REVIEW ARTICLE

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Immunopathogenesis of multiple sclerosis – mechanisms of autoimmunity, neuroinflammation and strategies of treatment

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Abstract

Introduction and Objective. The aim of the review is to summarize current understanding of multiple sclerosis (MS) immunopathogenesis, focusing on Th17 cells, regulatory T cells, B lymphocytes, and innate immune components, while outlining contemporary and emerging therapeutic strategies.

Review Methods. A literature search was conducted in PubMed and Scopus using the key words 'multiple sclerosis', 'immunotherapy', 'autoimmunity', 'Th17 Cells', and 'B-Lymphocytes' for publications occurring in publications between 2019–2025. A total of 412,560 articles were found – 173,450 were from PubMed and 239,110 from Scopus. After applying inclusion criteria to original research, reviews, book chapters, and editorials in English, 49 articles were selected for a narrative review. Over 96% of included studies were published within the last three years, reflecting a rapidly growing interest in the topic.

Brief description of the state of knowledge. MS results from complex interactions among Th17 cells, regulatory T cells, B cells, microglia, macrophages, and astrocytes, leading to blood–brain barrier disruption, demyelination, axonal injury, and neurodegeneration. Therapeutic strategies have evolved from interferons and glatiramer acetate to oral agents, sphingosine-1-phosphate receptor modulators, monoclonal antibodies, and B-cell depleting therapies, enhancing disease control. Emerging approaches, including haematopoietic stem cell transplantation and peptide- or nanovaccine-based therapies, aim to restore immune tolerance with minimal systemic immunosuppression.

Summary. MS arises from an imbalance between pro-inflammatory and regulatory immune mechanisms. Insights into these pathways have provided information about the development of targeted, individualized treatments. Further research into immune modulation and neuroprotection may enable durable remission, prevent neurodegeneration, and improve patient outcomes.

Key words

multiple sclerosis, immunopathogenesis, Th17 cells, regulatory T cells (Treg), B lymphocytes, blood–brain barrier, demyelination, microglia, disease-modifying therapies, Immune tolerance / tolerogenic vaccines

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory autoimmune disease determined by the degradation of oligodendrocytes, leading to demyelination and focal formation of pathognomonic plaques in the white matter of the brain and spinal cord [1]. In recent years, there has been a steady upward trend in the prevalence of MS. The new edition of the *Multiple Sclerosis Atlas* estimated that the number of people with MS worldwide increased to 2.8 million in 2020, using the same methodology as in 2013, an estimate that is 30% higher than in 2013. The global prevalence in 2020 is 35.9 per 100,000 people. High-quality epidemiological data worldwide are needed to better understand the risk of the disease and to support health policies aimed at meeting the diverse needs of people with multiple sclerosis [2]. Preclinical and clinical studies have shown that MS is a disease that shows a predilection for the female with a twice as high risk [3]. MS is mostly diagnosed in people between the ages of 20–40. Unfortunately, the number of disease in children is increasing. It is currently estimated that in 3–5% of all people diagnosed with MS, the disease begins before the age of 16 [4]. A common diagnostic method is magnetic resonance imaging (MRI), an imaging study useful for monitoring the spread of the disease in space and time [5]. Personalized medicine of MS aims at an individualized approach to treatment which gives a chance to improve the health and quality of life of MS patients. The aim of our review was to deepen knowledge of immunopathogenesis of MS with regard to current and future strategies of treatment.

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MATERIALS AND METHOD

The available literature was analysed using PubMed and Scopus databases. The key words 'multiple sclerosis', 'immunotherapy', 'autoimmunity', 'Th17 Cells' and 'B-Lymphocytes' were searched for and produced a total of 412,560 articles published between 2019–2025. A total of 173,450 articles were found in the PubMed database and 239,110 in the Scopus database. A total of 49 articles were selected for narrative review using the following inclusion criteria: original articles, scientific reviews, book chapters and editorials, all written exclusively in English. Exclusion criteria included conference abstracts and duplicate publications. Significantly, more than 96% of the selected contributions were from the last three years, indicating a growing recent interest in the topic.

Historical and experimental background. Multiple sclerosis was first described in 1868 by Jean Martin Charcot, who noticed 'sclerosed plaques' in the periventricular area, pons and spinal cord [6]. Although the immunopathogenesis of multiple sclerosis is still not fully understood, recent discoveries have allowed for a better understanding of the mechanisms that determine the disease. In addition to the conclusions provided by studies on patient material, a valuable resource is the animal model of experimental autoimmune encephalomyelitis (EAE), which shows both histological and clinical similarities to multiple sclerosis. However, it should be emphasised that in the EAE model, self-limitation of the disease after a single relapse is often observed, which is in opposition to MS, which is a chronic inflammatory disease, and therefore any study with EAE should be carefully analysed. Additionally, the different methodologies, as well as the different strains of mice used in the studies, make diagnosis difficult [7].

Immunopathogenesis of MS – the role of Th-17 cells. Multiple sclerosis is classified as an autoimmune disease in which cellular and humoral immunity plays the main role [8]. MS is believed to be a T helper (Th)-17-driven pathology. Th17 cells are characterized by the expression of retinoic acid receptor-related orphan receptor gamma t (RORγt) and the production of interleukin (IL)-17, which increases the permeability of the blood-brain barrier by stimulating the generation of reactive oxygen species. IL-17 also induces the expression of C-C motif chemokine ligand 20 (CCL20), highly activated in inflammatory sites, and by interacting with cells of the central nervous system (CNS), it contributes to the production of inflammatory mediators [9, 10]. Interferon (IFN)-γ secreted by T helper (Th)-1 stimulates the expression of major histocompatibility complex (MHC) class II molecules and adhesion molecules on cerebrovascular endothelial cells, thanks to which activated T lymphocytes migrate to the site of autoantigen [11]. The cross-functional immune response is most likely directed mainly against myelin basic protein (MBP), as well as myelin-associated glycoprotein (MAG), proteolipid protein and myelin oligodendrocyte glycoprotein (MOG). [12] Infiltrating cells show many activation markers, e.g. CD25. Granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by Th1 and Th17 cells, and other pro-inflammatory cytokines are released, leading to the initiation of the inflammatory response. CD4+ T cells stimulate cytotoxic T lymphocytes (Tc), macrophages and B lymphocytes. Macrophages adhere to the myelin sheath, systematically destroying and phagocytising it [13, 14]. Initially, the destroyed myelin sheath is reconstituted, but with each successive flare-up, this process occurs less successfully and the exposed axon eventually degenerates. At the site of destruction, astrocyte proliferation occurs, leading to the formation of a glial scar. [15]. The resulting lesions may remyelinate, remain partially demyelinated, or slowly expand, due to the protective or neurotoxic role of oligodendrocyte precursor cells (OPC) [16, 17].

Regulatory mechanisms and the role of regulatory T cells in MS. Another group of cells that influence immune mechanisms important for the pathology of multiple sclerosis are regulatory T cells (Tregs). Tregs regulate various cell types, including Th1, Th17, cytotoxic CD8+ lymphocytes and antigen-presenting cells (APC) through various mechanisms, such as the secretion of IL-10 and transforming growth factor (TGF)-β [18]. It has been shown that in MS the number of Tregs decreases, which correlates with reduced Treg suppressive activity and the resistance of pathogenic T lymphocytes to regulation by Tregs increases. This contributes to the survival, proliferation and differentiation of myelin-reactive CD8+, Th17 and B cells [19, 20].

Unconventional T cell subsets in MS – iNKT and γδ T cells. In addition to conventional T lymphocytes, unconventional cells such as invariant natural killer T (iNKT) cells – the classic type I NKT cells – are also involved in the pathogenesis of MS. In the early stages of inflammation, iNKTs can rapidly release cytokines and exhibit cellular cytotoxicity. From studies of peripheral blood of patients in remission or relapse of the projection-remission form of MS versus healthy patients, it appears that there is an over-expression of RORγT and IL-23 receptor (IL-23R) in iNKT in the first comparison group, and a significant increase in iNKT17 is observed during remission. However, the small number of iNKT cells in the patient material makes it difficult to draw firm conclusions, which is not a limitation for studies in EAE models. This is supported by studies in mice with insufficient numbers of iNKT, which correlated with a more severe course of EAE. Adequate stimulation of iNKT seems to lead to IL-4 production, and thus the formation of T helper 2 (Th2) cells and Treg cells with partly protective functions against EAE. [7]. Numerous studies indicate that T γδ lymphocytes are also involved in the pathogenesis of MS. They may contribute to demyelination through cytotoxic effects on oligodendrocytes. In addition, it has been observed that in the initial course of EAE, γδ T cells demonstrate the ability to produce IL-17 contributing to inflammation, and thus exacerbating the disease, and IFN-γ which acts suppressively on Th17 cells and attracts Treg cells [21].

The role of B cells in the pathogenesis of MS. Initially, it was believed that T lymphocytes were mainly involved in the development of multiple sclerosis, however, numerous studies indicate that B lymphocytes also play an important role in the pathology of the disease. CNS damage is based on two mechanisms: antibody-dependent and antibody-independent [22]. Once activated, B cells differentiate into memory cells (Bmem) or plasma cells that produce autoantibodies against specific myelin antigens involved in antibody-dependent cytotoxicity (ADCC) and complement damage [8, 23].

An indicator of the intrathecal synthesis of IgG and IgM immunoglobulins in the CNS is the presence of oligoclonal bands (OCB) in the cerebrospinal fluid in over 90% of patients with multiple sclerosis, which is an important diagnostic criterion of the disease [24]. In addition to their antibody-producing function, B cells can release pro-inflammatory cytokines, such as lymphotoxin alpha, tumour necrosis factor (TNF)-α, GM-CSF, and anti-inflammatory cytokines such as TGF-β1, IL-10, IL-35, which regulate inflammation in experimental models of multiple sclerosis [25]. B cells also have a role as antigen-presenting cells (APCs) involved in lymphocyte activation and the formation of ectopic follicle-like aggregates in the meninges in progressive multiple sclerosis. [26] In addition to B cells, they may also include T lymphocytes and follicular dendritic cells, which contribute to the demyelination of oligodendrocytes [27] (Tab. 1).

Table 1. Main role of selected cells in pathogenesis of MS

Type of cells	Main function in the pathogenesis of MS
Th17	Production of IL-17, which increases T-cell proliferation, promotes neutrophil recruitment and activity, promotes cytokine and chemokine production
Tregs	Decreased inhibition of pathogenic T-cell
CD8+ cytotoxic T cells	Release of TNF- α, IFN-γ, secretion of perforin and granzyme
B cells	Antibody production, antigen presentation, release of lymphotoxin and TNF-α
Microglia and macrophages	Involvement in neurodegeneration, phagocytosis of myelin sheath, antigen presentation

Abbreviations: Th17 T – helper 17 cells; IL-17 – Interleukin-17; Tregs – Regulatory T cells; TNF-α – Tumour necrosis factor alpha; IFN-γ – Interferon gamma

Integrated immunopathogenesis of multiple sclerosis. Damage to the CNS is driven by activated immune cells within the CNS [1]. Pathogenic Th subsets secrete pro-inflammatory cytokines, such as TNF-α, IFN-γ, and IL-17, which induce pathogenic responses in microglia and macrophages. This activation and recruitment of immune cells are supported by astrocyte activity, which promotes additional immune responses through the secretion of cytokines and chemokines, leading to microglial activation and monocyte recruitment. This response drives further pathogenic behaviours mediated by macrophages, B cells, and cytotoxic T lymphocytes [2]. Multiple mechanisms contribute to myelin and axonal damage, primarily through the production of soluble neurotoxic molecules, including MMPs, TNF-α, ROS, and RNS, secreted by astrocytes, macrophages, and microglia, as well as activated CD8+ T cell cytotoxicity, ADCC, and complement. Further damage is facilitated by astrocytes, which not only exhibit neurotoxic activity through NO release, but also show reduced production of neurotrophic factors and diminished metabolic support for neurons, thereby contributing to neuronal injury [3]. Local CNS inflammation associated with MS relapses is limited and resolved by FOXP3+ Tr1 Treg cells through the secretion of immunoregulatory cytokines, such as IL-10 and TGF-β, along with additional mechanisms (Fig. 1).

Immunological classification of therapeutic strategies in multiple sclerosis. Understanding the pathomechanism of multiple sclerosis enables the development of therapeutic strategies aimed at halting disease progression and improving

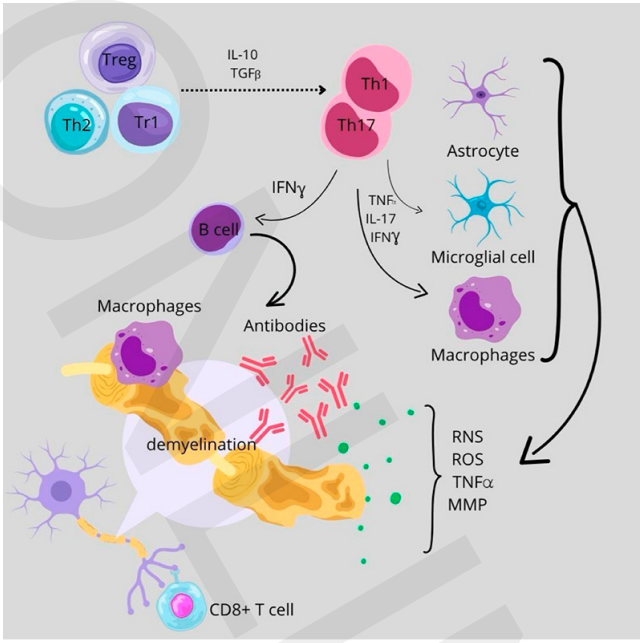

Figure 1. Immunopathogenesis of multiple sclerosis: interactions between Th17, Treg, B cells, cytotoxic T cells, microglia, macrophages, and astrocytes leading to CNS inflammation, demyelination, and neurodegeneration. Key mediators include TNF-α, IFN-γ, IL-17, ROS, RNS, and MMPs, with Treg cells contributing to local immunoregulation. Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CNS, central nervous system; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; MS, multiple sclerosis; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor; Tr1, type 1 regulatory T cell; Treg, regulatory T cell

patients' quality of life. Knowledge of the stages of pathogenesis provides potential targets for pharmacological intervention during MS therapy. Historically, the gold standard included interferons β-1a, β-1b, natural interferon β-1a, and glatiramer acetate, whereas currently, two oral agents are available: dimethyl fumarate (DMF) and teriflunomide. Beyond these, sphingosine-1-phosphate (S1P) receptor modulators, including fingolimod, ozanimod, ponesimod, and siponimod, constitute another class of disease-modifying therapies. Monoclonal antibodies – including natalizumab, alemtuzumab, ofatumumab, ocrelizumab,and ublituximab-offer highly effective disease modification through targeted immune mechanisms. Cladribine, in turn, represents a distinct therapeutic category, exerting selective and long-lasting depletion of B and T lymphocytes through short oral treatment courses, which ensures high efficacy with limited annual exposure compared with other therapeutic classes. Optimal therapy should be tailored to the individual needs of each patient, depending on the clinical phenotype and degree of disease activity.

Classical immunomodulatory therapies – interferons and glatiramer acetate. The first group of drugs with immunomodulatory activity are recombinant interferons (IFN) β-1a, β-1b, natural interferon β-1a and glatiramer acetate. Interferons are effective in milder form of relapsing MS. Their action is based on the fact that it balances the expression of pro- and anti-inflammatory cytokines in the brain and reduces the number of inflammatory cells that cross the blood-brain barrier. The effect is to reduce neuronal inflammation. Additionally, IFN-β significantly reduces the Th17 population and IL-17 cytokines, which are involved in the immunopathophysiology of MS. Drugs are administered

in the form of intramuscular or subcutaneous injections and this method is associated with relatively common side-effects, which include local allergic reaction, erythema, and in some cases, even local necrosis. The use of IFN should be continuously monitored and subjected to periodic check-ups because more serious side-effects may occur, such as thrombotic microangiopathy (TPA), haemolytic uremic syndrome and thrombocytopenic purpura. [28] Modern therapies are based on modifying immune cell activation pathways by influencing elements that stimulate and lead to the body's autoimmune response. One of many such methods is the use of IFN-β, which inhibits T-cell activation, diverts T-cell differentiation into helpful anti-inflammatory T2 cells (activation of IL-10 production), and further impedes the penetration of aggressive lymphocytes into target nerve cells by blocking adhesion molecules and metalloproteases. [1] Opportunities in modifying the course of the disease are also provided by the fact that T cells are aggressive towards the myelin sheath, which allows immunomodulation by promoting lymphocytes to an anti-inflammatory phenotype, and this leading to reduced autoreactivity towards myelin. T-cell and B-cell division is activated by, among other things, the enzyme dihydroorotate dehydrogenase. If this is inhibited, T and B cell proliferation will stop. In addition, if there is sequestration of lymphocytes in the lymph nodes through inhibition of the sphingosine-1-phosphate (S1P) gradient, this will also result in a reduction in the number of lymphocytes circulating in the blood, and thus a reduction in the number of inflammatory cells that could attack myelin cells in the CNS. Another possibility of reducing the number of T and B cells is the impaired synthesis of their deoxyribonucleic acid (DNA). Also, the solution for preventing lymphocyte migration into the CNS is to inhibit their adhesion to the blood-brain barrier endothelium by disrupting the alpha integrin chain (VLA-4). The use of anti-CD20 and anti-CD52 monoclonal antibodies will also reduce the number of B and T lymphocytes [29]. Glatiramer acetate is also given by subcutaneous injection. The preparation is used in the relapsing-remitting form of multiple sclerosis and effectively reduces the symptoms of the disease and slows down its development. However, like interferons, it is not very effective in reducing the activity of disease. Side-effects result from this method of administration (pain, redness at the injection site) [30]. Compared to interferons, glatiramer acetate does not carry an increased risk of depression, hallucinations or suicidal thoughts [31].

Oral immunomodulatory agents in multiple sclerosis therapy. Teriflunomide inhibits the enzyme dihydroorotate dehydrogenase, which limits the proliferation of activated T and B lymphocytes, thereby modifying the autoimmune response. It functions primarily as a regulator of lymphocyte proliferation rather than inducing their full depletion, which results in a relatively favourable safety profile but only moderate efficacy. In terms of classification by mechanism of action, it belongs to the group of drugs with mild to moderate immunomodulatory effects, and it is less effective in reducing recurrence and progression of disability [32].

Dimethyl fumerate (DMF) works by activating the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway. It significantly delays the onset of the first clinical demyelinating episode in individuals with radiologically isolated syndrome (RIS). The risk of RIS conversion to the first symptomatic relapse of MS was significantly lower in the DMF-treated group than in the placebo group (HR = 0.18; 95% CI = 0.05–0.63; p = 0.007). The DMF safety profile was favourable [33].

Selected strategies of treatment. The newer class of drugs includes, among the others, cladribine, natalizumab and fingolimod. Natalizumab is a monoclonal antibody against α4-integrin. It reduces the number of activated T lymphocytes in the CNS, has a neuroprotective effect, and visibly reduces the progression of the disease and the associated disability. It is Treatment with natalizumab, administered intravenously once a month, is indicated in highly active relapsing-remitting MS, but it is not the drug of choice for patients with secondary and primary progressive MS, as well as nor for patients struggling with immunodeficiencies. During therapy with natalizumab, patients may experience headaches and increased liver enzymes activity. [34] The most serious side-effect is the risk of progressive multifocal leukoencephalopathy (PML), a disease caused by the reactivation of the John Cunningham virus (JCV). People who are prone to development of PML are primarily those who are treated with chemotherapy drugs and monoclonal antibodies, i.e. those whose immune system response is disturbed. [35]

Fingolimod, sphingosine-1-phosphate receptor (S1PR) modulator, is a drug approved for oral home therapy. The mechanism of action concretises on binding to lymphocytes, resulting in receptor internalisation. As a result, reactivity to the S1P gradient, which regulates the exit of lymph nodes by lymphocytes, decreases. This decreases the proportion of inflammatory cells reaching the CNS. Conducting fingolimod therapy increases the number of regulatory T cells and naive B cells with a decrease in memory B cells and naive T cells. The result is an inhibition of the inflammatory response [36]. Today, similar therapeutics have been approved: ozanimod, siponimod and ponesimod. It is necessary to monitor the first dose of fingolimod due to the possibility of cardiac arrhythmias. Fingolimod reduces the infiltration of potentially autoreactive lymphocytes into the CNS, which causes them to remain in the lymph nodes. This prevents the destruction of the myelin sheath. Additionally, fingolimod slows brain atrophy in MS patients [37].

In 2020, cladribine, a chlorinated deoxyadenosine analogue, was recommended in more than 75 countries for the treatment of relapsing forms of multiple sclerosis. [38] The mechanism of action is based on the induction of preferential phosphorylation in B and T lymphocytes due to the high levels of deoxycytidine kinase (DCK) present, and the relatively low levels of 5'- NTase in comparison to other cells. Oscillation of DCK at high levels is important for the clonal expansion of lymphocytes during development and immune responses [39]. Cladribine does not interact with the innate immune system, but focuses on reducing cells of the adaptive immune system. This results in a rapid decline to the lowest level in the number of B and T lymphocytes, and consequently in the absolute number of lymphocytes. The return to the correct cell count starts smoothly and lasts for up to several months after the end of treatment [40]. According to the researchers' analysis, 58% of MS patients had no relapses during treatment, and 79% reported progression-free survival after treatment. Infections proved to be the most common adverse reactions after treatment, affecting 10% of people. The incidence of malignant tumours oscillated around 0.4% of patients. [41]

Emerging immunotherapies. Observations from recent clinical trials on immunotherapy for MS demonstrate that the pathomechanism of the disease is determined not only by the function of T lymphocytes, but also of B lymphocytes and myeloid cells. The aim of immunotherapy is to regulate these processes [42]; therefore, a good line of action would be to develop immunological tests to detect abnormalities in the patient's immune system. Based on the available information, a compilation has been made of the discussed drugs approved by the FDA for the treatment of multiple sclerosis (Tab. 2).

Challenges and innovations in multiple sclerosis immunotherapy. Unfortunately, immunotherapy is associated with side-effects. Attention should be paid to natalizumab therapy as it is associated with the occurrence of PML. Patients with a history of immunosuppressive treatment, treatment lasting more than two years, and the presence of anti-JCV antibodies are predisposed to its occurrence. Patients also have a higher risk of PML after treatment with fingolimod and dimethyl fumarate [44].

Another therapeutic option is autologous haematopoietic stem cell (HSCs) transplantation. The cells in question are harvested from bone marrow, and exposed to granulocyte colony-stimulating factor (G-CSF) and cyclophosphamide, after which they are purified and frozen until transplantation [45].

Conjugates of myelin peptides and mannan have also been shown to be promising peptide vaccines for immunotherapy in multiple sclerosis. Mannan serves as a carrier, delivering antigenic peptides to dendritic cells for presentation to T cells, while myelin epitopes, such as MOG 35–55, MBP 83–99, and PLP 131–145, exhibit immunomodulatory properties in experimental models. Novel methods for quantitatively measuring these peptide components have been developed as a prerequisite for clinical evaluation [46]. Another study describes A tolerogenic nanovaccine based on mesoporous polydopamine nanoparticles loaded with disease-specific autoantigens has also been described. The nanovaccine is designed to induce antigen-specific immune tolerance by promoting tolerogenic dendritic cells, which in turn stimulate regulatory T cells, reducing autoreactive T cell and inflammatory antigen-presenting cell activity [47]. A study from 2023 presents a multi-epitope Tregitope-based vaccine for multiple sclerosis, designed to induce tolerance in pathogenic myelin-specific T cells. The vaccine combines an anti-DEC205 antibody, T cell epitopes including Treg-inducing sequences, and a vasoactive intestinal peptide, with computational modelling supporting its structure and immunological properties, suggesting potential to modulate disease progression and prevent relapses [48].

Table 2. Targets and mechanisms of selected therapies on immune cells associated with multiple sclerosis [41,42]

	Natalizumab	Cladribine	Fingolimod
Targets	*Blocks α4-integrin*	*Purine analogue*	*Modulates S1PRs*
Mechanism	Limits immune cell trafficking into CNS	Accumulation of the drug leads to preferential depletion of lymphocytes	Sequesters recirculating immune cells in lymph nodes
Impact on CNS-resident T cells	Decreases microglia activation	Decreases microglia activation	Decreases pro-inflammatory cytokines and neurotoxicity, increases neurotrophic mediators
Impact on NK cells	Increases NK cell proportion	Decreases the cell count	Decreases $CD56^{bright}$ NK cells, increases $CD56^{dim}$ NK cells
Impact on B cells	Increases peripheral effector B cell count	Preferentially decreases memory B cells, increases transitional B cells and plasma cells	The count of all B-cell subsets is decreased, transitional B cells are less affected
Impact on myeloid lineage cells	Increases myeloid lineage-cell pro-inflammatory cytokines, decreases antigen-presenting cell function	Induces apoptosis in dendritic cells, decreases capacity of dendritic cells to polarise T cells	Count is unchanged, frequency is increased, decreases pro-inflammatory myeloid lineage cells
Impact on $CD20^{dim}$ T cells	Increases peripheral $CD20^{dim}$ T cells	Unknown	Decreases count, increases proportion
Impact on $CD8^{+}$ T cells	Increases peripheral effector CD8+ T cells	Decreases the cell count	CD8+ T cell count is decreased (less than that of CD4+ T cells)
Impact on $CD4^{+}$ T cells	Increases peripheral effector CD4+ T cells	Decreases the cell count	Naive T cells are preferentially decreased, the proportion of memory effector T cells is increased

Abbreviations: CNS – Central nervous system; *NK cells* – Natural killer cells; *S1PRs* – Sphingosine-1-phosphate receptors; $CD56^{dim}$ NK cells – cytotoxic NK cells; $CD56^{bright}$ NK cells – regulatory / cytokine-secreting NK cells

CONCLUSIONS

Multiple sclerosis is a chronic, immune-mediated disorder that develops as a result of complex interactions among T and B lymphocytes and components of the innate immune system. These processes ultimately cause demyelination, axonal injury, and progressive neurodegeneration. Our current understanding of MS pathogenesis indicates that the disease is not driven by a single immune pathway, but rather by an imbalance between pro-inflammatory and regulatory mechanisms. In particular, Th17 cells and their cytokines – especially IL-17 – are known to disrupt the blood–brain barrier and sustain neuroinflammation, while insufficient regulatory T-cell activity allows autoreactive responses to persist. Increasing evidence has also underscores the pivotal role of B cells, both as antibody producers and as antigen-presenting cells, which has significantly influenced the design of modern therapeutic strategies.

The evolution of disease-modifying therapies reflects the expanding knowledge of MS immunology. Early treatments, such as interferons and glatiramer acetate, offered modest clinical benefits by modulating cytokine profiles and limiting lymphocyte migration. The introduction of oral agents, including dimethyl fumarate and teriflunomide, improved adherence and accessibility, although their efficacy remains limited in highly active forms of the disease. A major advance came with the development of sphingosine-1-phosphate receptor modulators – fingolimod, ozanimod, siponimod, and ponesimod – which functionally sequester autoreactive lymphocytes and may provide additional neuroprotective effects.

Monoclonal antibodies, such as natalizumab, alemtuzumab, ocrelizumab, ofatumumab and ublituximab, have further reshaped the therapeutic landscape by targeting specific immune cell subsets and substantially reducing relapse rates. However, their potency also brings distinct safety concerns, most notably the risk of PML (Progressive Multifocal Leukoencephalopathy) in patients with John Cunningham (JC) virus reactivation. Another option, the oral lymphocyte-depleting agent cladribine, achieves durable immune reconstitution with limited cumulative exposure, combining long-term efficacy with a relatively low immunosuppressive burden.

In recent years, research has shifted toward approaches aimed at restoring immune tolerance rather than broadly suppress immune activity. Investigational strategies, such as haematopoietic stem cell transplantation, peptide-based vaccines, and nanovaccine platforms, seek to re-establish immune balance while minimizing systemic toxicity. These innovations are increasingly supported by advances in immunogenetics and computational modelling, which together pave the way for more personalized treatment design.

Overall, MS management is steadily moving toward precision medicine – an approach that integrates immunological profiling, disease phenotype, and patient-specific factors, to guide therapy selection. Instead of generalized immune modulation, future strategies should focus on recalibrating immune responses and preventing neurodegeneration. Continued exploration of neuroimmune mechanisms will be crucial for the development of therapies capable of achieving durable remission and long-term preservation of neural tissue.

Conflicts of Interest

The authors declare no conflicts of interest.

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