Review Article

"New advances in the management of multiple sclerosis: Disease-modifying therapies and beyond" a look at the latest treatments for multiple sclerosis, including novel disease-modifying therapies

Ramica Sharma

Department of Pharmacology, University School of Pharmaceutical Sciences, Rayat Bahra University, Sahibzada Ajit Singh Nagar, Punjab, India

Correspondence:
Dr. Ramica Sharma, Department of Pharmacology, University School of Pharmaceutical Sciences, Rayat Bahra University, Sahibzada Ajit Singh Nagar, Punjab, India.
E-mail: ramica.17740@rayatbahrauniversity.edu.in

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ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by the destruction of the myelin sheath in the central nervous system, leading to a wide range of neurological symptoms. Advances in disease-modifying therapies (DMTs) have revolutionized MS treatment, aiming to reduce relapse rates, slow disease progression, and improve quality of life. This review discusses recent developments in oral and infusion-based DMTs, including ozanimod, siponimod, ocrelizumab, and alemtuzumab, highlighting their mechanisms, efficacy, and safety profiles. Emerging therapies such as ofatumumab, evobrutinib, and ibudilast show promising potential in clinical trials, offering new approaches for B-cell depletion, neuroprotection, and immunomodulation. The review also examines the role of combination therapies, rehabilitation strategies, and lifestyle modifications, which are critical in addressing specific symptoms such as spasticity, fatigue, and mobility issues. Complementary therapies, including mindfulness, yoga, and acupuncture, are discussed as supportive measures in MS care. As research continues to advance, personalized treatment approaches incorporating DMTs, lifestyle changes, and symptom management provide hope for improving outcomes in MS patients. This article aims to provide a comprehensive overview of contemporary strategies in MS management and emerging therapeutic options.

Keywords: Disease-modifying therapies, multiple sclerosis, neuroprotection, ocrelizumab, siponimod

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by the immune system mistakenly attacking the myelin sheath that insulates nerve fibers in the central nervous system (CNS). This demyelination disrupts communication between the brain and the body, leading to a wide range of symptoms, including muscle weakness, vision problems, and cognitive impairments. The disease typically progresses through different stages, with relapsing-remitting MS (RRMS) being the most common form, where patients experience episodes of symptom flare-ups followed by periods of remission. Over time, many individuals may transition to secondary progressive MS (SPMS), where symptoms gradually worsen without distinct relapses.

Early and effective treatment is crucial in managing MS as it can significantly alter the disease's course and improve long-term outcomes. Initiating therapy promptly after diagnosis helps to reduce the frequency and severity of relapses, limit the development of new lesions in the brain, and slow down overall disease progression. This

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proactive approach is essential for preserving neurological function and enhancing patients' quality of life.

Disease-modifying therapies (DMTs) play a pivotal role in MS management by targeting the underlying inflammatory processes that contribute to neuronal damage. DMTs are designed to reduce relapse rates, delay progression, and minimize the formation of new lesions. Over the years, numerous DMTs have been developed and approved for use in MS, offering various mechanisms of action and routes of administration. Recent advances in DMTs include new monoclonal antibodies and oral agents that provide more options for patients, allowing for personalized treatment plans based on individual needs and preferences.

The purpose of this article is to review the latest advances in the management of MS, focusing on novel DMTs and emerging treatment strategies that aim to improve patient outcomes. By exploring these developments, we can better understand how contemporary approaches are shaping the future of MS care and providing hope for those affected by this challenging condition.[1]

Epidemiology and Prevalence of MS

MS is one of the most common neurological disorders affecting young adults, with an estimated prevalence of approximately 1 million people in the United States and over 2 million worldwide. The disease predominantly affects individuals between the ages of 20 and 40, with a higher incidence in women compared to men, reflecting a female-to-male ratio of about 2 to 3:1. The prevalence of MS also varies geographically, being more common in regions further from the equator, which suggests that environmental factors, such as Vitamin D deficiency and viral infections (e.g., Epstein-Barr virus), may play a role in its development.[2]

Classification of MS

MS is classified into several distinct forms based on clinical presentation and progression:

- RRMS: This is the most common form, accounting for approximately 70%–80% of cases. Patients experience episodes of acute neurological symptoms (relapses) followed by periods of partial or complete recovery (remissions). During remission, symptoms may improve significantly or resolve entirely
- Primary Progressive MS (PPMS): This form affects about 10%–15% of patients and is characterized by a gradual worsening of symptoms from the onset without distinct relapses or remissions. Patients experience a steady decline in function over time
- SPMS: Many patients initially diagnosed with RRMS may transition to SPMS, where the disease progresses steadily after an initial relapsing phase. While some patients may continue to experience relapses, the overall trend is toward increasing disability
- Progressive-Relapsing MS: This rare form involves a progressive course from the beginning, with occasional acute relapses superimposed on the gradual decline
- In addition, other categories such as clinically isolated syndrome (CIS) and benign MS are sometimes recognized within the spectrum of MS.[3]

Pathophysiology

The pathophysiology of MS involves an immune-mediated attack on myelin, the protective sheath surrounding nerve fibers in the CNS. This autoimmune response leads to inflammation and demyelination, resulting in scar tissue formation known as sclerosis or plaques. The inflammatory process is characterized by perivascular infiltration by immune cells, including T lymphocytes and B lymphocytes, which contribute to myelin destruction.

As myelin is damaged, nerve conduction becomes impaired, leading to various neurological symptoms depending on the location and extent of lesions. In addition to demyelination, progressive neurodegeneration occurs, characterized by axonal loss and atrophy of both white and gray matter within the CNS. This dual mechanism acute inflammation followed by chronic neurodegeneration contributes to both relapses and long-term disability in patients with MS.[4]

DMTs

Oral DMTs

Fingolimod, teriflunomide, and dimethyl fumarate: Mechanism of action, clinical efficacy, and side effects oral DMTs have revolutionized MS treatment by providing convenient administration options. Fingolimod works by sequestering lymphocytes in lymph nodes, thereby reducing their availability to enter the CNS and cause damage. Clinical trials have shown that fingolimod can reduce relapse rates by about 54% compared to placebo.

Teriflunomide inhibits dihydroorotate dehydrogenase, leading to a decrease in lymphocyte proliferation and activation. It has demonstrated a reduction in Annualized Relapse Rate (ARR) by approximately 31%. Dimethyl fumarate activates the Nrf2 pathway, promoting antioxidant responses and reducing inflammation; it has been shown to decrease relapse rates by about 44%.[1]

Common side effects for these oral agents include gastrointestinal disturbances (e.g., diarrhea), liver enzyme elevations (particularly with teriflunomide), and lymphopenia (with dimethyl fumarate). Fingolimod carries risks of serious infections and potential cardiovascular effects on initiation.

Advantages of oral therapies over injectables

The primary advantage of oral DMTs is their ease of administration compared to injectable therapies. Patients often prefer oral medications due to reduced discomfort associated with injections and improved adherence to treatment regimens. In addition, many oral therapies offer flexible dosing schedules that can enhance patient convenience.

Infusion-based DMTs

Ocrelizumab and alemtuzumab: Recent data on efficacy and safety profiles

Ocrelizumab is a humanized monoclonal antibody that targets CD20-positive B-cells, leading to their depletion. It has been shown to significantly reduce relapse rates in relapsing forms of MS and slow disease progression in PPMS a notable advancement as it is the first therapy approved for this form of the disease. Clinical trials indicate that ocrelizumab reduces the risk of disability progression by approximately 24% compared to placebo.

Alemtuzumab is another monoclonal antibody that targets CD52 on lymphocytes, resulting in profound immune reconstitution. It has demonstrated substantial efficacy in reducing relapse rates by about 49% compared to interferon beta-1a in clinical trials but is associated with significant risks such as infections and autoimmune conditions.[5]

Immune reconstitution therapy and its impact on disease progression

Immune reconstitution therapy represents a novel approach in MS management where therapies like alemtuzumab lead to a reset of the immune system. This mechanism can potentially halt disease progression more effectively than traditional treatments by allowing for a more robust immune response against MS pathology while minimizing ongoing inflammation. However, this approach requires careful monitoring due to the risks of serious adverse effects associated with immune reconstitution.[6]

Recent Advances in Disease-modifying Therapies

Ozanimod and siponimod

In recent years, two new oral DMTs have been approved for the treatment of MS: Ozanimod and siponimod. Ozanimod is a selective sphingosine 1-phosphate (S1P) receptor modulator that was approved by the Food and Drug Administration in 2020 for the treatment of relapsing forms of MS, including CIS, RRMS, and active SPMS. The approval was based on the results of the phase 3 SUNBEAM and RADIANCE trials, which demonstrated that ozanimod significantly reduced annualized relapse rates and the risk of disability progression compared to interferon beta-1a in patients with RRMS.

Siponimod, another S1P receptor modulator, was approved in 2019 for the treatment of active SPMS in adults. The approval was based on the phase 3 EXPAND trial, which showed that siponimod reduced the risk of disability progression and the annualized relapse rate in patients with SPMS. Real-world data from the MSDS3D study have further supported the efficacy and safety of siponimod in clinical practice.[7]

Clinical trials and real-world data

The clinical trials supporting the approval of ozanimod and siponimod have demonstrated their efficacy in reducing relapse rates, slowing disability progression, and improving magnetic resonance imaging outcomes in patients with relapsing forms of MS. Real-world data from post-marketing studies have also confirmed the effectiveness and tolerability of these therapies in clinical practice, with similar safety profiles to those observed in clinical trials.

Emerging therapies

Promising therapies in late-stage clinical trials

Several promising DMTs are currently in late-stage clinical trials, offering novel mechanisms of action and potential benefits for patients with MS. These include:

- Ofatumumab: A fully human anti-CD20 monoclonal antibody that depletes B-cells. The phase 3 ASCLEPIOS trials have shown that ofatumumab significantly reduced the annualized relapse rate and the risk of disability progression compared to teriflunomide in patients with relapsing MS
- Evobrutinib: An oral Bruton's tyrosine kinase (BTK) inhibitor that modulates B-cell and myeloid cell function. The phase 2 trial demonstrated that evobrutinib reduced gadolinium-enhancing lesions in patients with RRMS
- Ibudilast: A phosphodiesterase inhibitor with neuroprotective and anti-inflammatory properties. The phase 2 SPRINT-MS trial suggested that ibudilast may slow brain atrophy in progressive MS.

Novel mechanisms of action

These emerging therapies target various aspects of MS pathogenesis, offering novel mechanisms of action beyond traditional DMTs. B-cell depletion therapies like ofatumumab aim to reduce the autoimmune response, while BTK inhibitors like evobrutinib modulate B-cell and myeloid cell function. Neuroprotective agents like ibudilast have the potential to target neurodegeneration and slow disease progression, particularly in progressive forms of MS.[8]

Combination therapies

Synergistic effects and challenges

The combination of DMTs with other treatment strategies, such as immunosuppressants or neuroprotective agents, may offer synergistic effects and improved outcomes for patients with MS. However, the use of combination therapies also presents challenges, including an increased risk of adverse events, potential drug interactions, and the need for careful patient selection and monitoring.

Clinical trials evaluating the safety and efficacy of combination therapies are ongoing, but real-world data on their use are limited. Healthcare providers must carefully weigh the potential benefits against the risks when considering combination therapy for individual patients, taking into account factors such as disease severity, comorbidities, and patient preferences.[9]

Beyond Disease-modifying Therapies

Therapies addressing specific symptoms

Effective symptom management is crucial for enhancing the quality of life for individuals with MS. Symptoms such as spasticity, fatigue, and mobility issues require targeted therapies. Spasticity, characterized by

muscle stiffness and involuntary contractions, can be managed with medications such as baclofen, tizanidine, or botulinum toxin injections. Fatigue, one of the most common and debilitating symptoms of MS, can be addressed through pharmacological options such as amantadine and modafinil, alongside nonpharmacological strategies such as energy conservation techniques and scheduled rest periods.

Mobility issues are often tackled through physical therapy, which focuses on improving strength, balance, and coordination. Occupational therapy can also assist patients in adapting their daily activities to maintain independence. Rehabilitation strategies may include the use of assistive devices such as canes or walkers to enhance mobility and safety during daily activities.

Rehabilitation strategies, physical therapy, and occupational therapy

Rehabilitation plays a key role in managing MS symptoms. Physical therapy helps patients improve their physical function through tailored exercise programs that enhance mobility and reduce spasticity. Techniques such as aquatic therapy can be particularly beneficial for individuals with heat sensitivity or those who experience fatigue during traditional exercise. Occupational therapy focuses on helping patients adapt their environments and routines to maximize independence and functionality in daily tasks.[10]

Lifestyle modifications

Role of diet, exercise, and mental health interventions

Lifestyle modifications are essential components of managing MS effectively. A balanced diet rich in fruits, vegetables, whole grains, and healthy fats can support overall health and may help manage symptoms. While no specific diet has been universally proven to benefit all MS patients, maintaining a healthy weight and ensuring adequate Vitamin D levels are often recommended.

Regular exercise is also crucial for managing fatigue and improving physical function. Engaging in moderate-intensity aerobic exercises, strength training, and flexibility exercises can enhance endurance and reduce symptoms of depression and anxiety commonly experienced by individuals with MS. Mental health interventions such as cognitive-behavioral therapy can help patients cope with the emotional challenges of living with a chronic illness.

Complementary therapies: Mindfulness, yoga, and acupuncture

Complementary therapies have gained popularity among MS patients seeking additional symptom relief. Mindfulness practices and yoga can help reduce stress and improve mental well-being while promoting physical flexibility and strength. These practices have been shown to alleviate symptoms such as anxiety and depression.

Acupuncture is another complementary approach that some individuals find beneficial for managing pain and spasticity. While evidence regarding its efficacy varies, many patients report positive experiences with acupuncture as part of their holistic treatment plan.

Neuroprotective and remyelinating therapies

Advances in neuroprotective agents and remyelination strategies

Research into neuroprotective agents aims to prevent neuronal damage in MS by targeting the underlying mechanisms of inflammation and neurodegeneration. Recent advances have identified potential neuroprotective compounds that may help preserve neuronal integrity during inflammatory attacks.

Remyelination strategies focus on repairing damaged myelin sheaths to restore nerve function. Emerging therapies are exploring the use of agents that promote oligodendrocyte precursor cell differentiation into mature oligodendrocytes, which are responsible for myelin production. These approaches hold promise for reversing some of the damage caused by MS.[11]

Stem cell therapies: Current research and potential future applications

Stem cell therapies represent a cutting-edge area of research in MS treatment. Current studies are investigating the use of hematopoietic stem cell transplantation (HSCT) to reset the immune system in patients with aggressive forms of MS. Preliminary results suggest that HSCT may lead to significant improvements in disease activity and disability outcomes for some patients.

Patient-centered Care and Personalized Medicine

Patient-centered care and personalized medicine are becoming increasingly important in the management of various diseases, including psychiatric disorders. By tailoring treatments to individual patient profiles, considering both genetic and environmental factors, healthcare providers can optimize therapeutic outcomes and minimize adverse effects.

Importance of tailoring treatments to individual patient profiles

Each patient presents with a unique combination of genetic and environmental risk factors that contribute to the development and progression of their condition. Recognizing this heterogeneity is crucial in selecting appropriate treatments. For example, in schizophrenia, patients with a predominance of negative symptoms may benefit more from a combination of antipsychotics and antidepressants, while those with prominent positive symptoms may respond better to high-potency antipsychotics. Similarly, in depression, individuals with a history of early life stress or trauma may require a combination of pharmacotherapy and psychotherapy to address the complex interplay of genetic and environmental factors.[12]

Biomarkers for predicting treatment response

The identification of biomarkers, including genetic and epigenetic markers, can help predict an individual's response to specific treatments. For instance, the serotonin transporter gene (5-HTTLPR)

has been associated with differential response to selective serotonin reuptake inhibitors (SSRIs) in patients with depression. Individuals with the short allele of this gene may be more likely to benefit from SSRI therapy compared to those with the long allele. Similarly, the catechol-O-methyltransferase gene has been linked to cognitive function and response to antipsychotics in schizophrenia.

The role of genetic and environmental factors in therapy selection

Both genetic and environmental factors play a crucial role in therapy selection and treatment outcomes. Genetic factors can influence an individual's susceptibility to certain disorders and their response to specific medications. For example, the dopamine D4 receptor gene has been associated with the development of attention-deficit/hyperactivity disorder and may also impact the efficacy of stimulant medications used in its treatment.

Environmental factors, such as early life stress, trauma, and socioeconomic status, can also shape an individual's response to treatment. Patients with a history of adverse life events may require more comprehensive interventions, including psychotherapy and social support, in addition to pharmacotherapy. Addressing these environmental factors is essential for optimizing treatment outcomes and preventing relapse.[13]

Conclusion

Recent advances in MS management, particularly with new DMTs, have significantly improved outcomes by reducing relapses and slowing progression. Treatments such as ocrelizumab, siponimod, and emerging options such as ofatumumab and evobrutinib provide more effective care. Personalized approaches, combining DMTs with lifestyle modifications, are crucial for comprehensive care. However, challenges remain in optimizing long-term efficacy, managing side effects, and developing neuroprotective strategies. Future research should aim to enhance treatment precision and explore new methods for neural repair, ultimately improving the quality of life for MS patients.

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