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REVIEW

The Evolving Landscape of Multiple Sclerosis Therapy

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Abstract: The therapeutic landscape for multiple sclerosis has evolved markedly in recent years, with an expanding arsenal of disease-modifying therapies offering clinicians more tools to manage the disease. This progress presents both opportunities and complexities, as treatment decisions increasingly require individualized strategies balancing efficacy, safety, and long-term outcomes. While current therapies effectively reduce inflammation and delay disease progression, they fall short in halting neurodegeneration, highlighting a critical unmet need. Treatment paradigms range from escalation strategies prioritizing safety to early high-efficacy approaches aimed at aggressive disease control. Data increasingly support early initiation of high-efficacy DMTs in patients with poor prognostic indicators, but concerns over long-term safety and tolerability remain. Shared decision-making, informed by patient preferences and evolving evidence, is central to modern MS care. The future is promising, with new therapies in advanced stages of research, which seek to exceed the limits of current therapy, to act in a targeted manner, limiting both inflammation and neurodegeneration, for better control of disease activity, with an improved safety profile.

Keywords: Multiple sclerosis; Disease-modifying therapies; Treatment strategies; Neurodegeneration; High-efficacy therapy; Escalation approach; Personalized medicine; Shared decision-making; Long-term safety; Neuroprotection.

INTRODUCTION

Multiple sclerosis (MS), an autoimmune disease of the central nervous system, predominantly affects young people, especially women, and is the leading cause of non-traumatic disability among them (1). Although the etiology is unknown, studies show that it occurs as a consequence of a complex interaction between genetic and environmental factors (2). The clinical manifestations and the evolution of the disease are extremely variable and unpredictable.

Despite this heterogeneity, treatment options were once limited, making therapeutic decisions relatively straightforward. However, in recent years, the treatment of MS patients has evolved significantly due to the availability of new disease-modifying therapies (DMTs). While this progress marks a significant advancement, it also presents new challenges for clinicians, who must now navigate complex treatment decisions tailored to individual patients. Compounding these challenges is the uncertainty surrounding the long-term safety of newer DMTs.

Current treatments do not stop the underlying neurodegeneration, even though they successfully reduce inflammation and provide clinical and radiological benefits. The goal of ongoing research is to close this gap. New treatments with a higher safety profile are needed because the existing ones have long-term immunologic hazards and side effects.

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MULTIPLE SCLEROSIS PATHOGENESIS

Under physiological conditions, the central nervous system (CNS) is considered an immune-privileged environment, as the passage of cells and molecules across the blood–brain barrier (BBB) is tightly regulated. However, in MS, this protective mechanism becomes compromised. Autoreactive B and T lymphocytes are able to cross the BBB and infiltrate the CNS, where they induce lesions, particularly in the white matter (3). These lesions are characterized by inflammation, demyelination, and axonal loss (4). Notably, MS has significant immunopathological variability: certain forms are dominated by inflammation and relapses, whilst others are driven predominantly by neurodegeneration, as shown in progressive forms of the illness (5), (6). Although the full pathophysiologic mechanisms remain unclear, crucial stages in lesion formation have been discovered, and current DMTs are meant to target various locations.

The autoimmune process in MS is initiated in the peripheral immune system. Antigen-presenting cells, primarily dendritic cells, present self-antigens (myelin-derived autoantigens) to lymphocytes, which may then become autoreactive (7), (8). Under normal conditions, physiological defense mechanisms such as immune tolerance act to prevent this. Regulatory T cells, regulatory B cells, and natural killer (NK) cells play key roles in identifying and eliminating autoreactive lymphocytes. However, when the function of these regulatory cells is impaired, autoreactive cells can escape immune surveillance and contribute to disease progression (9), (10), (11). As a result, DMTs have been developed to target the antigen presentation process or to enhance the function of regulatory T cells

The role of T lymphocytes in the pathogenesis of MS is well established and represents a major target of DMTs (12), (13). B lymphocytes also contribute to the disease process, generating antibodies as evidenced by the increased intrathecal synthesis of immunoglobulins, seen as oligoclonal bands in the cerebrospinal fluid (CSF). Additionally, inflammatory infiltrates containing B cells have been identified in the meninges of MS patients. These infiltrates are associated with more severe clinical manifestations, greater cortical involvement, and enhanced neurodegeneration (6).

Sphingosine 1-phosphate (S1P) receptors on the surface of T lymphocytes play an important role in regulating their migration. During activation and clonal expansion, the expression of S1P receptors increases, enabling T cells to exit the lymph nodes and migrate to sites of inflammation, where they carry out their immune functions (14). This mechanism underlies the therapeutic action of S1P receptor modulators in MS. By inhibiting these receptors, such drugs sequester lymphocytes within lymph nodes, thereby limiting the inflammatory response (15).

The precise mechanisms by which activated immune cells cross the BBB in MS are not completely understood yet. Potential contributing factors include dysfunction of tight junction proteins and alterations in BBB efflux pump activity (16), (17), (18). MS lesions typically form around small veins and venules, which are sites particularly susceptible to immune cell infiltration.

Glial cells also contribute to maintaining CNS homeostasis (19). Under pathological conditions, activated microglia and macrophages release proinflammatory cytokines, produce reactive oxygen and nitrogen species, and promote excitotoxicity by impairing glutamate reuptake, all of which contribute to neuronal injury (3). Additionally, excitatory neurons become more vulnerable due to ion channel dysregulation, mitochondrial dysfunction, and reduced inhibitory signaling (20). Emerging research also highlights a possible role for meningeal lymphatic vessels in transporting immune cells and macromolecules from the cerebrospinal fluid to peripheral immune sites, though this pathway remains poorly understood and is not yet a target of current disease-modifying therapies (21).

AVAILABLE DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS

MS was the first neurological disorder to benefit from the advancement of effective disease-modifying medicines. The DMT approved for the treatment of MS was interferon beta-1b in 1993, followed three years later by glatiramer acetate and interferon beta-1a. These treatments represented a significant milestone, reducing annual relapse rates by 20–30% and delaying the progression to MS in individuals with clinically isolated syndrome (22). Over time, the number of available therapies has grown dramatically. In general, improved treatment efficacy is associated with higher hazards, particularly with immunosuppressive medicines, which may increase the incidence of infections or malignancies. By contrast, interferon beta and glatiramer acetate are considered immunomodulators and are associated with a more favorable safety profile. Choosing a treatment for MS is challenging and must be individualized for each patient. The decision should always consider the overall risk–benefit profile, comorbidities, and, importantly, the patient's preferences, as part of a shared decision-making process.

Beta interferons, the first known therapy for multiple sclerosis, are administered via subcutaneous or intramuscular injections. Although their exact mechanism of action is not fully understood, they appear to modulate the immune system by interacting with specific receptors on the surface of leukocytes. They decrease antigen presentation to T cells and promote the activity of regulatory T cells. Additionally, they reduce the passage of inflammatory cells across the BBB, increase the production of anti-inflammatory cytokines, and inhibit the release of pro-inflammatory cytokines (23). Interferons are considered safe during pregnancy and lactation.

Glatiramer acetate is a synthetic polymer administered subcutaneously. It is an immunomodulator with a peptide structure that resembles myelin basic protein. As a result, it competes with self-antigens for binding to MHC class II molecules and redirects the autoimmune response away from myelin. Although its exact mechanism remains unclear, it is known to shift the immune environment

toward an anti-inflammatory state and promote regulatory T cell activity (24). Glatiramer acetate requires no routine lab monitoring, has no known drug interactions, and is not associated with opportunistic infections or malignancies. Like interferon beta, it is considered safe for use during pregnancy and breastfeeding.

Teriflunomide inhibits the proliferation of activated T and B lymphocytes. It interferes with the de novo synthesis of pyrimidines in rapidly dividing cells by inhibiting dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme. Additionally, it exerts effects independent of DHODH inhibition by suppressing protein tyrosine kinase activity and modulating cytokine production (25). It is administered orally. Due to its long half-life (18–19 days) and enterohepatic recirculation, elimination from the body can take up to eight months. It is contraindicated in pregnancy because of its teratogenic potential.

Fumarates, primarily dimethyl fumarate, are also administered orally and function by activating the Nrf2 pathway, which plays a key role in the cellular response to oxidative stress. This activation provides neuroprotective effects by reducing oxidative damage to neurons and astrocytes (26). Fumarates are not recommended during pregnancy or lactation.

S1P receptor modulators, including fingolimod (non-selective), siponimod, ozanimod (selective for S1P1 and S1P5), and ponesimod (selective for S1P1), regulate immune cell trafficking by down-modulating S1P receptors on lymphocytes. This results in the functional sequestration of lymphocytes within lymph nodes, reducing their migration into the bloodstream and CNS. These agents also cross the BBB, where they may influence neurogenesis, glial function, and potentially promote remyelination (27). Despite their efficacy, S1P modulators carry risks such as cardiovascular side effects and disease rebound upon discontinuation. They are contraindicated during pregnancy.

Cladribine, an oral therapy, is particular in its mode of action, immune reconstitution therapy. This approach involves two distinct phases. In the first phase, cladribine induces a targeted reduction of lymphocytes over several weeks. This results in selective immunosuppression, primarily affecting T cell–mediated cellular immunity and B cell–mediated humoral responses. This immunosuppressive effect is achieved through cladribine's cytotoxic mechanism: once phosphorylated within lymphocytes, it disrupts essential intracellular processes by interfering with DNA synthesis and repair, inhibiting ribonucleotide reductase, and ultimately inducing apoptosis (28). The second phase consists of a gradual repopulation and remodeling of the immune system over the following months. During this time, peripheral lymphocyte populations recover, resulting in a qualitatively and quantitatively altered immune profile (29), (30). This distinctive mechanism enables cladribine to provide sustained disease control and prolonged remission with a limited number of treatment cycles. However, despite well-established treatment protocols, long-term data remain limited, particularly for patients who do not respond adequately or may require additional treatment courses. Due to its cytotoxic effects, cladribine is contraindicated during pregnancy.

Natalizumab is a monoclonal antibody directed against α4β1 integrins (VLA-4), which are expressed on the surface of B and T lymphocytes. By binding to these integrins, it blocks their interaction with adhesion molecules such as VCAM-1 on the vascular endothelium, thereby preventing lymphocyte migration across the BBB (24). It is administered via intravenous infusion and, more recently, subcutaneously, and is considered a highly effective therapy. However, its high efficacy must be weighed against the significant risk of opportunistic infections, most notably progressive multifocal leukoencephalopathy (PML). Additionally, natalizumab carries a substantial risk of disease rebound upon treatment discontinuation, an important consideration when planning a therapeutic switch.

Ocrelizumab and ofatumumab are monoclonal antibodies targeting CD20, a surface antigen expressed on pre-B cells, mature B cells, and memory B cells. They induce B cell depletion at these stages through mechanisms such as antibody-dependent cellular cytolysis and complement activation (31).

Alemtuzumab is a monoclonal antibody targeting CD52 on the surface of lymphocytes and monocytes. It induces profound immunosuppression through complement-mediated cytolysis (32). Depletion occurs rapidly within days of treatment, followed by partial immune recovery over the next 8–12 months. $CD4^+$ T cells are the slowest to repopulate (33), (34). This delayed immune reconstitution contributes to the long-term reduction in inflammation associated with multiple sclerosis. However, due to the depth of immunosuppression it causes, the associated risks are significant and cannot be overlooked. For this reason, alemtuzumab is typically reserved for patients who have failed at least two prior DMTs.

Mitoxantrone is a cytotoxic agent that intercalates into DNA and inhibits topoisomerase II, thereby disrupting DNA repair and inducing cell death (35). Due to its dose-dependent risk of cardiotoxicity and secondary leukemia, its use has become rare and highly restricted.

Autologous hematopoietic stem cell transplantation (AHSCT) has been used as a therapeutic approach in carefully selected patients with autoimmune diseases since 1995 (36). It involves the elimination of autoreactive T cells, followed by immune system repopulation and the promotion of a more tolerant immune phenotype (37), (38), functioning as a form of immune reconstitution therapy. By restoring the balance between proinflammatory and regulatory immune cells, AHSCT suppresses CNS inflammation and may offer additional neuroprotective effects (39), (40). Stem cells used in this therapy are also believed to contribute to CNS repair. Their ability to migrate to brain lesions and differentiate into neuronal and myelin-producing cells supports remyelination and tissue regeneration (41) (42). Initially tested in patients with chronic progressive MS, outcomes were less favorable in that group. However,

retrospective studies have shown significantly better results in younger patients with aggressive, relapsing disease and shorter disease duration (43). As such, the ideal candidates for AHSCT are young, ambulatory individuals with highly active RRMS (39), (44). Studies suggest that up to 70–80% of these patients may achieve long-term remission, lasting four to five years or more (44).

THERAPEUTIC APPROACHES IN MULTIPLE SCLEROSIS

Therapeutic approaches primarily follow one of two strategies: escalation therapy or early high-efficacy treatment.

The escalation strategy involves starting with a treatment that offers moderate efficacy but a favorable safety profile (45). Disease activity is closely monitored through clinical assessment and MRI, with treatment intensified only if relapses or progression occur, thus prioritizing safety and minimizing exposure to high-risk medications.

In contrast, the strategy of initiating highly effective therapy early in patients with moderate to high disease activity allows for rapid control of inflammation from the outset, significantly improving long-term outcomes (46), (47). However, this approach also exposes patients to more intensive immunosuppression, increasing the risk of adverse effects, which must be carefully monitored. Meta-analyses and retrospective studies suggest that initiating high-efficacy DMTs at a younger age is linked to better treatment responses, slower disability progression, and delayed transition to secondary progressive MS (48), (49), (50). Data from national registries, such as the Swedish registry, support the observation that patients treated early with highly effective therapies reach significant disability milestones later in life (2), (51). To identify patients most likely to benefit from this approach, several poor prognostic factors have been established. These include demographic variables (age over 40, male sex, non-White ethnicity, and comorbidities), clinical indicators (frequent relapses, severe attacks requiring steroids or hospitalization, significant impact on daily function, involvement of multiple functional systems, severe motor, cerebellar, or brainstem symptoms, and incomplete relapse recovery), and radiological features (new gadolinium-enhancing T1 or T2 lesions, high T2 lesion burden, spinal cord lesions, and brain atrophy) (52).

Therapeutic Switching in MS

In MS, switching DMTs is primarily driven by lack of efficacy or issues with tolerability. Historically, treatment response was assessed using tools such as the Rio and Modified Rio scores, and more recently using the No Evidence of Disease Activity (NEDA) criteria. NEDA-3 means the absence of clinical relapses, disability progression, and MRI activity (new or larger T2 lesions and T1 gadolinium-enhancing lesions), while NEDA-4 includes the absence of rapid brain atrophy (53). A patient receiving DMT treatment who experiences a high relapse rate, moderate to severe relapses with functional impairment or involvement of the motor system, cerebellum, brainstem, or sphincters, incomplete recovery, or MRI activity should be evaluated for a possible treatment change. These indicators suggest suboptimal treatment response and warrant re-evaluation of the therapeutic approach to prevent long-term disability accumulation (52).

Before evaluating the effectiveness of a DMT, it is essential to allow sufficient time for the therapy to take full effect. The time to clinical response varies: natalizumab typically acts within one month; interferon-beta, teriflunomide, dimethyl fumarate, fingolimod, and ocrelizumab within three months; glatiramer acetate requires about six months; and cladribine and alemtuzumab reach full efficacy only after completing a two-year treatment course (52).

When considering a treatment switch, clinicians must account for lingering immunologic effects from the previous therapy, especially in the case of long-acting agents. The pharmacodynamics and mechanism of action of each DMT can influence both the effectiveness and safety of subsequent treatments. Short-acting DMTs (e.g., interferon, glatiramer acetate, dimethyl fumarate) clear within days to weeks, whereas medium-duration agents (e.g., fingolimod and natalizumab) may require weeks to months. Long-acting therapies, such as mitoxantrone, alemtuzumab, ocrelizumab, and teriflunomide, can exert effects lasting months to years. Careful balance is needed between washout duration and the risk of disease reactivation (55).

Discontinuation of DMT

The decision to stop DMT in MS is complex. The concept of immunosenescence refers to an age-related decline in immune system function that may both reduce MS inflammatory activity and increase susceptibility to adverse effects from immunotherapy. The DISCOMS study explored this issue by enrolling 259 patients aged over 55 with at least five years of stable disease. Participants were randomized to either continue or discontinue their DMT and monitored for two years. While the study did not yield definitive conclusions, it suggested that discontinuing therapy may be a reasonable consideration for older patients with prolonged disease stability. However, it did note a slightly increased risk of new MRI activity following discontinuation (54).

Shared Decision-Making in MS Therapy

Choosing the appropriate therapy in multiple sclerosis involves a shared decision-making process, where the physician carefully considers the patient's values, preferences, and lifestyle when selecting from evidence-based treatment options. This joint strategy has proven to enhance adherence and patient satisfaction. However, shared decision-making is not a one-time event but an ongoing dialogue, as MS is a chronic and evolving disease. Patients should be informed from the time of diagnosis that treatment may need to change over time for various reasons—such as suboptimal response, progression of the disease (e.g., from relapsing-remitting to

secondary progressive), safety concerns, or adverse effects. In cases of suboptimal response, clinicians should be vigilant for signs such as increased relapse rates, incomplete recovery, or new MRI lesions, all of which may warrant prompt and effective adjustments to the treatment plan.

THERAPIES UNDER DEVELOPMENT AND FUTURE PERSPECTIVES

Current treatments for MS primarily target inflammation, the dominant pathophysiological mechanism in the early stages of the disease. With the advent of highly effective DMTs, many patients with relapsing MS remain relapse-free and show no new demyelinating lesions on MRI. However, as the disease progresses, neurodegeneration becomes an increasingly central component of its pathology (55).

Unfortunately, existing therapies are largely ineffective in addressing these degenerative processes, and progression independent of relapse activity (PIRA) often continues. Even more concerning is that this subtle progression may not be fully captured by current clinical assessments, imaging techniques, or biomarkers, allowing disability to accumulate silently. Therefore, there is a pressing need for new therapies that target all aspects of MS pathology at every stage of the disease, not only inflammation, but also axonal damage and neuronal loss (56).

In terms of targeting the immune response, current anti-CD20 therapies have limitations, as they do not affect all stages of B-cell development. As a result, there is growing interest in therapies that also target the plasmablast and plasma cell stages, which are believed to play a significant role in the chronic phase of MS. One example is anti-CD19 therapy, which is discussed below (59).

Future treatment approaches also aim to reduce the significant adverse effects associated with current DMTs, such as immunosuppression-related infections, hepatotoxicity, and potential oncogenic risks. Developing safer, more tolerable therapies could significantly improve the long-term quality of life for individuals living with MS (57).

Novel monoclonal antibodies are currently under investigation in early clinical trials. Elezanumab targets repulsive guidance molecule A (RGMa), a protein that inhibits neural regeneration following CNS injury or inflammation (58). Temelimab is a monoclonal antibody targeting the human endogenous retrovirus W envelope protein (HERV-W-ENV), which may be involved in the pathogenesis of multiple sclerosis and other neurodegenerative diseases. Inebilizumab, a monoclonal antibody against CD19, acts on a broader spectrum of B cells, including plasmablasts and plasma cells that escape CD20-targeted treatments (58).

Cell-based therapies are also under development. Beyond AHSCT, mesenchymal stem cell therapy, using the regenerative and immunomodulatory properties of multipotent cells found in various tissues, is being explored in phase 2 trials. Oligodendrocyte progenitor cell therapy, aimed at enhancing remyelination, is also under investigation, although current results remain inconclusive (58).

One of the most revolutionary developments is the use of chimeric antigen receptor T (CAR-T) cell technology, which is derived from oncology (59). These genetically modified T cells are engineered to recognize and destroy specific cell targets, offering a potentially long-lasting therapeutic effect due to their ability to proliferate and persist in vivo (60). In MS, CAR-T cells targeting B cell markers such as CD19 show particular promise and are currently undergoing phase 2 clinical trials (61).

A significant limitation of current MS therapies is their limited ability to address compartmentalized inflammation within the CNS, which plays a critical role in long-term disability (62), (63). While existing treatments are effective in modulating peripheral immune responses and preventing relapses in relapsing forms of MS, they show reduced efficacy in progressive forms of the disease, where chronic inflammation within the CNS persists (62).

Bruton's tyrosine kinase (BTK) is a new therapeutic target. It is expressed in B lymphocytes, where it regulates their development and function, but is also present in other immune cells, including T cells, macrophages, dendritic cells, mast cells, and microglia, where it contributes to activation and phagocytosis, processes implicated in myelin damage (64), (65). Its role in ongoing neuroinflammation is supported by post-mortem analyses of brain tissue from patients with progressive MS, which have shown increased BTK expression in active white matter lesions (66).

Bruton's tyrosine kinase inhibitors (BTKi) are small molecules capable of crossing the BBB. This enables them to act both peripherally on the immune system and centrally within the CNS, targeting inflammation at both levels (67). First-generation BTKi, originally developed for oncology, lack selectivity and are associated with significant adverse effects, such as increased risks of bleeding, infection, and atrial fibrillation, which limit their suitability for long-term use in chronic autoimmune diseases (68). In contrast, second-generation BTKi offer greater selectivity and improved safety profiles (69). They are currently being investigated in phase 3 clinical trials across all forms of MS, including relapsing-remitting, secondary progressive, and primary progressive MS. If proven effective, these agents could represent a major advancement in MS therapy, particularly by expanding treatment options for progressive forms of the disease, where current choices remain limited (70).

CONCLUSIONS

Currently, with multiple therapeutic options available, the treatment of MS is personalized. Growing evidence supports the early initiation of highly effective therapies in appropriately selected individuals. Despite significant advances in controlling inflammation, current treatments do not halt neurodegeneration, underscoring the need for next-generation therapies that directly target disease progression. Treatment decisions are increasingly complex, requiring shared decision-making that aligns medical evidence with patient preferences, risk tolerance, and lifestyle. Future therapeutic goals include improving long-term safety, reducing immunologic risks, and developing tools to detect and treat progressive disease more effectively.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

Authors' contribution

Conceptualization, A.P., C.-A.S., and O.V.; methodology, A.P.; software, A.P.; validation, A.P., C.-A.S., V.L., and O.V.; formal analysis, A.P.; investigation, A.P., V.L., A.B., and O.V.; resources, C.-A.S. and F.C.P.; data curation, A.P., A.B., and O.V.; writing—original draft preparation, A.P. and A.B.; writing—review and editing, A.P., C.-A.S., V.L., A.B., F.C.P., and O.V.; visualization, A.P. and F.C.P.; supervision, C.-A.S.; project administration, C.-A.S. All authors have read and agreed to the published version of the manuscript. No generative AI was used in the production of this article.

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