. At 60 mg, the number of new gadolinium-enhancing T1 lesions was reduced by approximately 85%, while new or enlarging T2 lesions were reduced by approximately 89% compared with placebo [8]. These findings supported selection of the 60-mg dose for subsequent clinical development.

Phase III data, however, substantially nuanced this initial picture. In the evolutionRMS1 and evolutionRMS2 trials, evobrutinib was not superior to teriflunomide in reducing the annualized relapse rate: 0.15 *versus* 0.14 in evolutionRMS1 and 0.11 *versus* 0.11 in evolutionRMS2 [9]. Similarly, in GEMINI 1 and GEMINI 2, tolebrutinib did not significantly reduce the annualized relapse rate compared with teriflunomide [10]. In contrast, the HERCULES trial yielded a different and clinically relevant result for progressive disease mechanisms: among 1,131 patients with nonrelapsing secondary progressive MS, 6-month confirmed disability progression occurred in 22.6% of patients treated with tolebrutinib and 30.7% of those receiving placebo (HR=0.69; 95% CI 0.55–0.88; p=0.003) [11].

These findings led to the European Union approval of tolebrutinib (Cenrifki) in June 2026 for the treatment of adults with secondary progressive MS without relapses in the previous two years. This represents an important therapeutic advance for nonrelapsing SPMS and supports the potential relevance of targeting persistent CNS inflammation in disability progression. However, the clinical benefit must be considered alongside the risk of hepatotoxicity, which requires appropriate liver function monitoring during treatment.

Strategies targeting axonal and neuronal injury

Neuroprotection represents a major area of research in MS because disability accumulation is not determined exclusively by inflammatory activity and relapses. Axonal and neuronal loss, mitochondrial dysfunction, oxidative stress, excitotoxicity, and persistent activation of glial cells contribute to progressive nervous tissue damage

and become particularly important in progressive forms of the disease [12]. From this perspective, the objective of neuroprotective therapies differs from that of conventional anti-inflammatory treatments: rather than merely preventing new lesions, these therapies aim to limit structural damage to already vulnerable nervous tissue.

One molecule investigated in this context is ibudilast, a phosphodiesterase inhibitor with effects on several pathways involved in neuroinflammation. Its efficacy was evaluated in SPRINT-MS, a randomized, placebo-controlled phase II trial involving 255 patients with primary or secondary progressive MS. Patients received ibudilast at doses of up to 100 mg/day or placebo for 96 weeks. The primary endpoint was the rate of change in brain parenchymal fraction, used as a measure of brain atrophy [13].

The results showed a lower rate of brain atrophy in patients treated with ibudilast than in those receiving placebo. The estimated annual rate of change in brain parenchymal fraction was −0.0010 in the ibudilast group compared with −0.0019 in the placebo group, corresponding to an approximately 48% difference in the rate of progression of brain atrophy [13]. This finding provided a favorable imaging signal regarding the potential effect of ibudilast on brain tissue loss. However, the study did not demonstrate that the observed effect on brain atrophy translated into a corresponding reduction in clinical disability progression.

Another pharmacological approach investigated in progressive MS is simvastatin, evaluated in the MS-STAT trial. This randomized, double-blind, placebo-controlled phase II study included 140 patients with secondary progressive MS who received simvastatin 80 mg/day or placebo for 24 months. The primary endpoint was the annualized rate of brain atrophy assessed by magnetic resonance imaging [14].

Simvastatin treatment was associated with a significant reduction in the rate of brain volume loss. The annualized rate of brain atrophy was 0.288% in the simvastatin group and 0.584% in the placebo group, representing an approximately 43% reduction in the rate of brain atrophy after adjustment [14]. Treatment was generally well tolerated, with no major differences between groups in the proportion of participants experiencing serious adverse events. Although these findings suggest a potential effect on brain tissue loss, the phase II study was not sufficient to establish a definitive effect on long-term disability progression.

However, this promising Phase II atrophy signal did not translate into a clinical disability benefit in the subsequent Phase III MS-STAT2 trial. In MS-STAT2, simvastatin 80 mg was evaluated against placebo in secondary progressive multiple sclerosis with disability progression confirmed over time as the primary outcome. Despite the rationale that slowing neurodegeneration might reduce longer-term disability accumulation, the trial did not demonstrate a statistically significant slowing of EDSS-confirmed disability progression *versus* placebo. Together, MS-STAT and MS-STAT2 highlight a common translation gap in progressive MS therapeutics: improvements in imaging biomarkers such as brain atrophy rate may not necessarily predict effects on patient-centered disability outcomes, underscoring the need for biomarker–endpoint alignment when selecting neuroprotective strategies [15].

Remyelination

Remyelination represents an important therapeutic area in MS because current disease-modifying therapies do not directly restore myelin in established demyelinated lesions. Persistent demyelination increases axonal vulnerability and promotes axonal damage, thereby contributing to progressive disability accumulation. Remyelinating strategies therefore aim to stimulate oligodendrocyte precursor cell differentiation and restore the myelin sheath, with the goal of improving nerve conduction and protecting axons from further damage [16].

One of the first clinical demonstrations that remyelination might be pharmacologically enhanced was provided by the ReBUILD trial, published by Green *et al.* in 2017. This randomized, double-blind, placebo-controlled crossover study included 50 patients with relapsing MS and chronic demyelinating optic neuropathy receiving stable immunomodulatory treatment. Patients received clemastine fumarate 5.36 mg twice daily or placebo, and the primary endpoint was change in P100 latency measured using visual evoked potentials [17].

Clemastine reduced P100 latency delay by 1.7 ms per eye compared with placebo, a statistically significant difference (95% CI 0.5–2.9; p=0.0048) [17]. All 50 patients completed the study, and fatigue was the main treatment-associated adverse effect, with no serious adverse events reported. These findings were interpreted as an initial clinical proof of concept that myelin repair can be pharmacologically stimulated even in chronic demyelinating lesions. However, the small magnitude of the effect and limited sample size do not establish that this electrophysiological improvement translates into clinically meaningful long-term neurological recovery.

Another remyelination strategy was evaluated in the CCMR One trial, which investigated bexarotene, a non-selective retinoid X receptor agonist. The therapeutic rationale was based on preclinical evidence suggesting that activation of RXR-γ receptors may promote oligodendrocyte

differentiation and remyelination. The randomized, double-blind, placebo-controlled phase IIa trial included 52 patients with relapsing-remitting MS who were equally assigned to receive bexarotene or placebo for six months [18].

Unlike ReBUILD, the primary efficacy endpoint of CCMR One was not met. The change in magnetization transfer ratio was 0.25 percentage points in the bexarotene group and 0.09 in the placebo group, with an adjusted difference of 0.16 percentage points (95% CI −0.39–0.71; p=0.55) [18]. Tolerability was also an important limitation: all patients treated with bexarotene experienced at least one adverse event, and central hypothyroidism and hypertriglyceridemia were common. Five of the 26 participants treated with bexarotene discontinued therapy because of adverse events [18].

Targeting microglia, astrocytes, and compartmentalized CNS inflammation

Compartmentalized inflammation within the CNS is considered an important mechanism involved in MS progression, particularly when peripheral inflammatory activity and relapses become less evident. Activated microglia and astrocytes may maintain a persistent neuroinflammatory environment, contributing to oxidative stress, axonal injury, and neurodegeneration. At the same time, microglia also perform functions involved in nervous tissue homeostasis and repair, making their therapeutic modulation more complex than simply suppressing cellular activation [19].

The importance of microglia in disease progression is supported by molecular imaging studies that enable the assessment of immune cell activation within the CNS. Sucksdorff *et al.* used positron emission tomography (PET) with the radioligand [^{11}C]PK11195, which binds to the 18-kDa translocator protein (TSPO), to evaluate microglial and macrophage activation in patients with MS. The study included 69 patients with MS and 18 healthy controls, with participants followed clinically and by imaging for a mean period of approximately four years [20].

At baseline, patients with MS showed greater immune cell activation in normal-appearing white matter and the thalamus than healthy individuals. More importantly, increased activation in normal-appearing white matter was associated with a greater risk of subsequent disability progression (OR=4.26; p=0.048). Of the 69 patients, 51 experienced no relapses during follow-up. Within this subgroup, increased microglial/macrophage activation in normal-appearing white matter surrounding lesions remained associated with disability progression (OR=4.57; p=0.013) [20].

A pharmacological approach targeting innate immunity has been investigated using masitinib, an oral tyrosine kinase inhibitor acting on cell populations involved in chronic inflammation, including mast cells and microglia. Vermersch *et al.* evaluated masitinib in a randomized, double-blind, placebo-controlled phase III trial conducted across 116 centers in 20 countries. Patients with primary progressive or non-active secondary progressive MS without relapses during the previous two years were included, representing a particularly relevant population for investigating progression mechanisms independent of acute inflammation [21].

A total of 611 patients were randomized across the two parallel study groups. In the group evaluating the 4.5 mg/kg/day dose, 199 patients received masitinib and 101 received placebo. The primary endpoint was the overall change from baseline in EDSS score, repeatedly assessed between weeks 12 and 96 [21].

At 4.5 mg/kg/day, masitinib demonstrated a statistically significant benefit over placebo on the primary endpoint. The EDSS change was 0.001 in the masitinib group compared with 0.098 in the placebo group, corresponding to a between-group difference of −0.097 (97% CI −0.192 to −0.002; p=0.0256) [21]. Although statistically significant, the absolute between-group difference in EDSS was small, and the clinical relevance of this effect requires cautious interpretation and confirmation in further studies. In contrast, results for the dose-escalation regimen up to 6 mg/kg/day were inconclusive. The most common safety concerns included diarrhea, nausea, rash, and hematological events, with no increased risk of infection identified [21].

Cell-based therapies and immune system reconstitution

Cell-based therapies represent a different approach from conventional immunomodulatory treatments because they aim to profoundly modify the immune compartment involved in MS pathogenesis. Among the strategies investigated, autologous hematopoietic stem cell transplantation (aHSCT) is the most clinically advanced, whereas genetically modified T-cell therapies, such as anti-CD19 CAR-T cells, represent a much more recent and still experimental approach. Although both strategies involve cellular therapies, their main objective is immune reconstitution or modification rather than direct regeneration of nervous tissue.

Autologous hematopoietic stem cell transplantation aims to eliminate a substantial proportion of the autoreactive immune repertoire

through a conditioning regimen, followed by immune system reconstitution from autologous hematopoietic stem cells. One of the most important randomized evaluations of this strategy was the MIST trial, published by Burt *et al.* in 2019. The study included 110 patients with relapsing-remitting MS, with a mean age of 36 years, who had experienced at least two relapses while receiving disease-modifying treatment during the previous year and had EDSS scores ranging from 2.0 to 6.0. Patients were randomized to receive nonmyeloablative aHSCT or a disease-modifying therapy of greater efficacy or from a different class than their previous treatment [22].

The primary endpoint was disease progression, defined as an increase of at least one point in EDSS score confirmed at two assessments six months apart. During follow-up, progression occurred in 3 patients in the aHSCT group compared with 34 patients receiving disease-modifying therapies. Median time to progression could not be calculated in the aHSCT group because of the small number of events, whereas it was 24 months in the comparator group. The risk of progression was significantly lower following transplantation (HR=0.07; 95% CI 0.02–0.24; p<0.001) [22].

Important differences were also observed in disability outcomes. After the first year, mean EDSS score decreased from 3.38 to 2.36 in the aHSCT group, whereas it increased from 3.31 to 3.98 in the disease-modifying therapy group. The mean between-group difference was −1.7 points (95% CI −2.03 to −1.29; p<0.001) [22]. No deaths or grade 4 non-hematological toxicities were reported among patients who underwent transplantation. These findings were obtained in patients with highly active relapsing-remitting MS and should not be extrapolated to disability progression occurring independently of inflammatory disease activity.

A much more recent cellular approach involves T cells expressing chimeric antigen receptors (CAR-T cells). In MS, interest has focused on targeting CD19, which is expressed across a broad range of B-lineage cells. The rationale is to achieve profound B-cell depletion, potentially affecting B-cell populations involved in compartmentalized CNS inflammation.

In 2024, Fischbach *et al.* reported the first two cases of patients with progressive MS individually treated with KYV-101, a fully human anti-CD19 CAR-T-cell therapy [23]. The primary objective of these initial treatments was to evaluate feasibility and safety, given that CAR-T therapies may be associated with important adverse reactions, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS).

In both patients, anti-CD19 CAR-T-cell administration showed an initially acceptable safety profile. An important finding was the detection and expansion of CAR-T cells in the cerebrospinal fluid without the occurrence of ICANS. In one patient, a marked reduction in intrathecal antibody production was also observed following treatment, persisting through day 64 [23]. These observations suggest that CAR-T cells can reach the CNS compartment and exert biological effects on CD19-positive cells within this environment. However, evidence from two patients establishes feasibility and biological activity rather than clinical efficacy, which requires evaluation in larger controlled studies.

Targeting Epstein–Barr virus

Epstein–Barr virus (EBV) has emerged as an important therapeutic target in MS research because of increasingly consistent evidence supporting its involvement in disease pathogenesis. EBV infection almost invariably precedes the development of MS, and viral persistence in B lymphocytes has led to the hypothesis that latently infected cells may contribute to maintaining autoreactive immune responses and chronic inflammation. This perspective has encouraged the development of strategies aimed at intervening closer to a potential etiological factor rather than exclusively targeting its inflammatory consequences [24].

An important epidemiological argument supporting this direction was provided by the longitudinal study published by Bjornevik *et al.* in 2022. The authors analyzed a cohort of more than 10 million young adults serving in the United States military, of whom 955 were diagnosed with MS during follow-up. The risk of developing MS increased approximately 32-fold following EBV infection, while increases in serum neurofilament light chain concentrations were observed after EBV seroconversion [24]. These findings strongly support the temporal relationship between EBV infection and subsequent MS development, although they do not demonstrate that targeting the virus after disease onset can alter disease progression.

One of the first attempts to directly test this therapeutic hypothesis was performed by Pender *et al.*, who investigated adoptive immunotherapy using autologous EBV-specific T cells in patients with progressive MS. This open-label phase I study included 10 patients, five with secondary progressive MS and five with primary progressive MS [25].

For each patient, autologous EBV-specific T cells targeting the viral antigens EBNA1, LMP1, and LMP2A were generated *ex vivo*. Patients received four T-cell infusions at two-week intervals. The primary objective was to evaluate the safety and tolerability of the strategy, while clinical efficacy was an exploratory outcome [25].

Treatment was generally well tolerated, with no serious adverse events reported. Of the 10 patients who completed treatment, seven showed

clinical improvement, and six demonstrated both symptomatic improvement and objective neurological improvement. Reduced fatigue and improved quality of life were also reported, while three patients showed reduced intrathecal IgG production [25]. All six patients who received cell products with strong EBV reactivity showed clinical improvement, compared with only one of four patients who received cells with weak reactivity (p=0.033) [25].

Further development of this strategy led to the investigation of ATA188, an allogeneic EBV-specific cytotoxic T-cell immunotherapy designed to recognize and eliminate EBV-infected cells. Unlike the autologous approach, ATA188 was developed as a standardized allogeneic cellular product. Its efficacy and safety were evaluated in the EMBOLD study (NCT03283826), a phase I/II trial in patients with progressive forms of MS. The randomized part of the study used a double-blind, placebo-controlled design and evaluated the effect of treatment on disability [26].

The EMBOLD study was subsequently terminated after the primary endpoint of confirmed disability improvement at 12 months was not achieved [26]. This finding is important when interpreting anti-EBV strategies: a strong etiological association between EBV infection and MS does not automatically imply that eliminating infected cells after disease onset will halt progression. Consequently, EBV-specific immunotherapy remains biologically plausible, but its clinical efficacy must be demonstrated in controlled trials.

Selective immunotherapies and antigen-specific tolerance

The development of more selective immunotherapeutic strategies represents an important direction in MS treatment. High-efficacy therapies can effectively control inflammatory activity; however, broad modification of the immune response may be associated with an increased risk of infection and other consequences of immunosuppression. An alternative approach involves targeting well-defined immunological pathways or, at an even greater level of selectivity, inducing tolerance to antigens involved in the autoimmune response. The ultimate goal is to control pathological autoimmunity while preserving, as far as possible, the protective functions of the immune system [27].

One such strategy involves blocking the CD40–CD40L costimulatory pathway. The interaction between CD40 and its ligand CD40L contributes to adaptive immune activation and communication among T lymphocytes, B lymphocytes, and antigen-presenting cells. Frexalimab is a next-generation monoclonal antibody directed against CD40L and designed to inhibit this pathway without directly depleting lymphocyte populations [28].

Vermersch *et al.* evaluated frexalimab in a randomized, double-blind, placebo-controlled phase II trial involving 129 participants with relapsing MS. Patients were assigned to receive intravenous frexalimab 1200 mg every four weeks following an 1800-mg loading dose, subcutaneous frexalimab 300 mg every two weeks following a 600-mg loading dose, or matching placebo. The primary endpoint was the number of new gadolinium-enhancing T1 lesions at week 12 [28].

At week 12, the adjusted mean number of new gadolinium-enhancing T1 lesions was 0.2 in the 1200-mg intravenous frexalimab group and 0.3 in the 300-mg subcutaneous group, compared with 1.4 in the placebo group. The rate ratio *versus* placebo was 0.11 (95% CI 0.03–0.38) for intravenous administration and 0.21 (95% CI 0.08–0.56) for subcutaneous administration [28]. Secondary imaging endpoints showed findings in the same direction, supporting the biological effect of CD40L blockade on inflammatory activity.

During the 12-week double-blind period, the most frequent adverse events were COVID-19 infection and headache. The findings support continued investigation of selective CD40–CD40L pathway blockade in MS; however, the short study duration and predominantly imaging-based endpoint do not allow conclusions regarding effects on relapses or long-term disability progression. Larger and longer-duration studies are required to establish the efficacy and safety of this strategy [28].

An even more selective approach involves the induction of antigen-specific tolerance. Unlike generalized immunosuppression, this strategy seeks to reduce immune responses against self-antigens involved in disease pathogenesis without globally suppressing the immune system. In MS, myelin proteins represent some of the targets under investigation, and inducing tolerance to these proteins could theoretically limit autoreactive responses while preserving immunity against unrelated antigens [27, 29].

Ten patients were enrolled in this single-center, open-label, dose-escalation phase I trial; nine received treatment, including seven patients with relapsing-remitting MS and two with secondary progressive MS. Patients received a single infusion of autologous peripheral blood mononuclear cells coupled *ex vivo* to seven peptides derived from three myelin proteins: myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP), and proteolipid protein (PLP) [29].

The primary objective was to assess the feasibility, safety, and tolerability of the intervention. Administration of myelin peptide-coupled cells was feasible and well tolerated, with a favorable

safety profile. Clinical and imaging assessments did not indicate obvious disease activation induced by administration of myelin antigens [29].

A particularly important finding was observed among patients who received higher doses of peptide-coupled cells, exceeding 1×10^9 cells. These patients showed reduced T-cell responses specific to myelin antigens after treatment [29]. This effect supports the possibility of inducing antigen-specific tolerance in humans and is particularly relevant because the strategy seeks to selectively reduce autoreactivity rather than broadly inhibit immune responses.

However, the study included only nine patients, lacked a comparator group, and was primarily designed to assess safety and immunological mechanisms. Therefore, the findings do not allow conclusions regarding clinical efficacy, relapse reduction, or prevention of disability progression. Furthermore, the development of antigen-specific tolerance in MS is complicated by the heterogeneity of immune responses and by the fact that the antigens responsible for disease initiation and maintenance have not been fully defined [27, 29].

Biomarkers of disease activity and progression

The clinical and biological heterogeneity of MS makes it difficult to apply the same therapeutic strategy to all patients. Disease course, the relative contribution of acute inflammation and neurodegenerative processes, and responses to disease-modifying therapies vary considerably among individuals. In this context, biomarkers may help estimate an individual's risk of disease activity and progression, monitor treatment response, and support treatment selection according to the predominant disease mechanisms.

One of the most extensively studied biomarkers is serum neurofilament light chain (sNfL), which is released following axonal injury. Although elevated sNfL levels have been associated with disease activity and treatment response, the use of this marker at the individual level has been limited by the influence of physiological factors, particularly age and body mass index. To address this limitation, Benkert *et al.* developed a reference-value and Z-score system that allows sNfL to be interpreted according to individual patient characteristics [30].

The study used a reference database comprising 10,133 blood samples from 5,390 individuals without evidence of CNS disease from four cohorts in Europe and North America. The system was subsequently tested in the Swiss Multiple Sclerosis Cohort, including 1,313 individuals with MS and 7,769 samples, and validated in an independent cohort of 4,341 patients from the Swedish Multiple Sclerosis Registry [30].

sNfL concentrations increased with age, particularly after approximately 50 years, confirming the need to adjust values for individual factors. Among patients with MS, sNfL percentiles and Z scores showed progressive associations with both subsequent acute disease activity, represented by relapses and new lesion formation, and disability worsening. An sNfL Z score greater than 1.5 was associated with an increased risk of subsequent clinical or imaging activity (OR=3.15; 95% CI 2.35–4.23; p<0.0001). The association persisted among patients considered clinically and radiologically stable at the time of assessment (OR=2.66; 95% CI 1.08–6.55; p=0.034) [30].

However, sNfL primarily reflects axonal injury and is substantially influenced by acute inflammatory activity. Identifying biomarkers more closely associated with progression independent of relapses is therefore a priority. An important candidate is serum glial fibrillary acidic protein (sGFAP), an astrocytic structural protein that may provide information complementary to sNfL.

Meier *et al.* analyzed the roles of sGFAP and sNfL in MS progression in a cohort study based on data from the Swiss Multiple Sclerosis Cohort. The study included 355 patients with MS and 259 healthy controls, with patients analyzed in two cohorts to assess the relationship between biomarkers, disability progression, and acute inflammatory activity [31].

Among patients with progressive disease and disability worsening, sGFAP levels were 50.9% higher than among patients with stable disability after additional adjustment for sNfL. Higher baseline sGFAP levels were also associated with accelerated loss of cerebral gray matter volume, with each doubling of sGFAP associated with an additional loss of approximately 0.24% per year (p<0.001) [31]. Unlike sNfL, sGFAP values did not change significantly during exacerbations compared with remission periods, suggesting a weaker association with acute focal inflammation.

The prognostic value of sGFAP was further supported by the analysis of patients who subsequently developed confirmed disability worsening. These patients had higher baseline sGFAP Z scores than patients with stable disability. Moreover, concomitant elevation of sGFAP and sNfL was associated with an approximately four- to five-fold increased risk of confirmed disability worsening (HR=4.09; 95% CI 2.04–8.18; p<0.001) and PIRA (HR=4.71; 95% CI 2.05–9.77; p<0.001) [31].

Discussion

The analysis of emerging therapeutic strategies highlights an important shift in the approach

to MS. The eight directions examined in this review have different levels of clinical evidence and therapeutic maturity and target distinct components of the disease process, ranging from peripheral and compartmentalized CNS inflammation to axonal damage, remyelination, and biomarker-guided treatment selection.

Taken together, the available evidence does not support the existence of a single strategy capable of addressing all mechanisms involved in MS. Rather, the findings suggest the need for an integrated therapeutic approach involving control of peripheral and compartmentalized CNS inflammation, limitation of axonal damage, and, when biologically feasible, promotion of remyelination and nervous tissue repair. These objectives are not interchangeable, and future studies should use endpoints adapted to the mechanism being investigated.

Despite these limitations, the overall direction of research is clear. The future of MS therapy appears to be shifting from a model focused predominantly on relapse prevention toward one simultaneously addressing inflammation, progression, and repair. In this context, integrating targeted therapies with biomarkers of disease progression and treatment response may support more individualized, mechanism-based treatment selection.

Future developments in MS treatment will depend largely on the ability to control the mechanisms responsible for disability progression rather than only the inflammatory activity associated with relapses. Progression independent of relapse activity (PIRA) is increasingly recognized as an important component of disability accumulation, creating a need for therapies and endpoints capable of capturing progressive disease mechanisms [32]. In this context, compartmentalized CNS inflammation, glial activation, axonal damage and impaired remyelination represent priority therapeutic targets.

Within this model, the future of MS therapy does not appear to belong to a single pharmacological class, but rather to an integrated approach addressing complementary objectives: controlling peripheral and compartmentalized inflammation, protecting nervous tissue, and promoting remyelination and repair of existing lesions. The success of this transition will depend not only on the development of effective therapies, but also on identifying the appropriate patient, the optimal timing of intervention, and endpoints capable of demonstrating meaningful clinical benefit.

Conclusions

Therapeutic advances over recent decades have significantly changed the course of MS, particularly through improved control of relapses and inflammatory activity. Nevertheless, disability accumulation independent of relapses, compartmentalized CNS inflammation, and progressive nervous tissue loss remain inadequately controlled by current therapies. For this reason, future therapeutic strategies will need to address mechanisms of progression that remain insufficiently controlled by current treatments, including compartmentalized CNS inflammation, axonal damage, and impaired repair.

In the future, MS treatment may evolve toward an integrated approach combining control of peripheral and compartmentalized CNS inflammation with strategies aimed at limiting axonal damage and promoting remyelination and repair. Integration of biomarkers with clinical and imaging data may enable more precise patient selection and identification of the optimal timing for each intervention. Thus, the therapeutic goal in MS is expanding beyond relapse prevention toward preventing disability progression, preserving neurological function, and promoting repair.

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Conflict of interest

The authors declare no conflict of interest.

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