



International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	MULTIPLE SCLEROSIS: NEW IMMUNOMODULATORY STRATEGIES AND BIOMARKERS
----------------------	--

DOI	https://doi.org/10.31435/ijitss.3(51).2026.6099
------------	---

RECEIVED	13 July 2026
-----------------	--------------

ACCEPTED	15 September 2026
-----------------	-------------------

PUBLISHED	28 September 2026
------------------	-------------------

LICENSE	 The article is licensed under a Creative Commons Attribution 4.0 International License .
----------------	--

© The author(s) 2026.

This article is published as open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

MULTIPLE SCLEROSIS: NEW IMMUNOMODULATORY STRATEGIES AND BIOMARKERS

Natalia Kitala

Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

ORCID ID: 0009-0003-6357-3877

Justyna Karliczek

Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

Katarzyna Nycz

Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

ORCID ID: 0009-0001-0897-6855

Julia Knap

Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

ORCID ID: 0009-0003-6386-0833

Jędrzej Sztajura (Corresponding Author, Email: j.sztajura15@wp.pl)

Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

ORCID ID: 0009-0009-8975-731X

ABSTRACT

Introduction and purpose: Multiple Sclerosis (MS) disability accumulation is driven primarily by compartmentalized, subclinical neuroinflammation and diffuse neurodegeneration, termed smouldering MS. While traditional disease-modifying therapies (DMTs) control peripheral relapses and focal MRI activity, halting this progression remains a major challenge. Consequently, the therapeutic landscape is shifting toward novel central nervous system-targeting strategies to prevent Progression Independent of Relapse Activity (PIRA). The clinical utility of these interventions relies on highly sensitive fluid biomarkers, including serum neurofilament light (sNfL), serum glial fibrillary acidic protein (sGFAP), and kappa free light chains (kFLC), to track neuroaxonal injury, astrogliosis, and intrathecal immunoglobulin synthesis. This review evaluates the latest clinical evidence for next-generation immunomodulatory therapies, specifically autologous hematopoietic stem cell transplantation, Bruton's tyrosine kinase inhibitors, and anti-CD20 monoclonal antibodies, alongside the diagnostic and prognostic roles of these emerging biomarkers.

Materials and methods: The literature search was performed using PubMed, Scopus, Web of Science, and Google Scholar for articles published between 2020 and 2026. Keywords included: "multiple sclerosis", "MS", "serum neurofilament light", "sNfL", "serum glial fibrillary acidic protein", "sGFAP", "kappa free light chains", "kFLC", "autologous hematopoietic stem cell transplantation", "aHSCT", "brutons tyrosine kinase inhibitors", "BTK inhibitors", "tolebrutinib", "anti-CD20", "ofatumumab", and "ublituximab".

Conclusion: Preventing PIRA requires a paradigm shift toward early, high-efficacy DMT utilization guided by multimodal biomarker profiling (sNfL, GFAP, kFLC). Although socioeconomic barriers often restrict early access, long-term pharmaco-economic data demonstrate that timely intervention mitigates the substantial financial and societal burden of accumulated disability. Ultimately, combining these proactive clinical strategies with emerging therapeutic mechanisms, such as NLRP3 inflammasome inhibition or selective remyelination, offers the most promising avenue to alter the disease course and optimize healthcare resource utilization.

KEYWORDS

Multiple Sclerosis, Progression Independent of Relapse Activity, Fluid Biomarkers, Disease-Modifying Therapies, Pharmaco-economics

CITATION

Kitala, N., Karliczek, J., Nycz, K., Knap, J., & Sztajura, J. (2026). Multiple sclerosis: New immunomodulatory strategies and biomarkers. *International Journal of Innovative Technologies in Social Science*, 3(51). [https://doi.org/10.31435/ijitss.3\(51\).2026.6099](https://doi.org/10.31435/ijitss.3(51).2026.6099)

COPYRIGHT

© The author(s) 2026. This article is published as open access under the **Creative Commons Attribution 4.0 International License (CC BY 4.0)**, allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS), historically characterized by peripheral immune cell infiltration and acute focal demyelination. The highest prevalence of MS is encountered in European Countries and the Americas, with 111 to 300 cases per 100,000 inhabitants [1]. While traditional DMTs have achieved substantial success in controlling peripheral driven relapses and magnetic resonance imaging (MRI) lesion activity, halting insidious progression remains a formidable challenge. Recent pathophysiological insights indicate that long term disability accumulation is primarily driven by compartmentalized, subclinical neuroinflammation and diffuse neurodegeneration, a phenomenon often referred to as smouldering MS [2].

To effectively address this underlying pathology, the therapeutic landscape is shifting toward novel immunomodulatory strategies capable of targeting central nervous system mechanisms. Concurrently, the clinical utility of these advanced interventions relies heavily on the availability of highly sensitive, reproducible biomarkers that can track neuroaxonal injury, astrogliosis, and intrathecal immunoglobulin synthesis. This review evaluates the latest clinical evidence surrounding next generation immunomodulatory therapies, including autologous hematopoietic stem cell transplantation, Bruton's tyrosine kinase inhibitors, and anti-CD20 monoclonal antibodies, while exploring the diagnostic and prognostic roles of emerging fluid biomarkers.

Methodology

A comprehensive literature search was conducted to identify studies evaluating the new immunomodulatory strategies and biomarkers used in studying MS. The search was performed using PubMed, Scopus, Web of Science, and Google Scholar for articles published between 2020 and 2026. Keywords included: "multiple sclerosis", "MS", "serum neurofilament light", "sNfL", "serum glial acidic protein", "sGFAP", "kappa free light chains", "kFLC", "autologous hematopoietic stem cell transplantation", "aHSCT", "bruton's tyrosine kinase inhibitors", "BTK inhibitors", "tolebrutinib", "anti-CD20", "ofatumumab", and "ublituximab". Additional relevant publications were identified through a manual review of the reference lists of selected articles.

Biomarkers

Serum Neurofilament Light

Neurofilaments are major structural cytoskeletal proteins that are released into the cerebrospinal fluid (CSF) and subsequently into the bloodstream following neuroaxonal damage. Elevated CSF NfL (cNfL) levels strongly correlate with the infiltration of T lymphocytes, which drive the focal inflammation characteristic of MS and contribute to the transition from Relapsing Remitting MS (RRMS) to Secondary Progressive MS (SPMS). Clinically, a robust positive correlation exists between cNfL and sNfL concentrations, with cNfL levels remaining approximately 42-fold higher than those in peripheral blood [3].

Although cNfL provides a direct snapshot of central nervous system pathology, its quantification requires an invasive lumbar puncture. Measuring sNfL offers a far more accessible, minimally invasive alternative. However, traditional analytical methods long hindered its routine clinical adoption. Conventional enzyme-linked immunosorbent assays (ELISA) and electrochemiluminescence (ECL) assays lacked the analytical sensitivity required to detect the minuscule concentrations of NfL present in peripheral blood. This technological barrier was recently overcome by the development of the Single Molecule Array (SiMoA) platform. Boasting a 25-fold higher sensitivity compared to ECL, the SiMoA assay allows for the precise, reliable quantification of sNfL, thereby establishing it as a cornerstone biomarker for monitoring neuroaxonal injury in MS [4].

Serum Glial Fibrillary Acidic Protein

Glial Fibrillary Acidic Protein (GFAP) is the principal intermediate filament protein found in mature astrocytes and serves as a highly specific indicator of astrocyte activation and structural damage. In MS, marked upregulation of GFAP is characteristic of active plaque formations, reflecting reactive astrogliosis. Historically, quantification was limited to the CSF, where significantly elevated GFAP levels were observed in SPMS compared to RRMS, strongly correlating with sustained disability accumulation and neurological dysfunction [3].

Similar to sNfL, recent advances in SiMoA technology have enabled the precise measurement of brain derived GFAP directly from peripheral blood, bypassing its low baseline concentrations in systemic circulation. Serum levels of GFAP are significantly elevated in MS patients compared to healthy controls, with a pronounced distinction observed across clinical phenotypes. Specifically, sGFAP concentrations are notably higher in progressive subtypes, including PPMS and SPMS, than in RRMS, whereas patients with stable RRMS often display sGFAP levels comparable to healthy cohorts [4,5].

Crucially, emerging multicenter evidence demonstrates that sGFAP may serve as a more accurate and specific biomarker for insidious disease progression than sNfL. While sNfL predominantly mirrors acute, inflammatory neuroaxonal injury, sGFAP reflects the undercurrent of chronic neurodegeneration and chronic diffuse tissue damage. This is further supported by the robust correlation between elevated sGFAP levels and worsening scores on the Expanded Disability Status Scale (EDSS) in progressive MS cohorts, validating its clinical utility as a non-invasive tool for tracking disease trajectory and differentiating between relapsing and progressive phenotypes [5].

Kappa Free Light Chains

Intrathecal immunoglobulin synthesis, historically demonstrated by the presence of CSF restricted oligoclonal bands (OCBs) via qualitative isoelectric focusing, remains a hallmark of MS pathogenesis. However, while OCB detection is considered the traditional gold standard, its methodology is heavily rater dependent, structurally complex, and prone to laboratory variability. To address these limitations, the quantification of the kFLC index via automated immunochemical assays has emerged as a highly reproducible, objective, and affordable alternative. The kFLC index exhibits a diagnostic sensitivity (approximately 88%) and specificity (approximately 89%) comparable to OCBs, occasionally demonstrating superior sensitivity due to its capacity to reflect the overproduction of multiple immunoglobulin classes, including IgM, rather than IgG alone [6,7].

Beyond its diagnostic equivalence, the kFLC index possesses profound prognostic value in preclinical and early symptomatic stages of the disease, such as Radiologically Isolated Syndrome (RIS) and Clinically Isolated Syndrome (CIS). In patients presenting with RIS, a positive kFLC index is associated with a 3.5-fold increased risk of developing subsequent radiological activity on MRI, effectively capturing the undercurrent of silent neuroinflammation. Similarly, in CIS cohorts, an elevated kFLC index predicts a twofold higher risk of experiencing a second clinical attack and converting to clinically definite MS. Furthermore, higher baseline kFLC index values strongly correlate with increased disability accumulation on the EDSS, a greater burden of gadolinium accumulating lesions, and a shorter time interval before the initiation of high efficacy DMTs.

Recognizing this robust clinical and analytical validity, international expert panels have officially incorporated the kFLC index into the revised 2024 McDonald criteria, establishing it as a fully validated equivalent equivalent to traditional OCBs for demonstrating intrathecal immunoglobulin synthesis [8,9].

Immunomodulatory strategies

Autologous hematopoietic stem cell transplantation (aHSCT)

Autologous hematopoietic stem cell transplantation is a highly potent therapeutic intervention for MS. The primary purpose of this procedure is to ablate the dysfunctional immune system using biologics and cytotoxic drugs, subsequently rebuilding a novel, auto tolerant immune system with the aid of harvested autologous hematopoietic stem cells. Although first introduced into clinical practice over two decades ago, it took nearly twenty years before the first randomized controlled trials were fully concluded. The promising clinical outcomes from these trials ultimately led to the official approval of aHSCT by the Swedish Board of Health and Welfare as a standard therapeutic option for patients suffering from highly active RRMS [10,11].

Recent advances in monitoring the long-term biological outcomes of this cellular therapy have heavily focused on objective fluid biomarkers to evaluate ongoing axonal damage. In clinical trials evaluating intermediate intensity autologous hematopoietic stem cell transplantation (specifically the BEAM aHSCT regimen), sNfL concentrations demonstrated high sensitivity in mirroring the suppression of acute

neuroinflammation after transplant. At baseline, sNfL levels strongly correlated with active inflammatory markers, including the annualized relapse rate (ARR) and active (Gd+) lesion volume on brain MRI. By month 24 following transplantation, a remarkable and statistically significant reduction in sNfL was achieved ranging from 50% to 90% in a substantial proportion of individuals. That confirmed a definitive halt in ongoing neuroaxonal damage [12].

However, this biomarker response was highly compartmentalized to the RRMS cohort, where the longitudinal decline in sNfL closely aligned with sustained clinical stabilization or visible improvement in the EDSS score. Conversely, patients with SPMS derived limited benefit from the procedure. Their sNfL levels remained statistically unchanged from baseline, and clinical disability accumulation persisted). Notably, the lack of correlation between longitudinal sNfL trajectories and subsequent brain volume loss or confirmed disability progression suggests a distinct dual nature of the marker. While sNfL serves as a robust and reliable surrogate marker for monitoring acute anti-inflammatory treatment responses, it exhibits lower sensitivity in capturing or predicting the subtle, compartmentalized, and entirely independent of relapses mechanisms of smouldering neurodegeneration [12].

Bruton's tyrosine kinase inhibitors

To address the chronic, nonresolving neuroinflammation within the CNS that peripheral therapies (including interventions like aHSCT) fail to halt, the clinical focus has shifted toward brain penetrant small molecules. Bruton's tyrosine kinase (BTK) inhibitors represent a novel therapeutic class capable of crossing the BBB. As highlighted by recent literature, BTK is an essential enzyme in the activation pathways of microglia, macrophages, and B lymphocytes both in the periphery and within the CNS compartment. Rather than depleting these immune cells, BTK inhibition directly modulates their chronic activation, potentially addressing the underlying pathophysiological substrates of smouldering multiple sclerosis and chronic lesion formation [9,13].

This distinct, pharmacological profile specific for CNS has been robustly validated in phase II and III clinical data. While evobrutinib failed to demonstrate superiority over teriflunomide in controlling focal inflammatory activity and disability accumulation, tolebrutinib successfully reduced the risk of confirmed disability progression sustained for at least 6 months in patients with nonrelapsing SPMS. Remarkably, all events progressing disability in this cohort were independent of relapse activity [9,14,15].

This protective effect is closely linked to tolebrutinib's unique ability to effectively penetrate the CNS, reaching cerebrospinal fluid concentrations that exceed the 90% inhibitory concentration, which is not observed in other tested BTK inhibitors. Clinical evidence further demonstrates that tolebrutinib's efficacy is centered around the modulation of compartmentalized B cells and myeloid lineages, showing a particularly remarkable effect on disability progression in patients with paramagnetic rim lesions (PRLs) at baseline. Because tolebrutinib exerted only modest effects on markers of acute focal inflammation while significantly slowing disability accrual in nonrelapsing SPMS, it provides the first definitive evidence that progressive pathology can be successfully modulated independently of systemic, acute focal activity [9,14].

Anti-CD20 monoclonal antibody therapy

Growing evidence over the past decade has firmly established that B cells play a central role in the pathogenesis of MS. In individuals affected by MS, the inflammatory characteristics of B cell activity are significantly elevated. This dysregulation leads to an increased release of pro-inflammatory cytokines, a diminished production of anti-inflammatory cytokines, and a pathological accumulation of pathogenic B cells within the cerebrospinal fluid. Because these mature B cells express the specific surface molecule CD20, they have become an ideal target for monoclonal antibodies (mAbs) [16,17].

The therapeutic mechanism of anti-CD20 antibodies relies on the physical destruction and rapid depletion of mature B lymphocytes in the peripheral blood. This cytotoxic approach directly contrasts with the mechanism of BTK inhibitors, which focus on cellular modulation, altering B-cell behavior and functions while allowing the cells to survive [16].

While the chimeric antibody rituximab was historically the first anti-CD20 therapeutic utilized off label in MS, ocrelizumab, a humanized monoclonal antibody, became the first officially approved anti-CD20 treatment for both relapsing forms of MS (RMS) and PPMS based on positive phase III outcomes. Following this, ofatumumab, a fully human monoclonal antibody, was introduced as the first subcutaneous, self-administered anti-CD20 therapy approved for RMS. Most recently, the therapeutic landscape has expanded with the publication of phase III clinical trial results for ublituximab in patients with RMS [16].

Ofatumumab exhibits potent anti-inflammatory and radiological activity, and during its clinical development, its administration form was successfully transitioned from an intravenous infusion to a

subcutaneous injection. Phase II studies, including the MIRROR trial, demonstrated that subcutaneous administration effectively inhibited the development of new focal lesions on MRI in a clear dose dependent manner. Specifically, a cumulative dose of at least 30 mg allowed for greater than 90% suppression of new inflammatory lesions [16].

Crucial to the definitive evaluation of ofatumumab's efficacy were the multicenter phase III trials, ASCLEPIOS I and ASCLEPIOS II, in which the subcutaneous antibody was directly compared with oral teriflunomide. Clinical and radiological parameters confirmed the clear superiority of the anti-CD20 therapy. Ofatumumab reduced the annualized relapse rate (ARR) by approximately half compared to the active comparator, achieving remarkably low values ranging from 0.10 to 0.11. Neuroimaging studies showed an almost complete suppression of active inflammatory processes, which translated into a 94% to 97% reduction in the number of active (T1 Gd+) lesions and an 82% to 85% reduction in new or enlarging hyperintense T2 lesions.

In addition to controlling relapse and radiographic activity, ofatumumab was effective in inhibiting the progression of physical disability. A pooled meta-analysis of both phase III studies demonstrated a statistically significant reduction in the risk of disease progression. The percentage of patients with confirmed disability worsening after 3 months was 10.9% in the ofatumumab group compared to 15.0% in the teriflunomide group, while the 6-month follow-up showed a similar benefit of 8.1% versus 12.0%, respectively. A favorable trend toward sustained functional improvement after 6 months was also observed in favor of ofatumumab (11.0% vs. 8.1%), although this parameter did not reach the pre-specified threshold of statistical significance.

The impact of the therapy on diffuse neurodegenerative processes was further assessed using fluid biomarkers and volumetric brain measurements. Ofatumumab treatment led to a rapid and sustained reduction in sNfL concentrations, a surrogate marker of microscopic axonal damage. The difference in sNfL concentrations favoring the anti-CD20 antibody ranged from 26% to 27% after the first year and from 23% to 24% after 24 months of follow-up. The only analyzed parameter in which ofatumumab failed to demonstrate a statistically significant advantage over teriflunomide was the annual rate of global brain volume loss (atrophy). This rate remained statistically similar in both study groups, measuring approximately from 0.28% to 0.29% per year for ofatumumab and 0.35% for teriflunomide [16,18].

Ublituximab, which features a modified glycosylation profile (glycoengineering) designed to enhance antibody-dependent cellular cytotoxicity (ADCC), demonstrates high efficacy in resolving acute inflammatory activity. In the twin multicenter phase III trials, ULTIMATE I and ULTIMATE II, this molecule was compared directly to oral teriflunomide, demonstrating significant superiority in key clinical and radiological parameters. Ublituximab reduced the ARR by approximately half compared to the comparator, reaching low baseline values of 0.08 to 0.09. Concurrently, MRI data demonstrated an almost complete suppression of focal disease activity, as evidenced by a dramatic reduction in the number of active T1 Gd+ lesions and new or enlarging T2 weighted hyperintensities. This high radiological and clinical efficacy, driven by the immediate elimination of peripheral B cells (a 96% decrease in CD19+ cell counts within 24 hours of the first dose), led to robust disease stabilization. Consequently, over 43% of patients receiving ublituximab achieved a status of no evidence of disease activity, whereas in the teriflunomide cohort, this percentage ranged from only 11.4% to 15.0% [16].

The primary limitations of ublituximab became evident when evaluating neuroprotective endpoints and navigating the rigorous structure of the hierarchical statistical analysis. The pooled analysis failed to reveal a statistically significant difference between the groups in inhibiting confirmed disability worsening at 12 weeks, with progression rates of 5.2% for ublituximab and 5.9% for teriflunomide. Because this specific endpoint did not reach statistical significance, the assumptions of the hierarchical analysis dictate that all subsequent secondary parameters (including the annual rate of brain atrophy and the Symbol Digit Modalities Test for cognitive function) formally could not be considered statistically significant, regardless of the raw numerical differences observed between the groups.

Despite these formal statistical constraints, promising therapeutic signals emerged from predetermined tertiary analyses, from which methodologically binding conclusions cannot be drawn but which remain clinically relevant. Patients receiving ublituximab were twice as likely to achieve confirmed disability improvement (both at 12 and 24 weeks) and achieved consistently better scores on the Multiple Sclerosis Functional Composite (MSFC) scale compared to the teriflunomide group [16,19].

The key characteristics and clinical differences between ofatumumab and ublituximab are summarized in Table 1.

Table 1. Summary of ofatumumab and ublituximab characteristics.

Feature	Ofatumumab	Ublituximab
Molecular structure and origin	Fully human anti CD20 monoclonal antibody (IgG1)	Chimeric anti CD20 monoclonal antibody featuring a modified glycosylation profile (glycoengineering)
Primary cytotoxic mechanism	Relies on physical destruction and rapid depletion of mature B lymphocytes via action	Engineered explicitly to enhance ADCC
Administration	Subcutaneous injection; designed for self-administration by the patient	Intravenous infusion; administered by the healthcare workers
Dosing schedule	Administered monthly	Administered once every 24 weeks
Pivotal phase III clinical trials	ASCLEPIOS I and ASCLEPIOS II	ULTIMATE I and ULTIMATE III
Annualized relapse rate	Ranged from 0,10 to 0,11 (reduced by approximately half compared to teriflunomide)	Ranged 0,08 to 0,09 (reduced by approximately half compared to teriflunomide)
Impact on disability worsening	Achieved a statistically significant reduction in the risk of 3-month (10.9% vs. 15.0%) and 6-month (8.1% to 12.0%) progression	Showed no statistically significant difference in the pooled analysis at 12 weeks (5.2% vs. 5.9% for teriflunomide)

Limits

Biomarkers

While new potential biomarkers seem promising in the diagnostic workup and monitoring of MS, they are not without significant imperfections. A major limitation of NfL is its profound lack of disease specificity. Elevated levels in both CSF and serum are not exclusive to MS but are universally present across various neurodegenerative and neuroinflammatory pathologies. Furthermore, under physiological conditions, baseline NfL concentrations naturally increase with age and correlate with cognitive and motor impairment, which introduces confounding variables when establishing a reliable baseline for MS pathology. Another technical limitation is that reliable sNfL measurement requires highly sensitive platforms such as SiMoA, thereby restricting its widespread clinical availability. Consequently, there is currently a distinct lack of clinical consensus regarding universal diagnostic or prognostic sNfL thresholds, a challenge driven primarily by the lack of methodological harmonization between different commercial laboratory assays. The clinical interpretation of sNfL is further complicated by significant temporal fluctuations that occur naturally during active relapsing crises, making stable longitudinal tracking highly challenging. Lastly, while sNfL effectively mirrors acute focal disease activity (clinical exacerbations and gadolinium enhancing lesions) in RRMS, it shows a substantial limitation in progressive forms of MS, where it fails to demonstrate a clear correlation with disease activity [4].

A similar prognostic disconnection has been documented for astrocytic markers. While baseline GFAP concentrations significantly correlate with focal lesion volume, they lack commensurability with long-term disease progression as measured through the EDSS [4].

Despite its high diagnostic accuracy, several parallel limitations hinder the universal implementation of the kFLC index. Chief among these is the lack of a standardized consensus cut off, which is primarily driven by analytical detection limits specific for each instrument, such as 0.28 mg/L for the Optilite platform, or 0.09 mg/L for Siemens platforms. Furthermore, clinicians must exercise rigorous caution regarding systemic confounding factors, as comorbidities like impaired renal function or monoclonal gammopathies can artificially elevate systemic kFLC concentrations, potentially yielding false-negative index scores. Conversely, false-positive results may occur in other neuroinflammatory conditions. Finally, while its prognostic value in CIS is extensively validated, robust data for asymptomatic RIS cohorts remain limited, with larger international clinical trials currently ongoing to fully validate its predictive power in preclinical MS [8].

Immunomodulatory strategies

The clinical management of advanced MS features a complex landscape of highly effective but inherently constrained therapeutic interventions, spanning intensive cellular therapies, selective molecule inhibitors, and targeted monoclonal antibodies. While these strategies offer potent efficacy, their clinical utility is heavily bounded by shared toxicities, narrow therapeutic windows, and a persistent lack of predictive biomarkers.

As an intensive immune rebooting strategy, aHSCT represents a highly potent therapeutic intervention for MS. However, because aHSCT directly targets the lymphohematopoietic system, profound immunosuppression serves as an inevitable therapeutic effect rather than a simple adverse event. This profound state of immune depletion involves numerous complications secondary to aggressive chemotherapy conditioning and the subsequent administration of immunosuppressive drug, which manifest particularly during the hyperacute phase after aHSCT. The most prevalent clinical liabilities driving early phase morbidity include neutropenic fever, bacterial sepsis, gastroenteritis, urinary tract infections, severe pneumonia, and the acute reactivation of latent viral infections. Crucially, the clinical implementation of this high efficacy intervention remains severely limited by a predictive deficit, as validated biomarkers capable of anticipating or predicting the risk of these treatment related adverse events are currently missing [11,20,21].

Parallel to cellular therapies, novel small molecule approaches face distinct safety barriers. Despite the promising efficacy of BTK inhibitors in slowing disability accrual, the clinical utility of tolebrutinib is strictly constrained by substantial safety concerns, specifically regarding systemic infections and severe hepatotoxicity. Data from phase III clinical testing indicate a higher overall incidence of adverse events in the tolebrutinib group compared to placebo (81.5% vs. 78.1%), alongside a notable increase in serious adverse events (15.0% vs. 10.4%). Because the mechanism of BTK inhibition directly dampens peripheral B lymphocytes and myeloid lines, participants treated with tolebrutinib exhibit a higher susceptibility to respiratory tract infections. This vulnerability is evidenced by elevated rates of COVID-19 (25.5% vs. 22.7%), nasopharyngitis (9.3% vs. 6.9%), and influenza (5.6% vs. 3.5%) compared to the placebo cohort, with COVID-19 pneumonia representing the most frequent serious adverse event (1.1%) [14].

The most critical limitation governing the clinical implementation of tolebrutinib, however, is its distinct hepatotoxic profile. Elevated ALT levels exceeding three times the ULN were reported in 4.0% of the tolebrutinib group, compared to 1.6% in the placebo group. More significantly, severe liver injury, marked by hyperacute ALT increases greater than 20 times the ULN, occurred in 0.5% of treated participants, while 0.4% of patients met strict laboratory criteria for severe hepatotoxicity, presenting with concurrent elevations of ALT (greater than 3x ULN) and total bilirubin (greater than 2x ULN). The clinical gravity of this risk was underscored by a fatal case of liver failure directly swallowed by postoperative complications following liver transplantation. Notably, all severe hepatotoxic events clustered within the first 90 days of treatment. Following a protocol amendment that mandated intensive, weekly hepatic monitoring during the initial 12 weeks of exposure, subsequent transaminase elevations successfully resolved without long-term sequelae [14].

Furthermore, recent data have demonstrated that the effect of tolebrutinib on disability progression was exclusively observed in patients presenting with PRLs at baseline. This finding is particularly remarkable because tolebrutinib exerted only modest effects on markers of acute focal inflammation, thereby providing the first concrete evidence that the pathology of progression can be modulated independently of acute focal activity, centered primarily around the compartmentalized modulation of B cells or myeloid cells [9]. Consequently, while tolebrutinib addresses a critical unmet need in nonrelapsing SPMS, its therapeutic window is highly restricted by the necessity of stringent, intensive laboratory monitoring and a heightened risk of infection, demanding careful patient selection and rigorous clinical surveillance during the initial months of therapy [14].

In contrast to the hyperacute toxicities of tolebrutinib and aHSCT, the clinical implementation of anti-CD20 mAbs in MS is generally characterized by a more favorable baseline safety profile, though their long-term use remains bounded by distinct reactions associated with administration and chronic immunomodulatory risks. Infusion and injection related reactions (IRRs/IRSs) constitute the most prevalent acute adverse events associated with anti-CD20 therapies. These manifestations typically occur within the first 24 hours after administration, predominantly peaking during the initial treatment cycle and steadily decreasing in frequency with subsequent doses. However, the incidence and severity of these reactions vary substantially depending on the route of administration and the molecular structure of the specific antibody.

Ublituximab, which is administered intravenously, demonstrated IRRs in 47.7% of patients during the ULTIMATE I and II trials, with Grade 3 or higher events reported in 2.8% of participants, including rare Grade

4 life threatening reactions and multiple treatment discontinuations. Conversely, the subcutaneous administration of low dose ofatumumab exhibits a significantly reduced systemic reactogenicity profile compared to intravenous options, with data from the ASCLEPIOS I and II trials showing IRSRs in 20.2% of patients and localized ISRs in only 10.9% [17].

Targeting peripheral B-cell lines by anti-CD20 mAbs inevitably interfere with systemic humoral immunity, creating a temporal susceptibility to infections. While short term clinical trials of less than 52 weeks demonstrated similar infection rates between active and control cohorts, longitudinal surveillance indicates that infectious risks escalate with chronic, multiyear exposure. Pooled data indicate that common, non-opportunistic infections affect between 51% and 69% of patients across all agents [17,18].

This long-term infectious vulnerability is directly tied to secondary hypogammaglobulinemia, as prolonged administration of anti-CD20 therapies causes a progressive decline in serum immunoglobulin levels. Six-year longitudinal assessments of ocrelizumab cohorts reveal a linear correlation between falling serum IgG levels and elevated serious infection rates. In contrast, intermediate term data (3.5 years) for subcutaneous ofatumumab demonstrate relatively stable serum IgG retention, mirroring a lower overall incidence of serious opportunistic infections despite sporadic, transient drops in IgM below the lower limit of normal.

The most critical opportunistic safety considerations remain hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML). Fulminant HBV reactivation has been documented in patients undergoing anti-CD20 therapy, including cases where viral DNA was undetectable at baseline but emerged rapidly within weeks of treatment initiation, mandating absolute screening before treatment. Concurrently, rare cases after marketing of John Cunningham virus (JCV) mediated PML have been identified across the entire class. While a significant proportion of these occurrences are transitional cases directly secondary to prior DMTs, de novo cases of PML have been directly attributed to ocrelizumab monotherapy in previously untreated individuals, highlighting advanced age and immune suppression induced by treatment as key compounding risk factors [17].

Discussion

Progression Independent of Relapse Activity

The integration of novel therapies and biomarkers is redefining the criteria for therapeutic success in MS, shifting the focus toward preventing PIRA. Historically, disease monitoring centered on suppressing relapse activity and focal white matter lesions. However, PIRA represents a distinct clinical phenomenon where a patient experiences accumulation of disability without any association to preceding or concurrent relapses [22]. This underlying neurodegenerative process occurs across all clinical phenotypes of MS, including the early relapsing-remitting phase, and reflects continuous neuroaxonal loss that remains largely undetected by standard relapse tracking. Consequently, the disease progression now requires objective indicators that can predict and measure this insidious progression.

To address this challenge, sNfL and GFAP have emerged as essential biomarkers for risk stratification. While sNfL serves as a direct indicator of neuroaxonal damage, elevated GFAP levels specifically reflect astrocytic activation and microglial inflammation associated with the chronic lesions driving PIRA [23]. However, the diagnostic utility of these markers is inconsistent when evaluated in isolation, and they do not achieve uniform predictive accuracy across all clinical studies [24]. To overcome these limitations, current evidence supports a multimodal approach. Combining sNfL and GFAP evaluations, or pairing sNfL with quantitative inflammatory markers like kFLC, significantly enhances predictive sensitivity, allowing clinicians to identify patients at a high risk of developing PIRA before clinical disability becomes irreversible [25].

Suppressing this independent progression requires therapeutic agents that target mechanisms beyond peripheral immune cell infiltration. High-efficacy DMTs, particularly anti-CD20 monoclonal antibodies, have demonstrated significant clinical efficacy in mitigating this risk. Clinical trial data indicate that anti-CD20 therapies substantially reduce the incidence of PIRA compared to lower-efficacy first-line agents, largely through the continuous depletion of B-cells and the subsequent downregulation of chronic compartmentalized inflammation within the central nervous system [26]. By combining early high-efficacy anti-CD20 treatment with longitudinal, multimodal biomarker profiling, clinicians can better monitor subclinical neurodegeneration and optimize therapeutic strategies specifically to prevent PIRA.

Socioeconomical Barriers

Although clinical evidence supports initiating highly effective DMTs at the onset of MS, practical implementation is limited by financial and logistical barriers. In many healthcare systems, reimbursement authorities restrict early access to high-efficacy DMTs through strict, line-based escalation protocols. These regulations often relegate innovative monoclonal antibodies to second- or third-line options, reserving them only for patients with highly aggressive disease activity [27]. This economic restriction is further complicated by the operational difficulties of integrating novel biomarkers into routine care. As previously demonstrated, the clinical utility of sNfL and kFLC is limited by analytical variations and physiological confounding factors, which prevent their standardized use in clinical practice [28].

However, evaluating only the initial purchase costs of advanced diagnostics and therapies ignores the long-term economic consequences of disease progression. Cost-of-illness studies demonstrate that while direct pharmacological costs represent the primary expenditure during the early stages of MS, the total societal and economic burden increases substantially as physical and cognitive disability accumulates [29]. When patients progress to higher scores on the EDSS, costs associated with productivity losses, early retirement, informal care, and frequent hospitalizations rise sharply, eventually exceeding the initial expenditures on medication. Consequently, providing early, unrestricted access to highly effective interventions represents a clear economic advantage. By suppressing neuroinflammation early in the disease course, these therapies reduce long-term disability, maintain patient employment capacity, and optimize overall healthcare resource utilization [27]. In this context, specific high-efficacy therapies offer distinct pharmacoeconomic profiles. Economic modeling shows that fully human anti-CD20 monoclonal antibodies, such as ofatumumab, provide clinical efficacy in reducing relapse rates and disability progression comparable to other high-potency agents. Concurrently, they generate long-term savings by reducing costs related to drug administration, clinical monitoring, and non-pharmacological healthcare resources [30]. Ultimately, aligning immediate budgetary limits with long-term socioeconomic benefits requires healthcare systems to transition from reactive escalation protocols to proactive, personalized treatments that combine timely clinical efficacy with long-term cost-effectiveness.

New potential strategies

MS affects a significant global population, and currently available therapeutic protocols lack the efficacy to fully eradicate the pathology. Consequently, intensive research is ongoing to identify new pharmacological strategies. One of the ideas involved the repurposing of GV1001, a 16-amino-acid peptide derived from telomerase, originally developed for oncology, but ultimately failed to demonstrate sufficient clinical efficacy for that indication. Evidence indicates that GV1001 reduced demyelination in mice with experimental autoimmune encephalomyelitis (EAE). By increasing the expression of key myelin proteins and markers of the oligodendrocyte lineage while downregulating inflammatory pathways, it offers promising prospects for progressive MS [31]. Another promising molecule is MCC950, a compound currently in phase one clinical trials, which has also demonstrated positive therapeutic effects in mitigating symptoms in mouse models of EAE. Its mechanism is based on inhibition of the NLRP3 inflammasome, which induces the maturation and secretion of IL-1 β and IL-18 [32]. There is also compound PIPE-307, which is being investigated as a potential therapeutic agent using a novel molecular mechanism of action and binding site. This molecule exhibits the properties of a selective muscarinic receptor type 1 antagonist. By blocking this receptor on the surface of oligodendrocyte precursor cells, this compound stimulates their differentiation into mature cells capable of synthesizing myelin sheaths, thereby inducing functional remyelination of axons and restoring nerve conduction [33]. The continual development of novel potential MS therapeutics presents promising prospects for enhanced symptom management and the possible attainment of a definitive cure.

Author's contribution:

All authors contributed to the article.

All authors have read and agreed with the published version of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

Funding statement: No external funding was received to perform this review.

REFERENCES

1. Lorenzut, S., Negro, I. D., Pauletto, G., Verriello, L., Spadea, L., Salati, C., Musa, M., Gagliano, C., & Zeppieri, M. (2025). Exploring the pathophysiology, diagnosis, and treatment options of multiple sclerosis. *Journal of Integrative Neuroscience*, 24(1). <https://doi.org/10.31083/JIN25081>
2. Boutitah-Benyaich, I., Eixarch, H., Villaceros-Álvarez, J., Hervera, A., Cobo-Calvo, Á., Montalban, X., & Espejo, C. (2025). Multiple sclerosis: Molecular pathogenesis and therapeutic intervention. *Signal Transduction and Targeted Therapy*, 10(1), 324. <https://doi.org/10.1038/s41392-025-02415-4>
3. Mathur, D., Mishra, B. K., Rout, S., Lopez-Iranzo, F. J., Lopez-Rodas, G., Vallamkondu, J., Kandimalla, R., & Casanova, B. (2021). Potential biomarkers associated with multiple sclerosis pathology. *International Journal of Molecular Sciences*, 22(19), 10323. <https://doi.org/10.3390/ijms221910323>
4. Maroto-García, J., Martínez-Escribano, A., Delgado-Gil, V., Mañez, M., Mugueta, C., Varo, N., García de la Torre, Á., & Ruiz-Galdón, M. (2023). Biochemical biomarkers for multiple sclerosis. *Clinica Chimica Acta*, 548, 117471. <https://doi.org/10.1016/j.cca.2023.117471>
5. Huss, A., Otto, M., Senel, M., Ludolph, A. C., Abdelhak, A., & Tumani, H. (2020). A score based on NfL and glial markers may differentiate between relapsing–remitting and progressive MS course. *Frontiers in Neurology*, 11. <https://doi.org/10.3389/fneur.2020.00608>
6. Hegen, H., Walde, J., Berek, K., Arrambide, G., Gnanapavan, S., Kaplan, B., Khalil, M., Saadeh, R., Teunissen, C., Tumani, H., Villar, L. M., Willrich, M. A. V., Zetterberg, H., & Deisenhammer, F. (2023). Cerebrospinal fluid kappa free light chains for the diagnosis of multiple sclerosis: A systematic review and meta-analysis. *Multiple Sclerosis Journal*, 29(2), 169–181. <https://doi.org/10.1177/13524585221134213>
7. Yang, J., Hamade, M., Wu, Q., Wang, Q., Axtell, R., Giri, S., & Mao-Draayer, Y. (2022). Current and future biomarkers in multiple sclerosis. *International Journal of Molecular Sciences*, 23(11), 5877. <https://doi.org/10.3390/ijms23115877>
8. Levraut, M., Landes-Chateau, C., Mondot, L., Cohen, M., & Lebrun-Frenay, C. (2025). The kappa free light chains index and central vein sign: Two new biomarkers for multiple sclerosis diagnosis. *Neurology and Therapy*, 14(3), 711–731. <https://doi.org/10.1007/s40120-025-00737-7>
9. Klotz, L., Saraste, M., Airas, L., & Kuhlmann, T. (2025). Multiple sclerosis: 2024 update. *Free Neuropathology*, 6, 14–14. <https://doi.org/10.17879/freeneuropathology-2025-6762>
10. Zjukovskaja, C., Larsson, A., Cherif, H., Kultima, K., & Burman, J. (2022). Biomarkers of demyelination and axonal damage are decreased after autologous hematopoietic stem cell transplantation for multiple sclerosis. *Multiple Sclerosis and Related Disorders*, 68, 104210. <https://doi.org/10.1016/j.msard.2022.104210>
11. Ruder, J., Dinner, G., Maceski, A., Berenjano-Correa, E., Müller, A. M., Jelcic, I., Kuhle, J., & Martin, R. (2022). Dynamics of inflammatory and neurodegenerative biomarkers after autologous hematopoietic stem cell transplantation in multiple sclerosis. *International Journal of Molecular Sciences*, 23(18), 10946. <https://doi.org/10.3390/ijms231810946>
12. Mariottini, A., Marchi, L., Innocenti, C., Di Cristinzi, M., Pasca, M., Filippini, S., Barilaro, A., Mechi, C., Fani, A., Mazzanti, B., Biagioli, T., Materozzi, F., Saccardi, R., Massacesi, L., & Repice, A. M. (2022). Intermediate-intensity autologous hematopoietic stem cell transplantation reduces serum neurofilament light chains and brain atrophy in aggressive multiple sclerosis. *Frontiers in Neurology*, 13. <https://doi.org/10.3389/fneur.2022.820256>
13. Amin, M., & Hersh, C. M. (2023). Updates and advances in multiple sclerosis neurotherapeutics. *Neurodegenerative Disease Management*, 13(1), 47–70. <https://doi.org/10.2217/nmt-2021-0058>
14. Fox, R. J., Bar-Or, A., Traboulsee, A., Oreja-Guevara, C., Giovannoni, G., Vermersch, P., Syed, S., Li, Y., Vargas, W. S., Turner, T. J., Wallstroem, E., & Reich, D. S. (2025). Tolebrutinib in nonrelapsing secondary progressive multiple sclerosis. *New England Journal of Medicine*, 392(19), 1883–1892. <https://doi.org/10.1056/NEJMoa2415988>
15. Reich, D. S., Arnold, D. L., Vermersch, P., Bar-Or, A., Fox, R. J., Matta, A., Turner, T., Wallström, E., Zhang, X., Mareš, M., Khabirov, F. A., Traboulsee, A., Grand'Maison, F., Jacques, F., Tyblova, M., Meluzinova, E., Ampapa, R., Valis, M., Hradilke, P., ... Robertson, D. (2021). Safety and efficacy of tolebrutinib, an oral brain-penetrant BTK inhibitor, in relapsing multiple sclerosis: A phase 2b, randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*, 20(9), 729–738. [https://doi.org/10.1016/S1474-4422\(21\)00237-4](https://doi.org/10.1016/S1474-4422(21)00237-4)
16. de Sèze, J., Maillart, E., Gueguen, A., Laplaud, D. A., Michel, L., Thouvenot, E., Zephir, H., Zimmer, L., Biotti, D., & Liblau, R. (2023). Anti-CD20 therapies in multiple sclerosis: From pathology to the clinic. *Frontiers in Immunology*, 14, 1004795. <https://doi.org/10.3389/fimmu.2023.1004795>

17. Delgado, S. R., Faissner, S., Linker, R. A., & Rammohan, K. (2024). Key characteristics of anti-CD20 monoclonal antibodies and clinical implications for multiple sclerosis treatment. *Journal of Neurology*, 271(4), 1515–1535. <https://doi.org/10.1007/s00415-023-12007-3>
18. Hauser, S. L., Bar-Or, A., Cohen, J. A., Comi, G., Correale, J., Coyle, P. K., Cross, A. H., Seze, J. de, Leppert, D., Montalban, X., Selmaj, K., Wiendl, H., Kerloeguen, C., Willi, R., Li, B., Kakarieka, A., Tomic, D., Goodyear, A., Pingili, R., ... Kappos, L. (2020). Ofatumumab versus teriflunomide in multiple sclerosis. *New England Journal of Medicine*, 383(6), 546–557. <https://doi.org/10.1056/NEJMoa1917246>
19. Steinman, L., Fox, E., Hartung, H.-P., Alvarez, E., Qian, P., Wray, S., Robertson, D., Huang, D., Selmaj, K., Wynn, D., Cutter, G., Mok, K., Hsu, Y., Xu, Y., Weiss, M. S., Bosco, J. A., Power, S. A., Lee, L., Miskin, H. P., & Cree, B. A. C. (2022). Ublituximab versus teriflunomide in relapsing multiple sclerosis. *New England Journal of Medicine*, 387(8), 704–714. <https://doi.org/10.1056/NEJMoa2201904>
20. Kazmi, M., Muraro, P. A., Mehra, V., Gabriel, I., De Matteis, E., Brittain, G., Mariottini, A., Nicholas, R., Silber, E., Lee, J., Pearce, R., Paul, R., Sormani, M. P., Signori, A., Potter, V., Olavarria, E., Malladi, R., Sharrack, B., & Snowden, J. A. (2025). Autologous haematopoietic stem cell transplantation for multiple sclerosis in the UK: A 20-year retrospective analysis of activity and haematological outcomes from the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT). *British Journal of Haematology*, 207(3), 977–991. <https://doi.org/10.1111/bjh.20199>
21. Häußler, V., Ufer, F., Pöttgen, J., Wolschke, C., Friese, M. A., Kröger, N., Heesen, C., & Stellmann, J. (2021). aHSCT is superior to alemtuzumab in maintaining NEDA and improving cognition in multiple sclerosis. *Annals of Clinical and Translational Neurology*, 8(6), 1269–1278. <https://doi.org/10.1002/acn3.51366>
22. Kappos, L., Wolinsky, J. S., Giovannoni, G., Arnold, D. L., Wang, Q., Bernasconi, C., Model, F., Koendgen, H., Manfrini, M., Belachew, S., & Hauser, S. L. (2020). Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurology*, 77(9), 1–9. <https://doi.org/10.1001/jamaneurol.2020.1568>
23. Benkert, P., Maleska Maceski, A., Schaedelin, S., Oechtering, J., Zadic, A., Vilchez Gomez, J. F., Melie-Garcia, L., Cagol, A., Galbusera, R., Subramaniam, S., Lorscheider, J., Galli, E., Mueller, J., Fischer-Barnicol, B., Achtnichts, L., Findling, O., Lalive, P. H., Bridel, C., Uginet, M., ... Kuhle, J. (2025). Serum glial fibrillary acidic protein and neurofilament light chain levels reflect different mechanisms of disease progression under B-cell depleting treatment in multiple sclerosis. *Annals of Neurology*, 97(1), 104–115. <https://doi.org/10.1002/ana.27096>
24. Rodríguez-Jorge, F., Fernández-Velasco, J. I., Villarrubia, N., Gracia-Gil, J., Fernández, E., Meca-Lallana, V., Díaz-Pérez, C., Sainz de la Maza, S., Pacheco, E. M., Quiroga, A., Ramió-Torrentà, L., Martínez-Yélamos, S., Bau, L., Monreal, E., López-Real, A., Rodero-Romero, A., Borrega, L., Díaz, S., Eguía, P., ... Villar, L. M. (2024). Biomarkers of response to ocrelizumab in relapsing–remitting multiple sclerosis. *Frontiers in Immunology*, 15, 1480676. <https://doi.org/10.3389/fimmu.2024.1480676>
25. Cagol, A., Benkert, P., Schaedelin, S., Ocampo-Pineda, M., Montobbio, N., Lu, P., Ayci, B., Wenger, A., Shukur, A. A., Kaim, K., Melie-Garcia, L., Weigel, M., Signori, A., Calabrese, P., Kappos, L., Sormani, M. P., Kuhle, J., & Granziera, C. (2026). Assessing the relative importance of imaging and serum biomarkers in capturing disability, cognitive impairment, and clinical progression in multiple sclerosis. *Advanced Science*, 13(10), e12946. <https://doi.org/10.1002/advs.202512946>
26. Zhu, C., Zhou, Z., Kalincik, T., Roos, I., Buzzard, K., Skibina, O., Alroughani, R., Kuhle, J., Girard, M., Grammond, P., Lechner-Scott, J., Gerlach, O., John, N., McCombe, P., Macdonell, R., van Pesch, V., Laureys, G., Prevost, J., Horakova, D., ... Butzkueven, H. (2025). Persistent progression independent of relapse activity in multiple sclerosis. *Brain Communications*, 7(5), fcaf306. <https://doi.org/10.1093/braincomms/fcaf306>
27. Filippi, M., Danesi, R., Derfuss, T., Duddy, M., Gallo, P., Gold, R., Havrdová, E. K., Kornek, B., Saccà, F., Tintoré, M., Weber, J., & Trojano, M. (2022). Early and unrestricted access to high-efficacy disease-modifying therapies: A consensus to optimize benefits for people living with multiple sclerosis. *Journal of Neurology*, 269(3), 1670–1677. <https://doi.org/10.1007/s00415-021-10836-8>
28. Thebault, S., Booth, R. A., Rush, C. A., MacLean, H., & Freedman, M. S. (2021). Serum neurofilament light chain measurement in MS: Hurdles to clinical translation. *Frontiers in Neuroscience*, 15, 654942. <https://doi.org/10.3389/fnins.2021.654942>
29. Ponzio, M., Santoni, L., Molina, M., Tavazzi, E., & Bergamaschi, R. (2025). Economic burden of multiple sclerosis in an Italian cohort of patients on disease-modifying therapy: Analysis of disease cost and its components. *Journal of Neurology*, 272(1), 50. <https://doi.org/10.1007/s00415-024-12729-y>
30. Bhan, V., Clift, F., Baharnoori, M., Thomas, K., Patel, B. P., Blanchette, F., Adlard, N., Vudumula, U., Gudala, K., Dutta, N., Grima, D., Mouallif, S., & Farhane, F. (n.d.). Cost–consequence analysis of ofatumumab for the treatment of relapsing–remitting multiple sclerosis in Canada. *Journal of Comparative Effectiveness Research*, 12(9), e220175. <https://doi.org/10.57264/cer-2022-0175>

31. Suk, K., & Lee, W.-H. (2026). GV1001: Repurposing a telomerase-derived peptide for neurological therapeutics. *Expert Opinion on Investigational Drugs*, 35(5), 369–381. <https://doi.org/10.1080/13543784.2026.2674652>
32. Hou, B., Yin, J., Liu, S., Guo, J., Zhang, B., Zhang, Z., Yang, L., Tan, X., Long, Y., Feng, S., Zhou, J., Wu, Y., Wang, X., Han, S., Wang, Z., & He, X. (2024). Inhibiting the NLRP3 inflammasome with MCC950 alleviates neurological impairment in the brain of EAE mice. *Molecular Neurobiology*, 61(3), 1318–1330. <https://doi.org/10.1007/s12035-023-03618-y>
33. Poon, M. M., Lorrain, K. I., Stebbins, K. J., Edu, G. C., Broadhead, A. R., Lorenzana, A. J., Roppe, J. R., Baccei, J. M., Baccei, C. S., Chen, A. C., Green, A. J., Lorrain, D. S., & Chan, J. R. (2024). Targeting the muscarinic M1 receptor with a selective, brain-penetrant antagonist to promote remyelination in multiple sclerosis. *Proceedings of the National Academy of Sciences of the United States of America*, 121(32), e2407974121. <https://doi.org/10.1073/pnas.2407974121>