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Emerging Therapies in Multiple Sclerosis Management – Can We Stop the Demyelinating Process?

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ABSTRACT

Introduction. Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS) characterised by neuroinflammation and neurodegeneration leading to progressive disability. Its complex immunopathogenesis involves autoreactive T cells, B cells, and myeloid cells, with growing evidence highlighting the pivotal role of B lymphocytes. B cells contribute through antigen presentation, cytokine secretion, autoantibody production, and formation of ectopic lymphoid structures, making them key therapeutic targets. Current disease-modifying therapies (DMTs), including anti-CD20 monoclonal antibodies such as ocrelizumab, ofatumumab, and recently launched ublituximab, have significantly improved clinical outcomes. However, optimisation of long-term efficacy and safety remains challenging. The novel agent, frexalimab, which targets the CD40–CD40L pathway, aims to refine treatment precision and safety further.
Material and methods. A systematic search of PubMed, Scopus, and Web of Science (October–November 2025) was conducted to identify clinical trials and high-quality reviews on emerging MS therapies, with emphasis on anti-CD20 agents, BTK inhibitors, frexalimab, and CAR-T therapy. Eligible studies were critically appraised for mechanisms of action, clinical efficacy, safety, and relevance, with particular focus on recent phase II–III data.
Results. This review synthesises current insights into MS immunopathology and recent advances in B-cell-targeted therapies and CAR-T approaches, highlighting an evolving therapeutic landscape focused on improving disease control and long-term outcomes.
Conclusions. Continued development of targeted immunotherapies may bring the field closer to sustained remission, effective prevention of progression, and potentially enhanced CNS repair.

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune-mediated disease of the central nervous system (CNS) and the leading cause of non-traumatic neurological disability among young adults worldwide. Characterised by diverse neuroinflammatory processes and subsequent demyelination and neurodegeneration, MS is currently incurable and often leads to significant physical and cognitive impairment [1].

The pathogenesis of MS involves a complex interplay between various immune cells and signalling pathways. The disease is initiated when the immune system mistakenly targets components of the CNS, leading to inflammation within both white and grey matter. Autoreactive CD4+ T cells, particularly Th1 and Th17 subtypes, play a pivotal role in this process. Upon activation by antigen-presenting cells (APCs), which recognise pathogen-associated molecular patterns via toll-like receptors, naïve CD4+ T cells differentiate under the influence of cytokines such as interleukin (IL)-12, IL-23, and IL-4. Th1 cells secrete proinflammatory cytokines such as interferon-γ and tumour necrosis factor-α (TNF-α), which not only sustain inflammation but also inhibit the development of anti-inflammatory Th2 responses. During acute relapses, CNS inflammation is primarily driven by activated T cells, B cells, and myeloid cells. CD8+ T cells and proinflammatory microglia infiltrate the CNS and, together with CD4+ T cells, contribute to the destruction of the myelin sheath. B cells further amplify this immune response by presenting antigens to T cells, producing antibodies, and secreting immunoregulatory cytokines. These immune processes lead to focal demyelinating lesions visible on magnetic resonance imaging (MRI), characterised by immune cell infiltration, axonal damage, and the formation of CNS plaques. The resulting disruption of neuronal signalling underlies the wide range of neurological symptoms observed in patients with MS [2–4].

Although MS remains an incurable disease, significant progress has been made in its treatment due to the development of new immunomodulatory and biological therapies.

Given the complexity of the immune mechanisms involved in MS and the resulting challenges in its management, the primary aim of this paper is to highlight recently discovered and emerging therapeutic strategies that offer new potential in the treatment of MS. These novel approaches reflect a growing understanding of disease pathophysiology and represent a shift toward more targeted and individualized treatment options. Particular attention has also been paid to experimental therapies that are still in the early stages of investigation but hold the potential to revolutionise MS treatment in the future, offering hope for more effective disease control and even the regeneration of damaged neural tissue.

Material and methods

To ensure a comprehensive and up-to-date overview of emerging therapies in MS, the authors conducted a systematic literature search using the PubMed, Scopus and Web of Science databases between October and November 2025. The search strategy included a combination of Medical Subject Headings (MeSH) and free-text terms such as: *multiple sclerosis*, *MS treatment*, *anti-CD20 therapies*, *ocrelizumab*, *ofatumumab*, *ublituximab*, *frexalimab*, *BTK inhibitors* and *CAR-T cell therapy*.

The inclusion criteria were as follows: (1) articles published in English; (2) publication types including original clinical trials, systematic reviews, meta-analyses, and high-quality narrative reviews; and (3) studies addressing immunological targets, mechanisms of action, clinical efficacy, and safety profiles of disease-modifying therapies in MS. No limitations were placed on the publication date to identify both foundational studies and the most recent developments in the field.

Additional sources were identified through manual screening of reference lists from key review articles and clinical guidelines. Particular attention was paid to recent phase II and III clinical trials, early-phase studies of novel agents, and translational research exploring future therapeutic directions. All relevant studies were critically appraised for methodological quality and relevance to the scope of this review.

Discussion

Frexalimab

In recent years, the CD40-CD40L costimulatory pathway has gained attention as a promising

therapeutic target in MS due to its crucial role in regulating both adaptive and innate immune responses. CD40 and its ligand, CD40L, are transmembrane proteins of the tumour necrosis factor (TNF) receptor superfamily that play a central role in initiating and maintaining inflammatory processes. CD40 is expressed on antigen-presenting cells (APCs), such as B cells, dendritic cells (DCs), macrophages, and monocytes, as well as on various non-immune cells, including epithelial, endothelial, and mesenchymal cells. CD40L is predominantly expressed by activated CD4+T cells but is also present on activated B cells and platelets. Under inflammatory conditions, both molecules can be upregulated on other cell types. Their interaction triggers several downstream signalling cascades, highlighting their importance in immune cell activation and the development of autoimmune diseases. In MS, dysregulation of the CD40-CD40L axis contributes to disease pathogenesis, and targeting this pathway offers a novel approach to modulating aberrant immune responses.

One of the most recent advances in this area is frexalimab, a second-generation monoclonal antibody targeting CD40L. Frexalimab is currently being evaluated in multiple clinical trials for its potential to improve key measures of disability associated with MS. These include reductions in composite confirmed disability progression (cCDP) and disease activity, as reflected by a lower annualised relapse rate (ARR) [3,5].

Frexalimab was recently investigated in a double-masked, randomised clinical trial involving patients with RMS, with results published in 2024 by Vermersch et al [5]. It has demonstrated encouraging early results: at week 12, 85% of participants receiving frexalimab at 1200 mg and 84% receiving 300 mg had no new gadolinium-enhancing lesions, compared with only 50% in the pooled placebo group. Furthermore, patients receiving frexalimab showed decreased plasma levels of neurofilament light chain (NfL), a biomarker of neuroaxonal injury, indicating a potential neuroprotective effect. The therapy also led to a reduction in C-X-C motif chemokine ligand 13 (CXCL13) concentrations, a chemokine associated with inflammatory activity in MS. Elevated serum levels of CXCL13 are often observed in patients with active disease, further supporting the relevance of this marker for monitoring treatment response [5].

Initial attempts to target the CD40L pathway with first-generation monoclonal antibodies, such as toralizumab, showed therapeutic potential in autoimmune conditions, such as MS; however, their clinical development was halted due to serious thromboembolic complications. These adverse events were primarily attributed to the unintended activation and aggregation of platelets, as CD40L is also expressed on their surface, thereby increasing the risk of thrombosis. In response to these safety concerns, second-generation agents, such as frexalimab, were designed with enhanced specificity and a reduced risk of off-target interactions. These newer therapies aim to lower the incidence of treatment-related adverse events while maintaining efficacy in slowing disability progression [3].

Frexalimab has demonstrated a favourable safety profile in clinical studies, with most adverse events (AEs) being mild to moderate in severity. The most commonly reported AEs included headache and COVID-19 infection. Notably, COVID-19 occurred in 10% of patients receiving the 300 mg subcutaneous (SC) dose, while no cases were observed in the 1200 mg intravenous (IV) or placebo groups. The incidence of infections varied across treatment arms: 24% in the 300 mg SC group, 8% in the 1200 mg IV group, and 4% in the placebo group. Additionally, transient elevations in liver enzymes and episodes of neutropenia were reported, but these resolved without the need to discontinue treatment. Importantly, no serious or severe adverse events, thromboembolic complications, or deaths were observed throughout the study. These findings suggest that frexalimab is well tolerated and support its potential as a safer alternative to existing immunomodulatory therapies [3,5].

Frexalimab represents a more targeted and refined therapeutic approach, offering the potential for enhanced efficacy and a reduced risk of adverse effects compared with traditional and other biologic treatments. However, further large-scale clinical trials are necessary to establish its long-term efficacy and safety, particularly when compared with well-established therapies that have demonstrated effectiveness in managing autoimmune diseases [5].

Table 1. Summary of key efficacy and safety outcomes from the phase 2 trial of frexalimab in multiple sclerosis [3,5].

Parameter / outcome	1200 mg IV every 4 weeks Frexalimab Group	300 mg SC every 2 weeks Frexalimab Group	Placebo Group
Mean age of participants	36.6 years	36.6 years	36.6 years
Percentage of women	66%	66%	66%
Participants with gadolinium-enhancing lesions at baseline	30%	30%	30%
Adjusted mean number of new gadolinium-enhancing T1-weighted lesions at week 12	0.2 (95% CI, 0.1 to 0.4)	0.3 (95% CI, 0.1 to 0.6)	1.4 (95% CI, 0.6 to 3.0)
Annualized relapse rate ratio compared to placebo	0.11 (95% CI, 0.03 to 0.38)	0.21 (95% CI, 0.08 to 0.56)	1 (reference)
Most common adverse events (AEs)	COVID-19 and headaches	COVID-19 and headaches	COVID-19 and headaches

CI – confidence interval; IV – intravenous; SC – subcutaneous.

A summary of key efficacy and safety results from the Phase 2 study of frexalimab is presented in **Table 1**.

In addition, a new randomised, double-blind, placebo-controlled phase III trial evaluating frexalimab in adults with nonrelapsing secondary progressive multiple sclerosis (nrSPMS) is currently ongoing. The study aims to assess the efficacy of frexalimab in delaying disability progression and further to characterise its long-term safety profile in this patient population. The trial is expected to provide important data regarding the potential role of frexalimab in progressive forms of MS [6].

A new anti-CD20 antibody

Although MS has long been considered a disease primarily driven by T cells, growing evidence has highlighted the significant contribution of B cells to its pathogenesis through multiple pathways. B cells can act as antigen-presenting cells, stimulate proinflammatory T-cell responses, and secrete cytokines that amplify inflammation. They also produce autoreactive antibodies that cross the blood-brain barrier, triggering complement-mediated damage to the myelin sheath in the CNS. In more advanced stages of the disease, B cells may contribute to the formation of ectopic lymphoid structures within the meninges that resemble germinal centres, which are thought to promote chronic inflammation, demyelination, and neurodegeneration [7,8].

CD20 is a surface protein found on both normal and malignant B lymphocytes, with low-level expression also observed on a minor population of T cells. In B cells, CD20 is closely associated with key immune signalling molecules, including MHC class II, CD40, the B-cell receptor (BCR), and C-terminal Src kinase-binding protein. This protein plays an important role in initiating and sustaining B-cell activation and proliferation. It is believed to be essential for effective BCR-mediated signalling, as well as for maintaining proper T-independent antibody responses and robust immune reactions to T cell–dependent antigens [1,9,10].

Anti-CD20 monoclonal antibodies (mAbs) are engineered to recognise and eliminate cells that express the CD20 surface marker. Their primary targets are B lymphocytes that co-express CD19 and CD20. By depleting these B cells, the treatment is believed to interrupt antigen presentation and limit the activation of autoreactive T cells. Additionally, it suppresses the production of proinflammatory cytokines by B cells. It promotes a shift in the immune environment from a highly activated, inflammatory state toward a more regulated one, characterised by a reduced presence of mature and activated B and T lymphocytes. Recent studies suggest that B-cell depletion contributes to reduced MS disease activity by modulating antigen-specific T-cell responses, including those targeting myelin (CD8+ T cells) and Epstein–Barr virus (EBV)- specific T cells, which are believed to play a key role in disease progression and pathogenesis [7]. Postmortem studies of SPMS brain tissue suggest persistent EBV infection in B and plasma cells, particularly within meningeal ectopic follicles, correlating with CD8+ T cell activation. However, recent single-cell RNA

sequencing found no EBV transcripts in CSF B cells of RMS patients. Other studies have shown that patients with active MS have more CD8+ T cells that target lytic (but not latent) EBV antigens, suggesting EBV reactivation during disease activity. TCRβ analyses also revealed a higher frequency of EBV-specific T cells in MS patients. A large cohort study reported a 32-fold increased MS risk following EBV infection, strongly implicating EBV in MS pathogenesis. [10,11].

It has been a few years since two anti-CD20 monoclonal antibodies, ocrelizumab and ofatumumab, received FDA/EMA approval for the treatment of MS and have been widely used in clinical practice. Ocrelizumab has been approved for the treatment of primary progressive MS (PPMS) and relapsing-remitting MS (RRMS) since 2017, while ofatumumab has been indicated for RRMS since 2020. Although rituximab also targets CD20, it has not been approved by the FDA or EMA for use in MS, nevertheless, it is used off-label in the treatment of the disease [1,12]. Therapy with anti-CD20 monoclonal antibodies has transformed MS treatment, yet there is still room to optimize clinical outcomes with these agents.

Ublituximab, a glycoengineered chimeric monoclonal antibody designed for enhanced B-cell depletion, has been recently launched to the pharmaceutical market. It may represent a promising new cornerstone in the treatment of MS. Unlike other anti-CD20 monoclonal antibodies, ublituximab binds to a distinct epitope on the CD20 molecule that is not targeted by other agents in this class. Most patients participating in the clinical study experienced effective B-cell depletion shortly after the first dose, and this effect was largely maintained throughout the treatment period [8]. The therapy showed encouraging results, with the majority of patients exhibiting no clinical or MRI signs of disease activity during 48 weeks of treatment. Notably, no new or active gadolinium-enhancing lesions, markers of inflammation and blood-brain barrier disruption, were observed on MRI at key timepoints. Favourable clinical outcomes accompanied these radiological improvements. Ublituximab was generally well tolerated, with infusion-related reactions (IRRs) being the most common side effects, primarily occurring at the first administration and diminishing over time. Given its efficacy and tolerability, ublituximab stands out as a promising future option in the therapeutic landscape of MS [8]. Ublituximab has been approved by the FDA for the treatment of adult patients with CIS, RRMS and SPMS, and for active relapsing forms of MS, as per the EMA label.

Summary data on the clinical profile of ublituximab are presented in **Table 2**.

Table 2. Summary of clinical profile of ublituximab [8].

Parameter	Details
FDA approval	Approved for adult patients with CIS; RRMS; and active SPMS
EMA approval	Approved for patients with active relapsing forms of MS
Mechanism of action	Type I anti-CD20 monoclonal antibody; glycoengineered to enhance ADCC
Administration	IV infusion; 450 mg over 1 hour; every 24 weeks
B-cell depletion	>95% depletion of CD19+ B-cells within 24h of first 150 mg dose >99% median depletion by week 4 Sustained depletion through weeks 24 and 48
MRI outcomes	T1 Gd-enhancing lesions: 0 lesions at week 24 and week 48 in all patients T2 lesions: Significantly reduced (>10% from baseline at week 48); most new lesions occurred before week 24
Clinical outcomes	93% relapse-free at 48 weeks 95% reduction in relapse rate from baseline 92% had no 24-week confirmed disability progression 17% had confirmed EDSS improvement
Safety and tolerability	No withdrawals due to AEs Most common AE: IRRs; mainly grade 1–2 IRRs most frequent at first dose and decreased over time No increased IRR rate with rapid 1-hour infusion
Long-term use	79% of patients remained on therapy in the extension phase

ADCC – Antibody-Dependent Cellular Cytotoxicity; AE – Adverse Event; CIS – Clinically Isolated Syndrome; EDSS – Expanded Disability Status Scale; Gd – Gadolinium; IRR- Infusion-Related Reaction; IV – Intravenous; MRI – Magnetic Resonance Imaging; RRMS – Relapsing-Remitting Multiple Sclerosis; SPMS – Secondary Progressive Multiple Sclerosis.

Rituximab, ocrelizumab, ofatumumab, and ublituximab are all IgG1 monoclonal antibodies, which are the IgG isotype most efficient at activating the complement system. These four drugs differ in the proportion of their immunoglobulin structure of human origin and in their mode of action [1,7,8]. The main features differentiating these antibodies are presented in **Table 3**.

It is important to note, however, that while these therapies have demonstrated efficacy in slowing disease progression, they are not without side effects, such as increased risk of infections, including hepatitis B virus (HBV) reactivation, and individual responses can vary significantly. Therefore, ongoing research remains essential to deepen our understanding of the role of B lymphocytes in MS and to develop more targeted and effective treatment strategies [1,7,8].

CAR-T

Chimeric Antigen Receptor (CAR) T-cell therapy involves collecting a patient's own T lymphocytes and genetically modifying them to express synthetic receptors (CARs) that enable the cells to selectively recognise and eliminate target antigens, most commonly those expressed on B cells, such as CD19. Once reinfused into the patient, these engineered T cells actively seek out and destroy the targeted immune cells. In the context of MS, researchers have focused on CAR

Table 3. Comparative Summary of Anti-CD20 Monoclonal Antibodies in MS [1,7,8].

Feature	Rituximab	Ocrelizumab	Ofatumumab	Ublituximab
Type	Chimeric IgG1	Humanized IgG1	Fully human IgG1	Chimeric IgG1 (glycoengineered)
Route of Administration	iv	iv or sc	s.c. (self-administered)	iv
Mechanism of Action	CDC > ADCC	ADCC > CDC	CDC > ADCC	ADCC > CDC (enhanced via low fucose)
Site of Binding on CD20 Epitope	Large extracellular loop	Large loop (ANPS)	Large + small loops (unique)	Unique + overlapping with rituximab/ocrelizumab
Bioavailability	100% (iv)	100% (iv)	Delayed systemic entry (s.c.)	100% (iv)
Half-Life	~22 days	~26 days	~16 days	Not fully established
B Cell Repletion	Naive: ~12–16 months Memory: >25 months	Median: 72 weeks (27–175)	Median: ~40 weeks >50% replete at 24–36 weeks	Limited data (sustained depletion at 48 weeks)
Ig Decline (at 96 weeks)	Data limited	IgG: 1.5% IgA: 2.4% IgM: 16.5% below LLN	IgM: 14.3% < 0.34 g/dL IgG: ↓4.3% (48 wks), ↑2.2% (96 wks)	Not reported
IRRs	34–51% (iv)	34–53%	20–52% (SC) No clear benefit from premedication	Theoretical lower IRR due to weaker CDC
Immunogenicity (ADA)	~7% HACA in PPMS	~1% ADA (0.2% neutralizing)	~0.2% ADA No neutralizing Abs	Not well established
Infection Risk	Higher risk (esp. serious infections)	9 PML cases (mostly carryover)	1 PML in CLL (not MS) More rapid B cell repletion = potential safety	No PML in MS trials
HBV Reactivation	Yes (non-MS use)	Yes (rare)	Yes (in CLL, high dose)	Not observed in MS trials
Efficacy in RRMS (Gd+ Lesion ↓)	~88–91% ↓	94–95% ↓ vs. IFN β-1a	94–97% ↓ vs. teriflunomide	No new/persisting lesions (48 wks, Phase II)
Efficacy in RRMS (ARR ↓)	↓14–20% (vs. placebo)	↓46–47% vs. IFN β-1a	↓50–58% vs. teriflunomide	93% relapse-free at 48 wks (Phase II)
Efficacy in PPMS	No significant benefit (except in subgroups)	Approved for PPMS:↓12-wk CDP: 32.9% vs 39.3%	Not approved for PPMS	Not studied in PPMS
Vaccination Response	Reduced if B cell depleted	Attenuated, but present response	Potentially better (faster repopulation)	Not studied

ADA – Anti-Drug Antibodies; ADCC – Antibody-Dependent Cellular Cytotoxicity; AE – Adverse Event; ARR – Absolute Risk Reduction; CDC – Complement-Dependent Cytotoxicity; CLL – Chronic Lymphocytic Leukemia; HACA – Human Anti-Chimeric Antibodies; IgG – Immunoglobulin G; IM – Intramuscular; IRR – Infusion-Related Reaction; IV – Intravenous; PPMS – Primary Progressive Multiple Sclerosis; RRMS – Relapsing-Remitting Multiple Sclerosis; SC – Subcutaneous; T1 Gd+ – T1-weighted Gadolinium-Enhancing (Lesions).

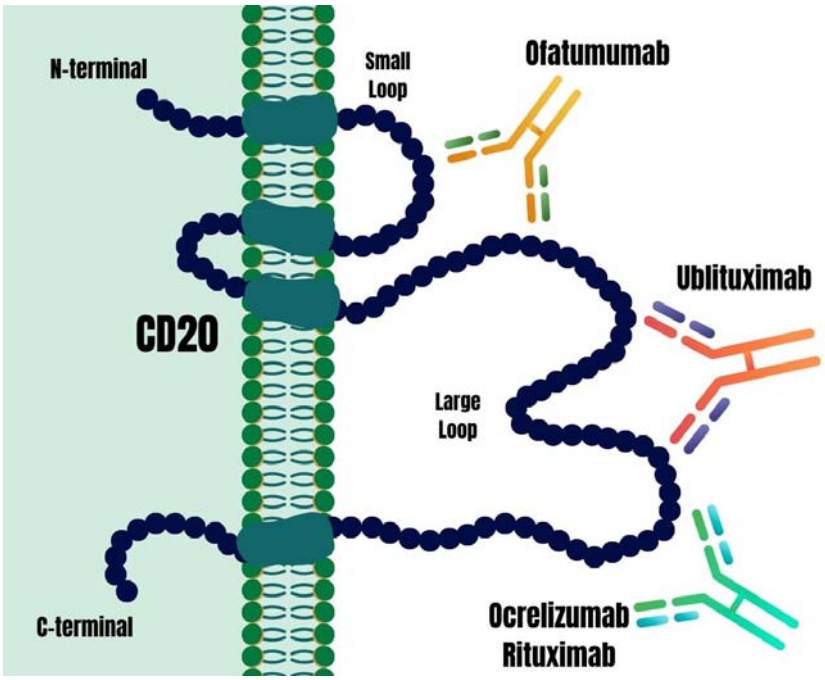

Figure 1. The configuration of the CD20 molecule with binding sites of CD20 monoclonal antibodies, ofatumumab, ublituximab, ocrelizumab and rituximab.

T cells directed against CD19+ B cells, which are thought to play a central role in driving the autoimmune response. Compared with monoclonal antibodies, CAR T cells demonstrate superior cytotoxic potential and the ability to penetrate immune-privileged sites such as the CNS. This suggests that more complete and durable depletion of pathogenic B cells may reset the dysfunctional immune system and halt the neurodegenerative processes characteristic of MS [4,7].

Given the transformative impact of CD19-targeted CAR T-cell therapy in hematologic malignancies and its emerging role in autoimmune diseases such as systemic lupus erythematosus, there is increasing interest in its application for MS. In a recent exploratory effort [4], CAR T-cell therapy was administered to two individuals with progressive forms of MS. Despite initial concerns about immune effector cell-associated neurotoxicity syndrome (ICANS), which is a known complication of CAR T-cell therapy, the treatment demonstrated a surprisingly favourable safety profile, even in the presence of CAR T cells detected in the cerebrospinal fluid. Notably, one patient exhibited a marked reduction in intrathecal antibody levels through day 64 post-treatment, suggesting significant modulation of the central immune environment. These preliminary observations support the hypothesis that, pending further research and controlled clinical trials, CAR T-cell therapy could become a viable and transformative strategy in the long-term management of MS [4].

Stem cell therapy and autologous hematopoietic stem cell transplantation (aHSCT)

Current therapeutic strategies for neurological disorders, including MS, are largely centred on symptom control and delaying disease progression, rather than directly targeting the root causes of the condition. This is largely due to the incomplete understanding of the precise pathophysiology underlying many neurological diseases, which hampers the development of truly disease-modifying treatments. As a result, there is an urgent need for innovative therapeutic approaches capable of not only halting disease progression but also promoting regeneration of damaged neural tissue, replacing lost neurons, and restoring functional integrity.

One of the most promising avenues in this regard is stem cell-based therapy. Stem cells are particularly attractive in regenerative medicine because of their unique abilities to self-renew and differentiate into various specialised cell types. A wide range of stem cell types, including mes-

enchymal stem cells (MSCs), neural stem cells (NSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs), has been explored for their potential to repair and regenerate the CNS [13]. Preclinical research in animal models has demonstrated that stem cells can differentiate into neuronal and glial lineages, integrate into existing neural networks, and contribute to functional recovery in various neurological conditions. Among these, autologous haematopoietic stem cell transplantation (aHSCT) has emerged as a clinically viable option for patients with aggressive or treatment-resistant forms of MS.

The procedure involves collecting the patient's own haematopoietic stem cells, followed by intensive immunoablative therapy and subsequent reinfusion of the harvested cells. This process is intended to eliminate autoreactive immune populations and promote the reconstitution of a more tolerant immune repertoire, thereby interrupting the pathological mechanisms responsible for CNS inflammation and demyelination [13,14]. Accumulating evidence indicates that aHSCT can induce prolonged remission and achieve high rates of no evidence of disease activity (NEDA), particularly in patients with relapsing forms of MS characterised by ongoing inflammatory activity. Comparative studies have demonstrated superior control of relapses and MRI activity following aHSCT compared with several conventional high-efficacy disease-modifying therapies, while long-term observational data suggest that many patients maintain stable neurological function and remain free from disability progression for five years or longer after transplantation [13–16]. In addition, some individuals experience sustained improvements in disability scores, supporting the possibility that immune reconstitution may not only halt disease activity but also facilitate functional recovery [13,15].

Despite these encouraging outcomes, aHSCT remains associated with significant challenges. Careful patient selection, optimisation of conditioning regimens, and minimisation of treatment-related toxicity are essential to maximise clinical benefits while reducing risks. Advances in transplantation protocols over the last two decades have markedly improved the safety profile of the procedure, leading to substantially lower treatment-related mortality and better overall outcomes [14–16]. Ongoing research is also focused on refining cell processing techniques, integrating personalised therapeutic strategies, and identifying biomarkers that may predict treatment response [13].

Future developments in regenerative medicine, cellular engineering, and precision medicine are expected to further enhance the efficacy and accessibility of stem cell-based therapies. Nevertheless, additional prospective studies and long-term randomised clinical trials are needed to better define the optimal timing of transplantation, establish standardised treatment protocols, and clarify the long-term benefits of aHSCT in different phenotypes of multiple sclerosis and other neuroinflammatory disorders [13–16].

Bruton tyrosine kinase inhibitors

Emerging evidence indicates that a substantial component of disability accumulation in MS occurs independently of overt relapse activity, a process defined as progression independent of relapse activity (PIRA) [17,18]. This observation challenges the traditional paradigm that primarily attributes disease worsening to focal inflammatory relapses and helps explain why B cell–depleting monoclonal antibodies, such as rituximab, ocrelizumab, and ofatumumab, despite their robust efficacy in suppressing clinical relapses, exert only a modest effect on long-term disease progression. The limited impact of these agents on PIRA is likely due to insufficient penetration into the CNS, which limits their ability to modulate compartmentalised inflammation in the brain and spinal cord, an increasingly recognised driver of progressive pathology. Moreover, prolonged use of non-selective B cell–depleting therapies leads to sustained peripheral B cell depletion, potentially increasing the risk of serious infections and malignancies [18,19].

In this context, Bruton's tyrosine kinase (BTK) inhibitors have emerged as a promising therapeutic strategy. BTK is a key proximal mediator of B cell receptor signalling, regulating B cell maturation, activation, survival, and cytokine production, as well as antigen-dependent T cell activation. Consequently, BTK has become an established therapeutic target in B cell malignancies and an expanding range of autoimmune diseases. Beyond B lymphocytes, BTK plays conserved functional roles in innate immune cells, including macrophages, microglia, and mast cells, where

it governs cellular activation and the release of pro-inflammatory cytokines [19–21]. Importantly, the development of CNS–penetrant BTK inhibitors offers a promising strategy to simultaneously modulate peripheral immune drivers of relapses and compartmentalised CNS inflammation implicated in disability progression in MS.

Evobrutinib is a highly selective, CNS-penetrant BTK inhibitor and was the first compound of this class to be evaluated in MS [18,21]. In 2024, results from several clinical trials investigating evobrutinib and tolebrutinib were reported. In the phase 3 evolutionRMS1 and evolutionRMS2 trials [21], evobrutinib did not demonstrate superiority over teriflunomide in reducing focal inflammatory activity or confirmed disability accumulation. In contrast, tolebrutinib showed efficacy in reducing confirmed disability progression across three clinical trials involving patients with RRMS and SPMS (GEMINI I, GEMINI II, and HERCULES) [18,20]. Notably, subsequent analyses revealed that the beneficial effect of tolebrutinib on disability progression was confined to patients with paramagnetic rim lesions (PRLs) at baseline. This finding is particularly noteworthy given tolebrutinib's modest impact on markers of acute focal inflammation, providing early evidence that progression-related pathology may be modulated independently of acute inflammatory activity, potentially through effects on B cells and/or myeloid cells [20].

Recent data have further strengthened the therapeutic rationale for BTK inhibition in MS, particularly through the development of fenebrutinib, a highly selective, reversible, and CNS-penetrant BTK inhibitor. Unlike other agents within this class, fenebrutinib has demonstrated efficacy across multiple MS phenotypes, including relapsing MS and primary progressive [22,23]. In the phase 2 FENopta study [B] and its open-label extension, fenebrutinib was associated with sustained suppression of clinical and radiological disease activity, with no disability progression over follow-up periods extending to 96 weeks. Ongoing phase 3 studies are currently evaluating its efficacy in RMS (FENhance 1 and 2) [22] and PPMS (FENtrepid) [23]. Preliminary phase 3 data [23] suggest superiority over teriflunomide in reducing disease activity in relapsing MS and indicate efficacy comparable to ocrelizumab in slowing disability progression in PPMS. Although these findings require confirmation in full peer-reviewed publications, they provide further support for the concept that CNS-penetrant BTK inhibition may address both acute inflammatory activity and progression-related pathology, including PIRA.

Clemastine

Clemastine fumarate, a first-generation antihistamine with anticholinergic properties, has been investigated for its potential to promote remyelination in MS by enhancing the differentiation of oligodendrocyte precursor cells into myelinating oligodendrocytes [24]. Early preclinical studies and a phase II clinical trial (*ReBUILD*) [25,26] demonstrated that clemastine treatment could accelerate conduction across demyelinated visual pathways and improve imaging biomarkers of myelin repair in people with MS, supporting its biological remyelinating activity. In a recent biomarker-guided clinical study (*TRAP-MS*) [25,27], clemastine was evaluated in patients with PIRA-driven progressive disease. However, the clemastine arm was terminated early for safety reasons, as treated patients exhibited a significantly greater rate of disability progression compared with other participants. Proteomic analyses of cerebrospinal fluid from these patients revealed pronounced activation of purinergic signalling and pyroptosis-related pathways after clemastine treatment, implicating inflammasome activation and inflammatory cell death in macrophages and oligodendrocytes as potential mechanisms underlying this adverse effect [27].

These findings highlight a complex and context-dependent role for clemastine in MS. While remyelinating effects have been observed in some settings, its administration in patients with advanced, non-lesional disease may exacerbate compartmentalised inflammatory injury through pyroptosis. Further research is needed to delineate the conditions under which clemastine's remyelinating potential might be harnessed safely and effectively [24,25].

These findings highlight a complex and context-dependent role for clemastine in MS. While remyelinating effects have been observed in select inflammatory settings, its administration in patients with advanced, non-lesional disease may exacerbate compartmentalised inflammatory injury via pyroptosis [25]. Accordingly, recent research [28] has focused on strategies to opti-

mise the remyelinating potential of clemastine by targeting additional biological constraints on oligodendrocyte precursor cell (OPC) function. Age-related intrinsic changes in OPCs have been shown to reduce their responsiveness to pro-differentiation signals, a deficit that can be reversed by metformin by modulating AMPK–mTOR signalling pathways. This mechanistic rationale underpins the ongoing phase IIa CCMR Two trial [28], which evaluates the combination of metformin and clemastine in patients with relapsing-remitting MS and chronic stable optic neuropathy. By simultaneously rejuvenating OPC responsiveness and promoting muscarinic-dependent differentiation, this combination approach aims to enhance remyelination in a biologically permissive disease context, in contrast to the adverse outcomes observed with clemastine monotherapy in progressive, PIRA-driven MS [28].

Future directions and conclusion

New therapeutic strategies for MS are rapidly reshaping the treatment landscape, moving beyond nonspecific immunosuppression toward targeted, mechanism-based interventions. Agents currently under advanced clinical investigation, such as frexalimab and CAR-T cell therapies [4–6], have demonstrated highly promising results in terms of both efficacy and safety, raising the prospect of long-lasting disease control and, in selected cases, profound immune reconstitution. In parallel, anti-CD20 monoclonal antibodies remain a cornerstone of high-efficacy treatment for relapsing forms of MS [7,9]. Among them, ublituximab represents a next-generation, glycoengineered antibody with enhanced antibody-dependent cellular cytotoxicity and rapid B-cell depletion, potentially translating into improved clinical and radiological outcomes [8].

Despite these advances, it has become increasingly evident that the suppression of focal inflammatory activity alone is insufficient to fully prevent the accumulation of disability, particularly PIRA [14,17]. This realisation has driven the development of CNS-penetrant therapies such as Bruton tyrosine kinase inhibitors, which target both peripheral B cells and compartmentalised innate immune responses within the CNS. Early clinical data suggest that modulation of progression-related pathology may be achievable independently of relapse suppression, marking an important conceptual shift in MS therapeutics.

At the same time, regenerative and reparative strategies are emerging as a critical next frontier. Remyelination-promoting approaches, exemplified by clemastine and combination strategies targeting oligodendrocyte precursor cell ageing, highlight both the potential and the challenges of enhancing CNS repair [25–28]. While remyelinating effects have been demonstrated in biologically permissive settings, recent studies underscore the context-dependent risks of such interventions in advanced disease, emphasising the need for careful patient selection. In parallel, stem cell–based therapies, particularly autologous hematopoietic stem cell transplantation, offer a means of immune system "resetting" and have shown durable disease stabilisation in aggressive MS phenotypes [14–17].

In summary, emerging therapies in MS collectively signal a transition toward precision medicine, integrating targeted immunomodulation, control of progressive pathology, neuroprotection, and CNS repair. Although no single therapy can yet be considered curative, the convergence of these approaches offers renewed optimism that sustained remission, meaningful inhibition of disability progression, and even partial reversal of existing CNS damage may become achievable goals in the foreseeable future. Continued long-term studies and real-world evidence will be essential to define the optimal positioning of these therapies and to tailor treatment strategies to individual patient biology and disease stage.

Declarations and statements

Conflict of interest statement

Anna Jamroz-Wiśniewska received honoraria for lectures and participated in conferences organised by pharmaceutical companies: Bayer, Biogen, BMS, Merck, Novartis, Roche, Sandoz, Teva.

Konrad Rejdak received honoraria for lectures and participated in conferences organised by pharmaceutical companies: Bayer, Biogen, BMS, Merck, Novartis, Roche, Sandoz, Teva. The other authors declare no conflict of interest.

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